Executive Functioning in Mild Cognitive Impairment, Frontotemporal Dementia, and Lewy Body Dementia

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Abstract

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Erin K. Johns

A thorough description of cognitive functioning in individuals with dementia and those at risk of developing dementia is essential for early and accurate diagnosis. Executive functioning is one cognitive domain in which deficits have been reported in various types of dementia, including mild cognitive impairment (MCI, often a transitional stage between normal aging and Alzheimer's disease), frontotemporal dementia (FTD), and Lewy body dementia (LBD). This thesis contains two papers addressing executive functioning in these patient groups, the first comparing MCI patients to normal controls and the second comparing FTD and LBD patients. In each study, we examined executive functioning across multiple domains (working memory, inhibitory control, verbal fluency, and planning), and compared groups in terms of statistical differences, the pattern of the severity of clinical impairment, and the frequency of impairment. Results indicated that MCI patients performed worse than controls on all of the tests administered, were clinically impaired in all 4 domains, and that clinical impairment was frequent in each of the domains. FTD and LBD patients performed remarkably similarly across all domains in group comparisons, pattern of clinical impairment, and frequency of impairment, with only one test producing results that could potentially differentiate the groups. All three patient groups were disproportionately impaired on measures of inhibitory control in comparison to other tests of executive functioning. Implications of these results are discussed.

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Executive Functioning in Mild Cognitive Impairment, Frontotemporal Dementia, and Lewy Body Dementia

It has become common knowledge that dementia is becoming an increasing problem in our aging population. Dementia involves progressive neurodegeneration, affecting a variety of areas of functioning, including memory, speech and language, visuospatial abilities, executive functioning, personality, and behaviour. According to the fourth edition (text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*), "the cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning" (American Psychiatric Association, 2000). Dementia increases in prevalence with age, and affects approximately 1 in 50 Canadians between the ages of 65 and 74, 1 in 9 between the ages of 75 and 84, and 1 in 3 aged 85 and over. Women are approximately two times more likely to suffer from dementia than men. Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 64 percent of all dementias (Canadian Study of Health and Aging Working Group, 1994). Other types of dementia include vascular dementia, frontotemporal dementia (FTD), and Lewy body dementia (LBD). Each type of dementia has a distinctive underlying pathology, and precise diagnosis will lead to a better understanding of prognosis and early treatment options.

Treatment of dementia can be severely limited by delays in diagnosis, where the disorder is not recognized until extensive damage to the brain has already occurred. Therefore, an early and accurate diagnosis could open the door to the development of preventative therapies that could delay or even stop the progression of the illness (e.g.,

NMDA receptor blockers, see Lopez & Belle, 2004). Importantly, because diagnosis of dementia is currently based on clinical symptomatology rather than underlying pathology, it is crucial to thoroughly describe the symptoms and cognitive deficits that occur in the different forms of dementia. This will create more testing options for early diagnosis, and greater diagnostic precision. In addition, a thorough categorization of the dementia syndrome will aid in the management of the disorder. Unfortunately, there is much overlap between the symptoms that present in the different forms of dementia, making diagnostic precision difficult. For example, anterograde amnesia (i.e., deficits in learning and memory) may be indistinguishable in different forms of dementia, and deficits in other cognitive domains, such as executive functioning are present in many types of dementia (Knopman, Boeve, & Petersen, 2003).

This thesis contains two papers that aim to advance our knowledge of executive functioning in different types of dementia and in a population at risk of developing dementia. The first paper examines executive functioning in mild cognitive impairment (MCI), which is often a transitional stage between normal aging and dementia, particularly AD (Petersen, Doody et al., 2001). As MCI patients are at high risk of developing dementia, this group is an important population to study for improving early diagnosis of dementia. The second paper analyzes executive functioning in two forms of dementia that are less well studied than AD, namely FTD and LBD. These two types of dementia have never been directly compared on measures of executive functioning, and doing so may contribute to improved differential diagnosis. In the review that follows, the construct of executive functioning will be discussed, as will the four domains of

executive functioning that are examined in the two papers, which are working memory, inhibitory control, verbal fluency, and planning.

Executive Functions

Though a large body of literature pertaining to executive functions has developed, a consensus on the meaning of the construct remains elusive. However, it is generally agreed that executive functioning involves processes in a high level of the cognitive system (Royall et al., 2002; Stuss & Levine, 2002). Numerous neuropsychological theories of executive functioning have been proposed, but the two that have perhaps been the most influential are the supervisory attention system model proposed by Norman and Shallice (1986), and the central executive model of working memory proposed by Baddeley and Della Sala (1996). Norman and Shallice proposed a two-tier model of the execution of activities, in which there is a lower level system, termed *contention scheduling*, that is concerned with routine cognitive and motor operations and a higher level system, termed the *supervisory attention system*, which modulates contention scheduling in non-routine situations. Thus, contention scheduling is concerned with automated behaviours such as drinking a cup of coffee and brushing one's teeth, and the supervisory attention system flexibly modulates the activities of the lower level system to allow for adaptation to non-routine situations. A key element of this theory is that there is a source schema that is triggered by a given situation for routine control of behaviour and that in novel situations, a temporary new schema must be constructed and implemented in order to cope with this non-routine situation. In addition, coping with a novel situation is proposed to involve several distinct processes, including goal setting, spontaneous schema generation, episodic memory retrieval (of information from related experiences),

delayed intention marker realization (for the implementation of a plan of action at a later time), implementation of the schema (which also involves working memory), monitoring the effectiveness of the schema, and rejection or alteration of the existing temporary schema (see Shallice & Burgess, 1996 for a complete description of these processes).

Baddeley and Della Sala's (1996) central executive model of working memory was influenced by Norman and Shallice's supervisory attention system. The central executive is conceptualized as a subcomponent of working memory, responsible for the attentional control of two slave systems: the phonological loop (which handles speech-based information), and the visuospatial sketch pad (which deals with visuospatial information). Baddeley and Della Sala proposed several possibilities for the involvement of the central executive, including dual task performance (coordinating the simultaneous operation of the two slave systems), selective attention (attending to one stimulus while ignoring another irrelevant stimulus), task switching (alternating between two overlearned tasks, such as numbers and letters, e.g., 1-A-2-B-3-C, etc.), and accessing and manipulating information in long-term memory (this was termed the episodic buffer in later writings, and represents the ability to hold a limited amount of information in storage and manipulate that information on-line, see Baddeley, 2002).

In the literature, executive functions have been inextricably linked to the frontal lobes, to the point that the terms "executive functions" and "frontal functions" have become (perhaps wrongly) interchangeable. The involvement of the prefrontal cortex in executive functioning makes intuitive sense, as the prefrontal cortex is uniquely positioned to integrate information from multiple brain regions. It is connected to more brain areas than any other cortical region, and it is a major target for both limbic and

basal ganglia-thalamocortical circuits (Fuster, 2002; Royall et al., 2002). While some researchers have argued for the separation of anatomy and function when discussing executive functions (e.g., Baddeley & Della Sala, 1996; Denckla, 1996; Stuss & Alexander, 2000), studies of frontal lobe function have produced several possibilities of cognitive functions that may be subsumed under the category of executive functions, such as divided and sustained attention, selective attention, inhibition, working memory, cognitive flexibility, set shifting, motor sequencing, planning, initiation, generative behaviour, and regulation of goal-directed behaviour (Elliott, 2003; Gazzaley & D'Esposito, 2007; Lezak, 1995; Royall et al., 2002; Spreen & Strauss, 1998; Stuss & Levine, 2002). Note that the domains of executive functioning generated from the study of frontal lobe functions are largely consistent with the executive processes proposed in the supervisory attention system and central executive models.

Patients with focal lesions to the frontal lobes (particularly the dorsolateral prefrontal cortex) have been found to perform poorly on tasks of verbal fluency, selective attention (e.g., flanker task, negative priming), working memory (e.g., delayed-response task), set shifting (e.g., Wisconsin Card Sorting test), planning (e.g., Tower of London), inhibition (e.g., Stroop test, Go/no-go). In addition, functional neuroimaging studies have consistently shown the activation of the prefrontal cortex in similar domains and tests (for reviews, see Collette, Hogge, Salmon, & Van der Linden, 2006; Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). However, functional neuroimaging studies almost always show activation of other brain regions in addition to the prefrontal cortex. In addition, several studies have found that some individuals with lesions to the frontal lobes perform within the normal range on tests of executive function and some patients with non-frontal

lesions perform poorly on those tests (see Alvarez & Emory, 2006 for a review). The exact nature of the relationship between executive functioning and the frontal lobes is still under debate, but it is clear that some relationship exists. Some researchers have suggested that the control of executive functions is not localized exclusively within the frontal lobes, but rather within the network of circuits connected to the prefrontal cortex (Gazzaley & D'Esposito, 2007; Royall et al., 2002).

It has recently been postulated that the primary role of executive functioning is unifying function over lower level processes that are largely carried out in non-frontal brain regions, including sensory input, internal states, and motor output (Gazzaley & D'Esposito, 2007). This unifying, goal-directed executive control requires many subprocesses. For example, selective and sustained attention is required to direct cognitive resources to the necessary stimuli. Working memory is required to hold information about the stimuli in mind and manipulate it as necessary to prepare for response. Planning is another component of response preparation, in which the individual must consider the different response options and select the sequence of responses most appropriate for the given situation. Fluency, or the ability to generate response options within certain criteria, is also important for planning. Further, inhibitory control is necessary to inhibit automated responses when necessary and to instead produce more appropriate responses. When carrying out the response, self-monitoring and cognitive flexibility are required to use feedback from the environment to modify responses as necessary. In addition, there are other cognitive processes that may play a role in executive control, such as abstract thinking, mental imagery, and divided attention. These executive processes have been studied on their own and in combination, but for our

purposes, we have chosen to focus on working memory, verbal fluency, inhibitory control, and planning, as these domains broadly cover many aspects of executive functioning.

Working memory. Working memory involves the short-term storage and maintenance of task-relevant information, while performing an interfering cognitive task or manipulating the information held on-line (D'Esposito, Postle, & Rypma, 2000; Miyake & Shah, 1999), and it has long been considered to be an important component of executive functioning (Stuss & Levine, 2002). Neuropsychological measures of working memory require the continuous maintenance and updating of information held in mind. These tasks have been linked to the dorsolateral prefrontal cortex (DLPFC) in lesion studies (e.g., delayed-response tasks, D'Esposito & Postle, 1999), and functional imaging studies (e.g., dual task, D'Esposito et al., 1995; monitoring and manipulation in spatial working memory, Owen, Evans, & Petrides, 1996). However, there is still debate surrounding the exact nature of the role of the frontal lobes in working memory, and it has been suggested that the primary role of the frontal lobes is the manipulation of information held on-line, particularly when interference is present (D'Esposito et al., 2000; Stuss & Levine, 2002). In the two papers presented here, the Brown-Peterson Task (BPT; Spreen & Strauss, 1998) and the Letter-Number Sequencing (LNS) subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1995) were used as measures of working memory. In the BPT, the participant must keep information in mind while performing another, interfering task (Bherer, Belleville, & Peretz, 2001; D'Esposito et al., 2000). Divergent results have been reported as to whether or not performance on the BPT is affected by age, with at least one study reporting a decline with age (Inman &

Parkinson, 1983), and other studies reporting no decline (Belleville, Peretz, & Malenfant, 1996; Bherer et al., 2001; Puckett & Lawson, 1989). The LNS test is a working memory task that requires participants to manipulate a sequence of letters and numbers held in mind by re-ordering the items. There is some evidence of a decline in performance on the LNS test with aging (Ryan, Sattler, & Lopez, 2000). The interference and the requirement of manipulation make both of these tests of working memory particularly sensitive to the executive component of working memory (Stuss & Levine, 2002).

Inhibitory control. Inhibitory control is another classic component of executive functioning, and it enables individuals to overcome prepotent, automatic behaviours and to suppress irrelevant responses and distracting information that is in direct competition with the task at hand (Shallice & Burgess, 1993). Lesion studies have linked inhibitory control to the frontal lobes (directed forgetting, Conway & Fthenaki, 2003), specifically the right superior medial cortex (stop signal task, Floden & Stuss, 2006), and the right prefrontal lateral cortex (Stroop test, Vendrell et al., 1995). Functional imaging studies have indicated that it is related to the DLPFC, ventrolateral prefrontal cortex, right parietal cortex, right frontopolar cortex, and anterior cingulate cortex, using the Stroop test, stop tasks, and go/no-go tasks (Bench et al., 1993; Braver, Barch, Gray, Molfese, & Snyder, 2001; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Garavan, Ross, Murphy, Roche, & Stein, 2002; Liddle, Kiehl, & Smith, 2001; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia, Smith, Brammer, & Taylor, 2003). There is also some evidence that inhibitory control declines with age (Butler & Zacks, 2006; Potter & Grealy, 2006; Radvansky, Zacks, & Hasher, 2005; Sweeney, Rosano, Berman, & Luna, 2001).

The Hayling test (Bugess & Shallice, 1997) and the Stroop test (Victoria version; Spreen & Strauss, 1998) were used in the present studies as measures of inhibitory control. The Hayling test consists of a number of sentences with the last word missing, and the participant is required to inhibit any response that would sensibly complete the sentence. Functional imaging studies have linked this test to the prefrontal cortex and anterior cingulate cortex (Collette et al., 2001; Nathaniel-James, Fletcher, & Frith, 1997), and normal aging has been associated with poorer performance on this test (Bielak, Mansueti, Strauss, & Dixon, 2006). The Stroop involves inhibition of the automated response of reading colour-words, requiring instead that the participant name the colour of the ink. Lesion studies have primarily linked the Stroop test to the DLPFC and superior medial regions (Stuss, Floden, Alexander, Levine, & Katz, 2001; Vendrell et al., 1995), whereas functional imaging studies have primarily found activation in the anterior cingulate cortex and middle frontal gyrus (Bench et al., 1993; Pardo, Pardo, Janer, & Raichle, 1990). Imaging studies have also found activation in non-frontal regions, including parietal, motor, and temporal regions, indicating that the Stroop test involves a distributed network of frontal and non-frontal regions (for reviews, see Alvarez & Emory, 2006; Stuss & Levine, 2002). An age-related decline has also been observed for performance on the Stroop (Troyer, Leach, & Strauss, 2006; West, 2004), but some have argued that this is an artifact of general cognitive slowing (Verhaeghen & De Meersman, 1998).

Verbal fluency. Fluency involves the ability to generate material quickly and efficiently under timed and limited search conditions. Fluency tasks require the use of many executive functioning components, including the organization of verbal material,

initiation of verbal responses, self-monitoring of words already produced, and inhibition of responses that do not meet the constraints given (Henry & Crawford, 2004). Certain verbal fluency tasks require the generation of as many words as possible that begin with a particular letter, and these are termed phonemic fluency tasks. Another type of fluency is semantic fluency, which requires the generation of words based on semantic categories (e.g., animals). Phonemic fluency tasks require novel search strategies, and therefore have been generally accepted as a measure of executive function. However, semantic fluency likely relies on well-established search strategies, and therefore is likely more reflective of semantic memory, while still requiring aspects of executive functioning (Henry & Crawford, 2004; Stuss et al., 1998). Furthermore, patterns of performance on phonemic and semantic fluency can be examined for clustering (production of words within subcategories) and switching (shifting between clusters). It has been suggested that switching is more related to executive functioning than clustering, as the number of switches is more important than mean cluster size for performing well on phonemic fluency, whereas clustering and switching are equally important for optimal performance on semantic fluency. In addition, clustering and switching have been reported to be negatively correlated with each other (as larger cluster sizes are necessarily associated with fewer switches), and positively correlated with the number of words generated on phonemic and semantic fluency. Thus, a balance between clustering and switching appears to be required for optimal performance on fluency tasks (Troyer, Moscovitch, & Winocur, 1997).

Lesion studies have found that phonemic fluency is particularly sensitive to left DLPFC functioning, whereas semantic fluency is affected by lesions to both the left and

right DLPFC as well as to the ventral prefrontal cortex. However, patients with left parietal damage also perform poorly on both semantic and phonemic fluency, and some studies have found that left temporal lesions cause impairment on semantic fluency tasks. Therefore, fluency tasks appear to be sensitive, but not specific to frontal lobe functioning (Henry & Crawford, 2004; Stuss et al., 1998; see Alvarez & Emory, 2006 and Stuss & Levine 2002 for reviews). Functional imaging studies have found a pattern of activation consistent with the pattern of deficits in lesion studies (Alvarez & Emory, 2006; Gourovitch et al., 2000; Stuss & Levine, 2002). Furthermore, verbal fluency tasks require temporal lobe functions for searching semantic memory to identify and generate clusters of words, and when a semantic category is exhausted, frontal lobe functions are required for switching to another effective search strategy (Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998). A meta-analysis of normative data for phonemic fluency revealed an age-related decline in performance on this task (Loonstra, Tarlow, & Sellers, 2001), and there is also evidence for an age-related decline in semantic fluency (Tombaugh, Kozak, & Rees, 1999).

Planning. The ability to plan and execute a series of actions necessary to achieve a certain goal is an integral part of higher-level functioning (Owen, 1997; Spreen & Strauss, 1998). Planning involves the ability to organize behaviour in time and space, and to execute set of intermediate steps to achieve a goal, when each step on its own does not necessarily lead to the goal (Owen, 1997). Patients with damage to the prefrontal cortex have shown deficits in planning (Tower of London, Owen, Downes, Sahakian, Polkey, & Robbins, 1990; virtual script generation and execution, Zalla, Plassiart, Pillon, Grafman, & Sirigu, 2001), and functional imaging studies have shown that planning tasks activate

the DLPFC, parietal cortex, and basal ganglia (Tower of Hanoi, Fincham, Carter, van Veen, Stenger, & Anderson, 2002; experimental planning task, Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). In addition, age-related deficits in planning have been observed (Allain et al., 2005). The Tower of London task (TOL; Shallice, 1982) was used as a measure of planning in the present studies. In this task, participants are presented with a board on which three balls of different colours are arranged in a certain way on three pegs, and they must plan and execute the necessary moves to rearrange balls in order to match a model configuration, within certain constraints. This task requires planning in advance, since one wrong move can render the problem virtually unsolvable, unless the previous moves are retraced in order to correct the incorrect move (Owen, 1997). Patients with lesions to the frontal lobes have been shown to perform more poorly on the TOL task (Carlin et al., 2000; Owen et al., 1990), and functional imaging studies have shown that the TOL activates the DLPFC and the superior parietal cortex bilaterally as well as the basal ganglia in healthy, normal controls (Baker et al., 1996; Newman, Carpenter, Varma, & Just, 2003; Owen, Doyon, Petrides, & Evans, 1996). There is also some evidence for age-related decline in performance on the TOL task (Zook, Welsh, & Ewing, 2006).

The Present Studies

The two studies presented here examined executive functioning in different patient groups with dementia or at risk of developing dementia. As the diagnosis of dementia is based on clinical symptomatology rather than underlying pathology, it is important to fully describe the profile of cognitive functioning in the different types of dementia. The first study compared performance of patients with MCI to controls. As

mentioned previously, many individuals with MCI go on to develop AD (Petersen, Doody et al., 2001), therefore MCI patients make up an important group to study for improving early diagnosis of dementia, improving prognostic accuracy and case management, and implementing preventative therapies and treatments of dementia. Recently, studies have begun to report the presence of executive dysfunction in early (e.g., Baddeley, Baddeley, Bucks, & Wilcock, 2001; Toepper, Beblo, Thomas, & Driessen, 2007) and even preclinical (Chen et al., 2001; Silveri, Reali, Jenner, & Puopolo, 2007) AD. Thus, the study of executive functioning in MCI may aid in the early diagnosis of individuals at risk of developing AD. In particular, the examination of performance on neuropsychological tests of executive functioning across different domains will help to determine which domains are affected and to what degree, and will also help to determine the usefulness of each of the tests of executive functioning for diagnostic purposes. In the introduction of the first study, a description of MCI is given, and previous findings regarding executive functioning in MCI and AD are reviewed. MCI patients were diagnosed according to Peterson and colleagues' (2001) criteria, which are presented in Appendix A.

As previous studies that have examined executive functioning in MCI have typically not examined multiple domains or examined the clinical significance of group differences, we aimed to address these issues in the first study. We had three main goals: (1) to determine whether or not executive dysfunction is present in MCI and in which domains, (2) to determine the severity of the deficits in each domain, and (3) to determine the frequency of impairment in each domain. Based on the literature that is reviewed in the first study, we made the following predictions. First, we predicted that there would be

group differences on all of the tests of executive functioning. Second, we predicted that MCI patients would exhibit clinically significant deficits on the measures of inhibitory control; that deficits in other domains would be smaller, perhaps failing to reach clinical significance; and that semantic fluency would be more impaired than phonemic fluency. Finally, we predicted a prevalence of impairment similar to that reported in previous studies (30 to 75 percent).

The second study compared performance of FTD and LBD patients on measures of executive functioning from FTD and LBD patients. Executive dysfunction has been reported in both of these patient groups (for reviews, see Elderkin-Thompson, Boone, Hwang, & Kumar, 2004; Simard, van Reekum, & Cohen, 2000), but the two groups have never been directly compared. Contrasting performance on measures of different domains of executive functioning in FTD and LBD may help to improve differential diagnosis for these two types of dementia. Executive functioning in FTD and LBD was compared in terms of differences in group means, average severity of impairment, and prevalence of impairment on each of the tests. In the introduction of the second paper, descriptions of FTD and LBD are given, studies of executive functioning in the two types of dementia are reviewed, and executive functioning in FTD and LBD is indirectly compared by examining previous studies comparing each of the two dementias to AD. FTD patients were diagnosed according to criteria outlined by Neary and colleagues (2005), and LBD patients were diagnosed according to McKeith and colleagues' (2004) criteria (see Appendix A).

The goals of the second study were similar to those of the first study. Our first goal was to determine whether there are reliable group differences between FTD and

LBD patients on performance on tests of executive functioning. Second, we aimed to determine if there are clinically significant differences between the two groups on the individual measures of executive functioning or on the pattern of performance on the different measures. The third goal was to determine if there are differences between the two groups in the prevalence of impairment across domains of executive functioning. Based on the literature reviewed in the second study, we predicted that both groups would exhibit impairment on each of the tests of executive functioning that were administered. However, as FTD is more typically thought of as a disorder involving prominent executive dysfunction, we predicted that performance on the tests of executive function would be lower for FTD patients in comparison to LBD patients.

The methods used in the two studies were identical. Patients were recruited and tested by investigators of the Consortium on Cognition and Aging (CCA) of the Quebec Research Network on Aging (see Appendix B for a complete list of participating investigators). The CCA is a network of researchers that was brought together under the Fonds de la Recherche en Santé du Québec to promote collaboration and pool resources across the province of Quebec for research into aging. The network developed a registry of patients with MCI, FTD, and LBD from across Quebec, common diagnostic tools, and protocols for clinical, neuropsychological, and brain imaging testing. The CCA also developed an extensive neuropsychological test battery with equivalent French and English forms for the purpose of delineating the cognitive deficits in these groups.

The CCA recruited 40 MCI, 24 FTD, and 15 LBD patients who met the criteria for testing. In addition, 37 healthy older adults were recruited to serve as a control group (27 of whom were used as the control group for determining clinical impairment in FTD

and LBD). The normal controls were tested at Concordia University and the Institut Universitaire de Gériatrie de Montréal. The patients were referred from eight different clinics from across the province (see Appendix C for a complete listing). They were initially seen by one of the participating physicians as part of their normal clinical work in one of the memory clinics. When the physician suspected a diagnosis of MCI, FTD, or LBD, the patient was invited to participate in the study. Informed consent was obtained from all participants who were able to consent and from their families in all other cases. Ethical approval for the study was obtained from all institutions involved.

Physicians confirmed the diagnosis of MCI, FTD, or LBD using agreed-upon diagnostic criteria. The physician also performed a mental status assessment and a physical evaluation before referring the patient for neuropsychological testing. In order to ensure a standard method of testing, common evaluation tools were provided to each of the testing centres. All tests were administered according to standardized procedures. The neuropsychologists, nurses, and graduate students who conducted the testing completed training sessions prior to testing, and a testing manual was developed and given to each centre. During the data collection phase, a study coordinator visited each of the sites to verify that uniform testing protocol was being used. Each participant was tested in his or her primary language (either French or English); therefore, equivalent French and English versions of each of the tests were employed.

Participants were administered six tests of executive functioning as part of a larger battery of neuropsychological tests administered in a standardized order (see Appendix D for a complete list of the tests and the order of testing). The six measures of executive functioning were: Brown-Peterson Task (BPT), Letter-Number Sequencing

(LNS), Stroop test (Victoria version), Hayling test, phonemic and semantic verbal fluency, and Tower of London (TOL). In addition, in order to investigate how any differences between groups may be related to other clinical factors, a clinical assessment was done, which included the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), the Barthel Index (BI; Mahoney & Barthel, 1965), the Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), the Geriatric Depression Scale (GDS; Yesavage et al., 1982), and the Subjective Memory Complaints Scale (SMCS; Schmand, Jonker, Hooijer, & Lindeboom, 1996). Descriptions of the clinical and executive measures are provided in each of the manuscripts.

Disproportionate Deficits in Inhibitory Control:

Profile of Executive Functioning In Mild Cognitive Impairment

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Abstract

Alzheimer's disease (AD) is thought to begin with episodic memory impairment; however, recent studies reveal executive functioning deficits in early and preclinical AD. Mild cognitive impairment (MCI) is often a transitional stage between normal aging and AD, and a thorough categorization of cognitive functioning in MCI may improve early diagnosis and treatment of AD. We examined executive functioning in MCI across multiple domains (working memory, inhibitory control, verbal fluency, and planning) in 40 MCI patients and 37 normal elderly controls (NECs). MCI patients performed significantly worse than NECs in all 4 domains ($p < .05$), and there was a clinically significant impairment (greater than 1.0 SD below the mean of the NECs) in each domain. Clinically significant impairment on each of the tests was frequent, with 100% of MCI patients exhibiting a deficit in at least one domain of executive functioning. Inhibitory control was the most frequently and severely impaired. These results indicate that executive dysfunction is common in MCI, particularly in the domain of inhibitory control, and should be assessed in neuropsychological test batteries used to detect MCI.

Keywords: mild cognitive impairment, Alzheimer's disease, dementia, executive functioning, Brown-Peterson task, Letter-Number Sequencing, Stroop, Hayling test, verbal fluency, Tower of London, working memory, inhibitory control, planning

Disproportionate Deficits in Inhibitory Control: Profile of Executive Functioning In Mild Cognitive Impairment

Traditionally, Alzheimer's disease (AD) has been described as beginning with episodic memory impairment and gradually progressing to a global decline in cognitive functioning (Becker, Huff, Nebes, Holland, & Boller, 1988; Collie & Maruff, 2000). This is consistent with the finding that the neuropathological features of the disease begin in mesial temporal areas, including the entorhinal cortex, hippocampus, and amygdala (Braak & Braak, 1997; Di Paola et al., 2007), before moving to the temporal, parietal, and posterior cingulate cortices and finally affecting the frontal lobes and anterior cingulate (Braak & Braak, 1997; Morris, 2004; Spinnler, 1999; see Thompson et al., 2007 for a review). However, more recent studies have demonstrated the presence of executive functioning deficits in AD (for reviews, see Duke & Kaszniak, 2000; Perry & Hodges, 1999), with some studies suggesting that the impairment may occur early in the progression of the disease (e.g., Baddeley et al., 2001; Baudic et al., 2006; Collette, Van der Linden, & Salmon, 1999; Lafleche & Albert, 1995; Toepper et al., 2007), perhaps even occurring in the preclinical phase (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Chen et al., 2001; Perri, Serra, Carlesimo, & Caltagirone, 2007; Silveri et al., 2007; Toepper et al., 2007). The finding of a very early executive impairment challenges the classical account of AD as a disorder involving primarily episodic memory deficits during the early phases. Therefore, it is important to more fully describe the profile of executive function in early and particularly preclinical AD, in order to aid in the identification of people at risk of developing the disease. Early identification of those at risk is essential for implementing strategies that are being developed for the prevention of

the irreversible neuronal damage that occurs in AD, as well as strategies for slowing the progression of the illness (see Lopez & Belle, 2004). In addition, early and precise diagnosis is necessary for accurate case management as well as for selecting appropriate subjects for pharmaceutical trials and other studies aimed at developing treatments for dementia and testing those treatments in the early stages of the disease.

Mild cognitive impairment (MCI) is an important concept in the study of preclinical AD, as individuals diagnosed with MCI often go on to develop AD (Petersen, Doody et al., 2001). Therefore, the objective of the present study was to describe the profile of executive functioning in MCI. Previous studies examining executive functions in MCI have typically focused on only one or two domains of executive functioning. However, we examined performance of MCI patients across multiple domains of executive functioning, namely working memory, inhibitory control, verbal fluency, and planning, in order to determine whether certain domains are more severely or frequently impaired than others. In the brief literature review that follows, we will first define executive functions, including the four domains listed above as well as the tests we used to assess each of those domains. Following that, we will describe previous research findings concerning executive functions in both AD and MCI.

Executive Functions

Despite a large body of literature on executive functions, a consensus on a precise definition of the construct has yet to be reached. Nevertheless, executive functions have commonly been conceptualized as higher-order cognitive capacities that are necessary to support independent, purposive, goal-directed behaviour or high-level control over lower level cognitive functions (Perry & Hodges, 1999; Royall et al., 2002; Stuss & Levine,

2002). Executive control is necessary in novel situations where automated functions are insufficient and in which the individual must formulate and implement a plan and monitor progress towards the goal, implementing strategy changes and correcting mistakes as necessary. As this definition suggests, executive functioning is not a unitary construct, but encompasses multiple domains. The subcomponents of executive functioning have not yet been agreed upon, but generally include planning, initiation, organization, self-monitoring, cognitive flexibility, set shifting, inhibitory control, generative behaviour or fluency, abstraction, working memory, and divided attention (Alvarez & Emory, 2006; Royall et al., 2002; Spreen & Strauss, 1998; Stuss & Levine, 2002). These subcomponents can be further reduced by examining tests that tap into four overarching domains that are frequently cited in the literature: working memory, inhibitory control, verbal fluency, and planning. The tests that cover these domains often tap into other subcomponents of executive functioning as well, and this is discussed for the individual tests below. We have chosen to focus on these four domains, as they succinctly cover many aspects of executive functioning.

Working memory has long been considered to be an important aspect of executive functioning (Stuss & Levine, 2002). It is required to hold information in mind temporarily while other cognitive functions are being performed. Typically, tasks that assess working memory require participants to continually maintain and update the information being held in mind. It has been suggested that the executive component of working memory is the manipulation of information held on-line, particularly when interference is present (D'Esposito et al., 2000; Stuss & Levine, 2002). The working memory measures used in the present study were the Brown-Peterson Task (BPT; Spreen

& Strauss, 1998) and the Letter-Number Sequencing (LNS) subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997). The interference present in the BPT and the manipulation required in the LNS make both of these tests of working memory particularly sensitive to testing executive functions (Stuss & Levine, 2002). Both working memory tasks also involve cognitive flexibility and set shifting, which is in the form of switching between letters and numbers in the LNS and switching between the working memory task and interference task in the BPT.

Inhibitory control is another important aspect of executive functioning, and it refers to the ability to suppress irrelevant responses and distracting information that is in direct competition with the task at hand. The ability to inhibit prepotent responses is a critical component of behaviour because it enables us to overcome automatic or routine behaviours (Shallice & Burgess, 1993). In the present study, we used the Hayling test (Bugess & Shallice, 1997) and the Victoria version of the Stroop test (Spreen & Strauss, 1998) as measures of inhibitory control.

Fluency refers to the ability to generate verbal or nonverbal output quickly and efficiently. Tests of fluency require individuals to generate material under timed and limited search conditions, and are considered to be measures of executive functioning because they require the organization of verbal material, initiation for generation of words, self-monitoring of responses given, and inhibition of responses that do not fit within the constraints (Henry & Crawford, 2004). There are two types of verbal fluency tasks: phonemic and semantic. Phonemic fluency tasks require the participant to generate words that begin with a particular letter, and semantic tasks require the participant to generate words based on semantic categories (e.g., animals). As generating words based

on orthographic criteria is an unfamiliar task requiring novel search strategies, phonemic fluency tasks have been generally accepted as a measure of executive function. However, while semantic fluency tasks do measure aspects of executive functioning, they also rely on well-established search strategies, and therefore are likely more reflective of semantic memory (Henry & Crawford, 2004; Stuss et al., 1998). Furthermore, patterns of performance on phonemic and semantic fluency can be examined for clustering (production of words within subcategories) and switching (shifting between clusters). It has been suggested that switching is more related to executive functioning than clustering, as the number of switches is more important than mean cluster size for performing well on phonemic fluency, whereas clustering and switching are equally important for optimal performance on semantic fluency (Troyer et al., 1997).

Planning and executing a series of responses has long been considered one of the central aspects of executive functioning (Owen, 1997; Spreen & Strauss, 1998). The cognitive aspect of planning can be defined as the ability to initiate and organize behaviour in time and space, monitor progress towards the goal, and adjust behaviour as needed. Planning is necessary when a set of intermediate steps is required to achieve a goal, but each step on its own does not necessarily lead to the goal (Owen, 1997). The Tower of London task (TOL; Shallice, 1982) was used as a measure of planning in this study. In this task, participants must plan and execute the necessary moves to rearrange balls on pegs of varying heights in order to match a presented model configuration, within certain constraints.

Executive functioning as an overall construct has long been linked to the frontal lobes, and studies have found that individuals with damage to the frontal lobes perform

significantly worse than controls on tasks of executive function. The dorsolateral prefrontal cortex (DLPFC) has been the most studied region in relation to executive functioning, and lesion and functional imaging studies have linked the DLPFC to many aspects of executive functioning, including verbal fluency, working memory, attentional switching, inhibitory control, selective attention, and planning (for reviews, see Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). However, several studies have found that some individuals with lesions to the frontal lobes perform within the normal range on tests of executive function and some patients with non-frontal lesions perform poorly on those tests. In addition, functional neuroimaging studies have implicated both frontal and non-frontal regions in executive functioning (see Alvarez & Emory, 2006, for a review). This has led some researchers to suggest that the control of executive functions is not localized exclusively within the frontal lobes, but rather within the system of circuits connected to the prefrontal cortex, including both anterior and posterior regions (Elliott, 2003; Royall et al., 2002).

Executive Function in Alzheimer's Disease

Many studies that have examined cognitive functioning in AD have used a cross-sectional design, in which patients are divided into very mild or minimal, mild, and moderate AD groups, usually based on a cognitive screening measure such as the Mini-Mental State Examination (MMSE). In general, these studies suggest that although executive deficits can be seen in the early phases of the disease, they are manifested after an initial episodic memory impairment, but before impairment in other cognitive domains such as visuospatial and language functioning (Greene, Hodges, & Baddeley, 1995; Lafleche & Albert, 1995; for a review, see Perry & Hodges, 1999). In addition,

longitudinal studies have shown that individuals who go on to develop AD show executive deficits even during the preclinical phase. For example, Albert et al. (2007) followed individuals who were normal or had MCI at baseline over four years and found that those who converted to AD during that time period had lower scores on executive functioning measures at baseline. Several other recent longitudinal studies have produced similar results (e.g., Chen et al., 2001; Perri et al., 2007). Furthermore, a recent meta-analysis of longitudinal studies examining cognitive impairment in preclinical AD found that the group that went on to develop AD performed significantly worse than controls on executive function measures at baseline. The effect size of executive dysfunction (d = 1.07) was greater than that of any other cognitive domain except general cognitive ability (d = 1.19) and perceptual speed (d = 1.11), and was approximately equal to the effect size for the episodic memory deficit (d = 1.03; Backman, Jones, Berger, Laukka, & Small, 2005). These findings suggest that executive dysfunction may be as important as episodic memory deficits in the early diagnosis of AD.

Several studies have examined various subcomponents of executive functioning in AD, and deficits have been found in a number of domains. For example, several studies have found a particular impairment on tasks that require concurrent manipulation of information, such as dual-task paradigms and working memory tasks like the Alpha-span Task and the Brown-Peterson Task (Baddeley et al., 2001; Belleville et al., 1996; Belleville, Rouleau, Van der Linden, & Collette, 2003; Greene et al., 1995; Lafleche & Albert, 1995). Many studies have also found an impairment in inhibitory control using measures such as the Stroop test (e.g., Belleville, Rouleau, & Van der Linden, 2006; Binetti et al., 1996), the Hayling test (Belleville et al., 2006; Collette et al., 1999), and the

Block Suppression Test (Toepper et al., 2007). In addition, AD patients commonly show deficits on verbal fluency tasks, with a greater deficit in semantic than phonemic fluency (Bhutani, Montaldi, Brooks, & McCulloch, 1992; Binetti et al., 1996; Collette et al., 1999; Greene et al., 1995; Lafleche & Albert, 1995; see Henry, Crawford, and Phillips, 2004 for a review). In fluency tasks, AD patients also produce smaller mean semantic and phonemic clusters than controls, and fewer switches between semantic clusters (Troyer et al., 1998). Furthermore, AD patients have shown deficits in planning as measured by maze tests (Mack & Patterson, 1995; Villardita, 1993) and "tower tests" (Rainville et al., 2002). Finally, impairments have also been reported in cognitive flexibility and set shifting using tasks such as the Trail Making Test (Chen et al., 2001; Grady et al., 1988; Lafleche & Albert, 1995) and the Wisconsin Card Sorting Test (Binetti et al., 1996; although see Bhutani et al., 1992). A recent study found that 76% of patients were impaired on at least one executive measure (Stokholm, Vogel, Gade, & Waldemar, 2006). In addition, impairment on the Stroop test, the Trail Making Test, and semantic fluency was common (47%, 42%, 36%, respectively), whereas impairment on phonemic fluency and the Wisconsin Card Sorting Test was less frequent (17% and 6%).

Executive Function in Mild Cognitive Impairment

The term mild cognitive impairment (MCI) was first used by Flicker, Ferris, and Reisberg in 1991. It was further defined by Petersen and colleagues (1999), who described MCI patients as non-demented individuals who have impaired memory, but normal activities of daily living and normal general cognitive function. Petersen and colleagues (Petersen, Doody et al., 2001) specified that the above description, which emphasizes memory loss, should be termed *amnestic* MCI, and argued that this type of

MCI is the most common presentation. However, they suggest that MCI patients could also present with impairments in multiple cognitive domains, or a single non-memory domain.

MCI patients have an elevated risk of developing dementia, with amnestic MCI patients converting to AD at a rate of 6% to 25% per year (see Petersen, Stevens et al., 2001 for a review), compared to the 1% to 2% conversion rate of healthy control subjects. In addition, approximately 80% of amnestic MCI patients go on to develop AD within 6 years (Petersen, Doody et al., 2001; Petersen et al., 1999). It is generally agreed that a diagnosis of MCI represents a substantial increase in the risk of developing dementia, but there is still controversy as to whether amnestic MCI represents a distinct transitional stage between normal aging and AD (Attix & Welsh-Bohmer, 2006; Petersen, Doody et al., 2001; Petersen et al., 1999), or simply early-stage AD (Morris, 2006). In either case, the increased risk of developing dementia makes accurate diagnosis important for developing and implementing early interventions for dementia.

Although Petersen and colleagues argue that the most common presentation of MCI is memory impairment with preserved functioning in other cognitive domains, recent studies are increasingly suggesting that impairment in multiple domains is common in MCI (Backman, Jones, Berger, Laukka, & Small, 2004; Loewenstein et al., 2006; Nordlund et al., 2005). For example, one study found that in a group of nondemented individuals with memory loss, 65% exhibited a deficit in an additional cognitive domain. Furthermore, whereas only 6% of the individuals with only memory loss progressed to AD in 2 years, 48% of those with multiple impairments progressed (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001). Another study examined a group

of individuals who met Petersen's criteria for amnestic MCI (as assessed by the Clinical Dementia Rating Scale), and therefore presumably should have had an isolated memory deficit. However, when MCI performance on a battery of neuropsychological tests was compared to controls and patients with AD, it was found that the MCI group performed less well than normal controls but better than AD patients on semantic fluency, design fluency, Stroop interference, and Part B of the Trail Making Test (Kramer et al., 2006). Thus, while MCI patients suffer deficits in many of the same domains (although to a lesser degree) as AD patients (Grundman et al., 2004; Petersen, 2004), executive functions seem to be a particularly common area of impairment.

Although fewer in number, there are studies that have shown that executive deficits similar to those seen in AD may be present in MCI. For example, several studies have found deficits in measures of working memory such as digit span backwards (Grundman et al., 2004; Lopez et al., 2006), the LNS test (Griffith et al., 2006), alpha span (Belleville, Chertkow, & Gauthier, 2007) and the BPT test (Belleville et al., 2007; however, see Nordlund et al., 2005). Variable results have been found with regards to inhibitory control, with some studies finding a deficit in MCI (Stroop test - Lopez et al., 2006; arithmetic inhibition task - Zamarian, Semenza, Domahs, Benke, & Delazer, 2007), and others finding no deficit (Hayling test - Belleville et al., 2007; Stroop test - Duong, Whitehead, Hanratty, & Chertkow, 2006; Nordlund et al., 2005). Many more studies have been done examining verbal fluency in MCI, in particular semantic fluency. Most studies have found a deficit in semantic fluency (e.g., Dwolatzky et al., 2003; Griffith et al., 2006; Loewenstein et al., 2006; Murphy, Rich, & Troyer, 2006; Phillips, Chertkow, Leblanc, Pim, & Murtha, 2004), but at least one study found no deficit (Karrasch,

Sinerva, Gronholm, Rinne, & Laine, 2005). Findings for phonemic fluency have been much more variable, with several studies finding a deficit (e.g., Dwolatzky et al., 2003; Loewenstein et al., 2006), and several finding no deficit (e.g., Griffith et al., 2006; Murphy et al., 2006; Phillips et al., 2004; see Taler & Phillips, 2007, for a review). Examination of clustering and switching in MCI revealed no differences in comparison to controls (Murphy et al., 2006). Few studies have been done examining planning in MCI patients, but deficits have been found on a maze task (Grundman et al., 2004), a functional measure of everyday planning (Farias et al., 2006), and a problem-solving task with a planning component (Beversdorf et al., 2007). Finally, variable results have been found in MCI patients in the domain of cognitive flexibility and set shifting, with one study reporting a deficit on Part B of the Trail Making Test (Lopez et al., 2006), and other studies reporting a deficit on an experimental task switching procedure (Belleville, Bherer, Lepage, Chertkow, & Gauthier, 2008; Sinai, Phillips, & Chertkow, 2006). However, one study reported no deficit on the Wisconsin Card Sorting Test (Nordlund et al., 2005).

A handful of very recent studies have looked at some aspects of the clinical significance of the executive impairment observed in MCI patients. Grundman and colleagues (2004) examined working memory (digit backwards), verbal fluency (semantic), and planning (a maze task), and Ribeiro, de Mendonca, & Guerreiro (2006) examined working memory (digit span) and verbal fluency (semantic) in MCI patients. They found significant group differences on each of the measures, but the average degree of impairment did not exceed one standard deviation below the mean of the control group. However, in both cases, the authors did not indicate if any of the individual

participants scored more than one standard deviation below the mean on any of the tasks relative to controls. In another recent study, Belleville and colleagues (2007) tested working memory (BPT and alphabetical recall) and inhibitory control (Hayling test) in MCI patients. They found significant group differences for the BPT only, and did not report the average degree of impairment for each measure. The authors did, however, indicate that three quarters of the MCI patients were impaired on the BPT, and approximately one third were impaired on the alphabetical recall task and the Hayling test. Ninety percent of MCI patients were impaired on at least one of the three measures.

Finally, Nordlund and colleagues (2005) examined a wider range of tests of executive functioning, testing MCI patients on verbal fluency (phonemic), inhibitory control (Stroop test and Picture-Word Test), divided attention (dual-task), cognitive flexibility (Wisconsin Card Sorting Test and trail making), and mental control (Parallel Serial Mental Operations). They found reliable group differences only for Parallel Serial Mental Operations (PaSMO) and the Picture-Word Test (PWT), with the difference on the PaSMO approaching clinical significance (z = -.95), and the PWT reaching clinical significance (z = -1.17). Standardized scores for the other executive measures were not reported, however, they did report that over half of the MCI patients had a deficit greater than 1.5 standard deviations below the mean of the control group on one or more test of executive functioning. While these studies suggest the presence of a clinically significant deficit on some measures of executive functioning, it remains unclear if only certain domains of executive functioning are affected. Furthermore, the relationship between the average degree of impairment and the frequency of impairment on different executive tests has yet to be examined.

The Present Study

Discerning the pattern of executive deficits in MCI is important because impairment on certain tests of executive functioning may help to predict conversion to AD (Albert, Moss, Tanzi, & Jones, 2001). Very few studies have examined executive functioning across multiple domains in MCI. In addition, while group differences between MCI patients and normal controls have been frequently reported, analysis of the clinical significance of these differences has rarely been done. As such, the present study examined executive functioning in MCI with the following three goals: (1) to determine whether or not executive dysfunction is present in MCI and in which domains, (2) to determine the severity of the deficits in each domain, and (3) to determine the frequency of impairment in each domain. Examination of group differences across multiple domains of executive functioning will provide valuable information as to whether MCI patients have deficits in certain domains of executive functioning and not others. However, group comparisons provide information about reliable differences, not clinical significance. The complimentary analyses of the degree and frequency of clinical impairment in each of the domains of executive functioning will be very illuminating in this respect.

We measured executive functioning in MCI and normal elderly controls (NECs) in four domains: working memory (Brown-Peterson Task and Letter-Number Sequencing), inhibitory control (Hayling test and Stroop test), verbal fluency (semantic and phonemic fluency), and planning (Tower of London). We chose these tests because of their sensitivity, their ability to tap into specific cognitive domains, and the availability of good normative data. Based on the literature, we made the following predictions. First, given that group differences have been reported in all of the domains of executive

functioning we examined (though the results for inhibitory control were variable), we predicted that there would be group differences on all of the tests of executive functioning. Second, with regards to degree of impairment, as inhibitory control is the only domain in which clinically significant deficits have been reported, we predicted that MCI patients would exhibit a clinically significant deficit on the measures of inhibitory control, and that deficits in other domains would be smaller, perhaps failing to reach clinical significance. Further, we predicted that semantic fluency would be more impaired than phonemic fluency, as semantic fluency has more consistently been reported to be impaired in MCI. Third, the few studies that have reported the prevalence of executive impairment have reported rates of 30 to 75 percent; therefore we expected a similar frequency of impairment in our sample.

Method

Participants

The Consortium on Cognition and Aging of the Quebec Research Network on Aging recruited 40 MCI patients who met the criteria for testing, and 37 normal elderly controls (NECs) were recruited to serve as a control group. The NECs were recruited to be comparable to the MCI group on age, education, and gender distribution. The patients were referred from seven different memory clinics from across the province and were initially seen by one of the participating physicians as part of their normal clinical work. Informed consent was obtained from all participants and ethical approval for the study was obtained from all institutions involved.

Physicians performed a mental status assessment and a physical evaluation for each of the patients referred and confirmed the diagnosis of MCI using agreed-upon

diagnostic criteria, as outlined by Petersen and colleagues (2001). This included a decline from a previous normal level of function, cognitive complaints from the patient or family, demonstrable abnormality on mental status testing, and impairment in one or more of the following domains: short term memory, long term memory, picture naming and object identification, visuo-spatial processing and construction, judgment and executive function, personality, or praxis. In addition, the impairment was not sufficient to meet clinical criteria for dementia or probable AD (McKhann et al., 1984).

NECs were recruited from the same community as the patients through posters advertising the study and visits to senior centres and residences. Participants in this group were excluded if they demonstrated an abnormal score on one of the mental status tests (MMSE < 25, Folstein et al., 1975; MoCA < 26, Nasreddine et al., 2005). Exclusion criteria for all participants included evidence of serious health problems, brain disease, or a chronic psychiatric disorder (other than mild depression), such as, cerebrovascular disease, head trauma, cerebral infection, metabolic dysfunction, thyroid dysfunction, B_{12} / folic acid deficiency, epilepsy, psychosis, schizophrenia, intoxication, or alcohol abuse. For MCI patients, this information was obtained through the physician's physical examination, and for control participants, through a self-report health questionnaire.

Demographic and clinical measures were assessed using separate analysis of variances (ANOVAs) or chi square tests in order to determine the comparability of the MCI and NEC groups (see Table 1). In terms of demographic characteristics, the two groups were comparable in age, education, and gender distribution. As Quebec is a bilingual province and participants were tested in their primary language (either French or English), the two groups were also compared in terms of language distribution, and the

MCI group had a significantly higher Francophone to Anglophone ratio than the control group. Pearson correlations between language and executive measures revealed significant correlations with some TOL variables (total time for N5 and T-, and planning time for T+ and T-) and all Hayling test variables (errors, overall scaled score, inhibition time), $p < .05$ (two-tailed). However, when participants were grouped based on language, there were no significant differences between Francophones and Anglophones on the TOL, therefore, language was considered in the analysis of group differences for the Hayling test only. Analysis of the clinical variables (measures are discussed below) revealed significant group difference for all variables: MMSE performance, Geriatric Depression Scale (GDS) scores, and Subjective Memory Complaints Scale (SMCS) scores. By definition, MCI patients would be expected to have lower MMSE scores and higher SMCS scores, therefore these variables were not considered in the analysis of group differences. However, in order to control for the possible effects of mild depression in the MCI group, we used GDS score as covariate for the tests with which it was significantly correlated. The GDS correlated with two TOL variables (number of moves for N3 and total time for T-), two Hayling test variables (errors and overall scaled score), and both phonemic and semantic fluency, $p < .05$ (two-tailed). As the GDS was correlated with only two of the 12 TOL variables and there was no obvious consistent pattern, the correlations were considered to be spurious, and the GDS was not used as a covariate for the TOL. However, it was considered in the analyses for the Hayling test and fluency tests.

Materials and Procedure

Testing of the MCI patients was conducted at each of the individual clinics, and testing for the control group was conducted at Concordia University and the Institut Universitaire de Gériatrie de Montréal. In order to ensure a standard method of testing, common evaluation tools were provided to each of the testing centres. All tests were administered according to standardized procedures. Training sessions were given to the neuropsychologists, nurses, and graduate students who conducted the testing, and a testing manual was developed and given to each centre. As Quebec is a bilingual province, each participant was tested in his or her primary language (either French or English), and equivalent French and English versions of each of the tests were employed.

Participants completed six tests of executive functioning as part of a larger battery of neuropsychological tests administered in a standardized order, which included tests of learning and memory, language, visual-spatial function, attention, and motor praxis. The six measures of executive functioning were: the BPT, the LNS, the Hayling test, the Stroop test (Victoria version), phonemic and semantic verbal fluency (PVF, SVF), and the TOL. In addition, in order to investigate how any differences between groups may be related to other clinical factors, a clinical assessment was done, which included the MMSE (Folstein et al., 1975), the MoCA (Nasreddine et al., 2005), the Geriatric Depression Scale (GDS, a 15-item measure of depressive symptoms; Yesavage et al., 1982), the Subjective Memory Complaints Scale (SMCS, a 10-item self-report measure of different types of memory complaints such as forgetting where things are left and confused thoughts; Schmand et al., 1996), the Barthel Index (BI, a measure of functional independence in 10 basic activities of daily living such as feeding, bathing, and

grooming; Mahoney & Barthel, 1965), and the Functional Activities Questionnaire (FAQ, a measure of abilities in 10 instrumental activities of daily living such as paying bills, shopping, and cooking; Pfeffer et al., 1982). The MMSE is a widely used test of cognitive functioning designed to detect the presence of cognitive disturbance and tests orientation, attention, memory, language, and viusuospatial abilities. The MoCA was administered to the control group only, as the test only became available in 2005, after the testing of the MCI patients was complete. The MoCA is a short screening test of cognitive functioning specifically designed to detect MCI that assesses several cognitive domains, including short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation. This test was included as a screen for control participants because it has been shown to be more sensitive to detecting MCI than the MMSE (Nasreddine et al., 2005; Smith, Gildeh, & Holmes, 2007). The BI and FAQ were not administered to the control group, as they are not applicable to healthy older adults.

Adapted Brown-Peterson Task. The adapted Brown-Peterson procedure was taken from the computerized Memoria Battery (Belleville, Chatelois, Fontaine, & Peretz, 2003; Bherer et al., 2001). Participants were orally presented with three consonants (consonant trigrams) randomly sampled from the alphabet, but which were not phonologically similar and did not form known acronyms. They were required to keep the trigrams in mind for time delays of 0, 10, 20, or 30 seconds, during which they were required to add one to a series of randomly generated numbers presented orally. The delays were randomly ordered, and an auditory cue signaled the end of the delay and the commencement of recall. Participants were asked to write down the three consonants on a

response sheet in the order in which they were presented. There were three practice trials and 12 test trials (3 trials of each of the 4 delay periods). The number of correct letters recalled for each delay period was recorded.

Letter-Number Sequencing. The LNS subtest of the WAIS—III was administered according to standardized procedure (Wechsler, 1997). The examiner read aloud a series of intermixed letters and digits, and the participant was required to recall the digits first in ascending order followed by the letters in alphabetical order. There are seven blocks of increasing length, with three trials per block. Participants were given one point for every correct trial, and the total number of correct trials was recorded.

Hayling test. The Hayling test consists of two sections, each containing 15 sentences missing the last word, but measuring two separate abilities. In Section 1, the examiner reads the sentences aloud, and the participant is required to make a verbal response that sensibly completes the sentence as quickly as possible. In Section 2, the examiner reads the sentences aloud, but the participant is required to make a response that in unconnected to the sentence in every way. For example, if the examiner reads the sentence "Most cats see very well at _____" the participant must suppress the response "night" and give a response that is not related to the sentence in any way, such as "banana". The English version of this test that was used was published by Burgess and Shallice (1997) and the French version of the test was published by Belleville and colleagues (2006). The response latencies for Section 1 and Section 2, and the number of connected errors (words that sensibly complete the sentence, e.g., "night") and somewhat connected errors (words that are related to the sentence in some way, e.g. "dog") in Section 2 were recorded. An inhibition time score was calculated by dividing the mean

response latency of Section 2 by the mean response latency of Section 1, thus controlling for differences in response initiation times. A weighted error score was obtained by weighting connected errors by 3 and somewhat connected errors by 1 and summing, as per the protocol outlined by Belleville and colleagues (2006), and the overall scaled score was calculated according to the procedure outlines in Burgess and Shallice (1997).

Stroop Victoria. The Victoria version of the Stroop test (Spreen & Strauss, 1998) has three parts, in which participants are presented with stimuli in blue, red, green, and yellow ink in 6 rows of 4 items. In the first part, participants are presented with 24 dots, in the second part, the dots are replaced with common words (e.g., when, hard, over), and in the third part, colour names are printed in each of the different colours, such that the print colour never corresponds to the colour name (i.e. the word 'blue' is never printed in blue ink). In each part, the participant is required to name the colour of the ink for each item and disregard any verbal content. The time to complete each section and the number of errors for each section were recorded. Interference scores were calculated for both time and errors, using the ratio between the colour and dot conditions for time and the difference between the colour and dot conditions for errors.

Verbal fluency. There are two components to verbal fluency tests: phonemic and semantic (Spreen & Strauss, 1998). For the phonemic task, participants were given a letter of the alphabet and asked to generate as many words as possible that begin with that letter, within certain parameters. For Anglophone participants, the three letters given were *F*, *A*, and *S*, and they were given 60 seconds to generate the words. For Francophone participants, the three letters given were *P*, *L*, and *T*, and they were given 90 seconds to generate the words, according to standard administration procedures. Before

analyzing this test for group differences, we tested for an effect of language using a multivariate ANOVA, with language as the between-subjects factor, collapsed across group, which revealed no significant difference. Furthermore, there was no significant correlation between language and phonemic fluency score (r = .153), or between language and semantic fluency score (r = .209). The examiner recorded all of the words the participant generated, in order. Any words that violated the parameters of the task were counted as errors. The numbers of correct words for each letter were recorded. For the semantic component, participants were asked to generate as many items as possible from a given category (animals) in one minute. The examiner recorded all the words the participant generated and the total number of correct words for the category.

The verbal fluency data were also examined for clustering and switching according to the procedure outlined by Troyer, Moscovitch, and Winocur (1997). Clustering refers to the consecutive production of words within the same phonemic or semantic subcategory. For phonemic fluency, clusters are defined as a group of words generated in succession that begin with the same two letters (e.g., *aim, air*), differ only by a vowel sound (e.g., *sale, sole*), rhyme (e.g., *fair, flair*), or are homonyms (e.g., *sun, son*). For semantic fluency, clusters are defined as a group of words generated in succession that are part of the same semantic subcategory, such as farm animals, pets, African animals, and various zoological categories (for complete scoring rules, refer to the Appendix of Troyer et al., 1997). Switching refers to the ability to shift between clusters, and the number of switches is calculated by summing the number of transitions between clusters, including single words. The total number of switches was recorded for both phonemic and semantic fluency.

Tower of London. The version of the TOL used in this study was the abridged version published by Shallice (1982). In this test, the participant is presented with two boards, each with three pegs of progressive lengths. There are three balls of different colours (red, yellow, and blue) arranged in a particular order on each of the boards. One ball fits on the shortest peg, two balls fit on the medium peg, and three balls fit on the longest peg. The balls are arranged on the examiner's board in a model configuration and the balls are arranged on the participant's board in a starting configuration. The participant must move the balls from the starting position on his or her board to match the examiner's model. The participant is instructed to (a) reproduce the examiner's model in as few moves as possible; (b) move only one ball at a time; (c) always move balls from one peg to another (i.e., not to place balls on the table or the base); (d) place no more than one ball on the shortest peg, two balls on the medium peg, and three balls on the longest peg.

There are 12 trials in the TOL, 3 of which require a minimum of 3 moves to complete (N3), and 9 of which require a minimum of 5 moves to complete (N5). Of the 5-move trials, 6 trials contain a trigger, which is an instance where one of the balls can be moved directly into its final position from the first move. Three of those trials contain a positive trigger (T+), where moving the ball directly to its final position helps in the resolution of the problem, and the other 3 of those trials contain a negative trigger (T-), where moving the ball directly to its final position hinders the resolution of the problem. For each problem, the examiner recorded the total time to completion (from the end of the instructions), the period of latency (the time between the end of the instructions and the first move), and the number of moves made by the participant.

Results

Group Comparison

Because we had specific hypotheses about each of the individual neuropsychological tests, and the different tests required different types of analyses, we treated each neuropsychological test as its own separate family of statistical tests. For example, the BPT has an inherent repeated measures ANOVA design, whereas the Hayling test is better analyzed with a multivariate ANOVA (MANOVA), which makes it difficult to analyze all the variables together with a single omnibus ANOVA. Therefore, we analyzed each neuropsychological measure separately and used the appropriate Bonferroni correction for multiple omnibus tests within the same neuropsychological measure, or follow-up comparisons. Where there were violations of sphericity, a Huynh-Feldt correction was used. Not all participants completed all tests, and missing data were primarily due to difficulties performing the task or discontinuation due to fatigue. The number of participants that completed each task is indicated below. Mean scores for MCI and NEC groups are presented in Table 2.

Working Memory. Thirty-seven patients with MCI and 32 control participants completed the each of the working memory tasks. The results for the BPT were analyzed using a mixed ANOVA with group (MCI, NEC) as the between-subjects factor and delay (0 s, 10 s, 20 s, 30 s) as the within-subjects factor. There was a significant main effect of group, $F(1, 67) = 13.70$, $p < .001$, $\eta^2 = .17$; a significant main effect for delay, $F(3, 201) = 44.08$, $\varepsilon = .939$, $p < .001$; $\eta^2 = .40$, and a significant Group × Delay interaction, $F(3, 201) = 4.12$, $\varepsilon = .939$, $p = .009$, $\eta^2 = .06$. MCI patients recalled fewer letters than NECs for all of the delay conditions except the 0 second delay ($p < .05$ in all cases; see Figure 1). The

total score on the LNS test was examined using a univariate ANOVA, which revealed a significant difference, $F(1, 67) = 19.42$, $p < .001$, $\eta^2 = .23$, with MCI patients scoring lower than controls.

Inhibitory Control. Thirty-eight MCI patients and 32 NECs completed the Stroop test. As MCI patients demonstrated a slowing on the baseline condition (dots), we accounted for this by calculating a ratio for the inhibition condition score for time by dividing the colour condition by the dot condition. Baseline errors were accounted for by subtracting the dot condition from the colour condition. The resulting scores were analyzed with a MANOVA, which revealed a significant difference, $\lambda(2, 67) = .899$, $p = .028$, $\eta^2 = .101$. Follow-up comparisons indicated a significant group difference for errors, $F(1, 68) = 7.34$, $p = .009$, $\eta^2 = .097$, with MCI patients making more errors than NECs. There was no group difference for time to complete the interference condition, $F(1, 68) = 1.69$, $p = .198$. Thirty-six MCI patients and 32 NECs completed the Hayling test and GDS. The Hayling was analyzed with a MANOVA, using GDS score and language as covariates, and this analysis revealed a significant group difference, $\lambda(3, 63) = .408$, $p < .001$, $\eta^2 = .592$. Follow-up comparisons revealed significant differences for the error score, $F(1, 65) = 88.15$, $p < .001$, $\eta^2 = .576$, and overall scaled score, $F(1, 65) = 59.66$, $p < .001$, $\eta^2 = .479$, with MCI patients performing worse than controls. Inhibition time did not differ between groups, $F(1, 65) = .105$, $p = .747$.

Verbal Fluency. Phonemic and semantic fluency were analyzed with a MANOVA, using GDS score as a covariate. Thirty-six MCI patients and 32 NECs completed the verbal fluency measures and the GDS. The omnibus test revealed significant group differences, $\lambda(2, 64) = .706$, $p < .001$, $\eta^2 = .294$. Follow-up comparisons

indicated significant group differences for both phonemic fluency, $F(1, 65) = 8.37$, $p = .005$, $\eta^2 = .114$, and semantic fluency, $F(1, 65) = 23.25$, $p < .001$, $\eta^2 = .263$, with MCI patients producing fewer words than controls in both cases. Clustering and switching were also analyzed together for phonemic and semantic fluency with a MANOVA. The omnibus test was significant, $\lambda(4, 64) = .754$, $p = .001$, $\eta^2 = .246$, and follow-up comparisons revealed significant group differences for mean cluster size for phonemic fluency, $F(1, 67) = 9.85$, $p = .003$, $\eta^2 = .128$, and for number of switches for both phonemic fluency, $F(1, 67) = 5.04$, $p = .028$, $\eta^2 = .070$ and semantic fluency, $F(1, 67) = 6.90$, $p = .011$, $\eta^2 = .093$. MCI patients produced a smaller mean cluster size for phonemic fluency, and fewer switches for both phonemic and semantic fluency.

Planning. Thirty-one MCI patients and 31 NECs completed the TOL. The results for total time, planning time, and number of moves were analyzed with separate mixed ANOVAs, with group (MCI, NEC) as a between-subjects factor and trial type (N3, N5, T+, T-) as the within-subjects factor. There was a significant main effect of group for total time only, $F(1, 60) = 15.16$, $p < .001$, $\eta^2 = .202$, with MCI patients taking longer to complete the trials than NECs (MCI: $M = 34.00$, $SE = 1.94$; NEC: $M = 23.30$, $SE = 1.94$). There was no main effect of group for planning time, $F(1, 60) = 1.78$, $p = .187$, but the main effect of group for number of moves approached significance, $F(1, 60) = 4.98$, $p = .029$, with MCI patients making slightly more moves overall (MCI: $M = 7.19$, $SE = 2.82$; NEC: $M = 6.30$, $SE = 2.82$). There were significant main effects of trial type for all three measures [total time: $F(3, 180) = 40.27$, $p < .001$, $\varepsilon = .937$, $\eta^2 = .402$; planning time: $F(3, 180) = 5.13$, $p = .004$, $\varepsilon = .797$, $\eta^2 = .079$; number of moves: $F(3, 180) = 66.04$, $p < .001$, $\varepsilon = .547$, $\eta^2 = 0.524$], generally corresponding to increasing trial difficulty. There were no

significant Group × Type interactions for any of the measures [total time: $F(3, 180) = 1.73$, $p = .165$, $\varepsilon = .937$; planning time: $F(3, 180) = .05$, $p = .971$, $\varepsilon = .797$; number of moves: $F(3, 180) = .68$, $p = .547$, $\varepsilon = .890$].

Profile of Executive Functioning

Comparisons of group means are valuable for determining whether reliable differences exist between groups, but cannot tell us if these differences are clinically significant. Thus, it is important to determine the magnitude deficits on measures of neuropsychological functioning if they are to be used in the diagnostic process. Therefore, we calculated standardized scores for each of the MCI patients based on the mean and standard deviation of the control group (see Figure 2). A mean standardized score between 1.0 and 1.5 standard deviations below the mean of the NECs was considered to reflect mild clinical impairment, and a score greater than 1.5 standard deviations below the mean was considered to reflect a more severe impairment.

In the domain of working memory, the mean standardized score for MCI patients did not reach clinical significance on the BPT, although performance in the 30 s delay condition approached clinical significance. However, patients did exhibit a significant mild impairment on the LNS. For inhibitory control, scores did not reach clinical significance for the Stroop (both errors and time), however, performance on Stroop errors approached clinical significance. The greatest magnitude of deficits was observed on the Hayling test, on which severe impairment was found for the errors scaled score and overall scaled score. However, scores did not reach clinical significance for inhibition time on the Hayling test. Clinically significant impairment in the mild range was observed for both phonemic fluency and semantic fluency, with a slightly greater degree

of impairment on semantic fluency. Finally, patients demonstrated a significant mild to moderate impairment in total time for three of the trial types on the TOL (N3, T+, and T-). There were no clinically significant deficits on any of the other TOL variables.

As cognitive impairment is usually determined based on published normative data in clinical practice, we also calculated standardized scores for the MCI patients based on published norms for those scores for which such norms were available (BPT - Belleville, Chatelois et al., 2003; Hayling test - Belleville et al., 2006; phonemic fluency - Loonstra et al., 2001; TOL - Shallice, 1982; Stroop - Spreen & Strauss, 1998; animal fluency - Tombaugh et al., 1999; LNS - Wechsler, 1997). This allowed us to determine if a different pattern of impairment emerged when using typical clinical procedures versus data from normal controls. In some cases, normative data were not available for scores we were able to use for the previous analyses, therefore in those cases we chose similar scores for which norms were available, and recalculated the standardized scores in comparison to normal controls for those scores. This was the case for the Stroop test, where we used norms for the colours condition in place of the ratio score for time and the difference score. For the Hayling test, norms were not available for interference time (ratio of response latency for Section 2 and response latency for Section 1), therefore standardized scores were calculated for response latency for Section 2. There were also no available norms for overall scaled score, therefore it was omitted from this analysis. The comparison of the degree of impairment found when using published norms versus our normal controls is presented in Figure 3. In general, a greater degree of impairment was found when comparing to our normal controls than when using published norms, with the exception of Stroop errors and TOL number of moves. Variables for which there

was a difference of greater than one standard deviation when comparing published norms with our control data were the 10- and 30- second delay conditions of the BPT, the LNS, Hayling errors, phonemic fluency, TOL N3 total time, and TOL N3 number of moves (with only the last representing a difference in which published norms resulted in a greater deficit).

Frequency of Impairment

The use of standardized scores provides information as to the mean severity of executive function deficits, but it is also important to determine the prevalence of impairment on each of the tests and in each domain. We analyzed individual performance using our normal controls as a comparison group in order to determine the percentage of MCI patients who were impaired on each of the measures. As shown in Figure 4, of those who completed all of the tests in a given domain, more than 75% of MCI patients were impaired in each of the domains (greater than 1.0 standard deviations below the mean), with impairment in inhibitory control being the most frequent, followed by fluency, planning, and working memory. Note that the majority of patients were also impaired at the -1.5 standard deviation level in all of these domains. Of the patients who completed all of the tests in this study, 100% were impaired in at least one domain of executive function, 96.4% were impaired in two or more domains, 92.9% were impaired in 3 or more domains, and 60.7% were impaired in all four domains.

Discussion

The goals of the present study were to determine whether MCI patients exhibited deficits in various domains of executive functioning as well as the severity and frequency of any impairment. Strikingly, there were reliable and significant group differences on all

of the tests of executive control administered. MCI patients performed significantly lower than normal controls across several domains of executive functioning, including working memory (BPT and LNS), inhibitory control (Stroop and Hayling), verbal fluency (phonemic and semantic), and planning (TOL). Furthermore, clinically significant deficits (greater than 1.0 SD below the mean of normal controls) were found in each of the domains, but not on each of the tests. MCI patients were mildly impaired on one working memory task (LNS), but not another (BPT), mildly impaired on verbal fluency and planning (TOL), and severely impaired on one measure of inhibitory control (Hayling test), but not impaired on another (Stroop). Finally, clinically significant impairment was frequent on each of the tests of executive functioning, ranging from 54% (LNS) to 95% (Hayling test).

The finding that MCI patients performed lower than controls on a variety of tests of executive functioning is consistent with the emerging literature, in which executive functioning deficits are increasingly being reported in MCI (Belleville et al., 2007; Dwolatzky et al., 2003; Griffith et al., 2006; Grundman et al., 2004; Loewenstein et al., 2006; Lopez et al., 2006). The group comparison in the present study revealed significant deficits in MCI patients on all of the tests administered. In the domain of working memory, MCI patients recalled fewer letters on the BPT for the 10-, 20-, and 30-second delay conditions and received a lower total score on the LNS. With regards to inhibitory control, MCI patients made more errors on both the Stroop and the Hayling test, and had a lower overall scaled score on the Hayling test. MCI patients also produced fewer words on both phonemic and semantic fluency, made fewer switches on both semantic and phonemic fluency, and produced a smaller mean cluster size on semantic fluency.

Finally, in the domain of planning, MCI patients took longer to complete TOL problems. These results call into question the view that MCI and early AD involve primarily deficits in episodic memory, and suggest that executive dysfunction may be an important area of impairment in these disorders. Previous studies have typically not examined multiple domains of executive functioning, and doing so in the present study allowed us to determine that MCI patients perform lower than controls in several aspects of executive functioning. The examination of multiple domains also allowed us to compare the different domains in terms of severity and frequency of impairment.

With regards to severity of impairment, inhibitory control (as measured by the Hayling test) was more severely impaired than working memory, verbal fluency, and planning. However, clinically significant deficits were observed across all four domains examined, offering further support for the importance of executive deficits in MCI. While a clinically significant deficit in inhibitory control was predicted, the severity of impairment that was found across domains of executive functioning is somewhat surprising, as the few studies that have examined the degree of impairment on measures of executive functioning in MCI found no clinically significant impairment in working memory, verbal fluency, planning, and cognitive flexibility (Grundman et al., 2004; Ribeiro et al., 2006). Furthermore, while one previous study has reported a clinically significant deficit in inhibitory control (on the Picture-Word Test; Nordlund et al., 2005), the deficit for errors on the Hayling test in the present study was over six times greater. However, several important differences between previous studies and the present study may explain these differences.

With regards to inhibitory control, the greater severity of impairment found in the present study as compared to the study by Nordlund and colleagues (2005) may be explained by the differences in the tasks used. Nordlund and colleagues found a mild impairment on the Picture-Word Test (a picture version of the Stroop test), and the impairment in the present study was on errors on the Hayling test. Therefore, the Hayling test may be more sensitive to detecting impairment in inhibitory control, which could be due to the infrequency of errors in normal controls. While Nordlund and colleagues found a clinically significant deficit on the Picture-Word Test, they did not find a significant deficit on the Stroop test, which is in line with the findings of the present study.

Differences in the tests employed may also explain the different findings in the domain of working memory. The studies that failed to find a clinically significant impairment on working memory used either digits backwards (Grundman et al., 2004) or digit span (Ribeiro et al., 2006) tests, whereas we found a clinically significant deficit on the LNS, but not the BPT (although performance on the 30 second delay condition approached clinical significance). The LNS is likely more sensitive to detecting deficits in working memory than digit span, as the LNS has an added component of requiring the mental manipulation of the information held in mind (re-ordering the sequence of letters and numbers), whereas the digit span task simply requires that the digits be repeated back in forwards and/or reverse order.

The difference between our results and previous findings for phonemic and semantic fluency is more difficult to explain, given that the fluency tasks were very similar across studies. However, the two studies that examined standardized scores for verbal fluency and reported the details of their comparison groups had substantially larger

sample sizes than that used in this study (Grundman et al., 2004; Nordlund et al., 2005). This could account for the larger standard deviations in the comparison group in previous studies, and therefore the smaller *z* scores. Indeed, when we compared our patients to published norms (which had larger sample sizes), we did not find an impairment on the fluency measures. However, this appears to be due to lower means in the normative values, rather than larger standard deviations.

Finally, in the domain of planning, we found a clinically significant impairment on time to complete the TOL and Grundman and colleagues (2004) found no impairment on a maze task. Both the TOL and maze tasks require advance planning to properly complete the task. Maze tasks require pre-planning in order to avoid entering blind alleys when completing the maze and the TOL requires pre-planning in order to complete the task in as few moves as possible. The TOL has been reported to have a moderate correlation with the Porteus Maze task (Krikorian, Bartok, & Gay, 1994), which is likely a reflection of the shared planning component. However, the TOL may be a more difficult task involving more complex problem-solving, and thus more sensitive to detecting impairment.

The very high prevalence of executive dysfunction demonstrated in this sample of MCI patients is also striking. Every MCI patient was impaired in at least one domain of executive functioning, and 61% were impaired in all four domains. Over 75% of the patients were impaired in each of the individual domains of executive functioning. Very few studies have done an individual analysis of executive impairment in MCI, but the few that have been done have been suggestive of a high prevalence of impairment. Using a cutoff of 1.5 standard deviations below the mean, Nordlund and colleagues (2005)

found that 52.7% of MCI patients were impaired on at least one measure of executive function. Belleville and colleagues found that 75% of their MCI patients were impaired on the Brown-Peterson task, which is comparable to the 68% that we found to be impaired on this task. However, Belleville and colleagues found that only 35% of their MCI patients were impaired on the Hayling test, whereas 95% of the patients in the present study were impaired. The other tests examined in the present study have not been previously examined for frequency of impairment, but this study suggests that executive dysfunction is common in MCI across many different tests, ranging from 61% (Stroop) to 95% (Hayling test).

The differences in results we obtained when comparing our patients to our normal controls versus published norms was very instructive. Clinical impairment was found on more tests when comparing to our normal controls than when comparing to published norms, with the impairment on LNS, verbal fluency, and total time on the TOL not reaching clinical significance when compared to published norms. In contrast, the Stroop test and the number of moves on the TOL were found to be impaired when comparing to published norms, but not when comparing to normal controls. However, the variable used for Stroop errors in the analysis using published norms was different that that used when comparing to NECs (errors for the colour condition instead of the difference between errors in the colour condition and errors in the dot condition), and this variable did produce a clinically significant deficit when comparing to NECs as well. The Hayling test was the only test that was found to be impaired in our MCI patients in both cases. There are several possible reasons for these differences. First, the samples used for the published norms vary in the extent to which they are comparable to our MCI sample, and

in many cases, important demographic information (e.g., education, gender distribution) is not considered. Occasionally, the published norms are not even equivalent to the patient sample in terms of age (e.g., TOL, Shallice, 1982). Furthermore, when using published norms, the comparison group for each of the tests is different (e.g. the sample used for Stroop norms is different than the sample used for Hayling test norms), making it difficult to compare results across tests. In addition, an advantage of comparing the MCI group to our normal controls is that the test results were obtained from each group after completing the same battery of tests, whereas the results used for published norms may have been obtained after the administration of just that one test, or after the administration of a different battery. Therefore, the normal controls likely represent a more accurate comparison group than the published norms. While it may not be feasible to collect data from normal controls specifically matched to different patient samples, it is instructive to note the differences that occur in the results when this is done.

An interesting pattern emerged across the different types of analyses, which consistently pointed to a particular deficit in inhibitory control in MCI patients. Specifically, the Hayling test produced the largest effect sizes in the group comparison (errors, $\eta^2 = .58$; scaled score, $\eta^2 = .48$), the greatest degree of impairment (errors, -7.16 *SD*; scaled score, -2.84 *SD*), and greatest prevalence of impairment (95%). Interestingly, the other measure of inhibitory control used in this study, the Stroop test, had substantially smaller effect sizes (errors, .10), a much smaller degree of impairment (errors, -0.97 *SD*), and a lower prevalence of impairment (61%). This is consistent with one recent study that examined both the Hayling test and the Stroop test in AD and found a higher prevalence of impairment on the Hayling test (92%) than the Stroop test (50%)

(Belleville et al., 2006). The study by Belleville and colleagues also reported a larger degree of impairment on the Hayling test. The results of the present study indicate that the Hayling test may be more sensitive than the Stroop test to impairment in inhibitory control in MCI patients. Given the frequency and severity of impairment on the Hayling test, these results also suggest that this test could have substantial clinical applications in both diagnosis of MCI and monitoring treatment efficacy.

Another potential implication of the high frequency and severity of executive impairment in MCI is the possibility of using tests of executive function to predict conversion to AD. It has been demonstrated that MCI patients with an impairment in another domain in addition to memory have a greater likelihood of progressing to AD (Bozoki et al., 2001). Therefore, the Hayling test may be useful in demonstrating the presence of a non-memory impairment in MCI patients, thus improving prognostic accuracy. Future research should be directed at examining the predictive utility of the Hayling test and other tests of executive functioning for conversion of MCI to AD.

Although executive dysfunction has been reported in the earliest stages of AD and in MCI, and the present study found deficits in several aspects of executive functioning in MCI, the neural substrates of these deficits remain unclear. It has been argued that frontal lobe degeneration is not characteristic of AD, particularly in the early phases (for reviews, see Morris, 1996; Spinnler, 1999). However, widespread neurofibrillary tangles have been found in the orbitofrontal cortex in AD (Van Hoesen, Parvizi, & Chu, 2000), a high concentration of senile plaques have been found in the frontal lobes in very mild AD (Morris et al., 1996), and a decreased volume in the inferior prefrontal cortex has been reported in mild AD (Salat, Kaye, & Janowsky, 2001). Furthermore, hypometabolism has

been found in various frontal regions in AD patients (Waldemar et al., 1994). MCI patients have been shown to have Alzheimer-type pathology, including gray matter atrophy in the inferior frontal gyrus, entorhinal cortex region of the parahippocampal gyrus, and temporal and fusiform gyri. In addition, MCI patients exhibit moderate loss in temporal, frontal, and parietal regions, with brain volume values between those of normal controls and AD (Duarte et al., 2006).

One possible explanation that has recently emerged for the executive dysfunction seen in early AD and MCI is that AD can be characterized as a disconnection syndrome. This is evidenced by neuronal damage in cortico-cortical connections and a loss of coherence in brain activity between anterior and posterior regions and between hemispheres (for reviews, see De Lacoste & White, 1993; Delbeuck, Van der Linden, & Collette, 2003). Therefore, the executive dysfunction seen in AD and MCI may be due to multiple neuropathological and metabolic changes in anterior and posterior regions. It is argued that this loss of anatomical and functional connectivity can explain deficits in cognitive areas that rely on distributed networks connecting different regions, such as executive functions (Delbeuck et al., 2003; Morris, 2004; Morris, 1996). Some groups are beginning to investigate cortical connectivity and its relation to cognitive functioning in MCI (e.g., van der Hiele et al., 2006), but more work is needed in this area.

In sum, we demonstrated that impairment in executive functioning is common in MCI across multiple domains of executive functioning. Significant group differences were found between MCI patients and normal controls on all of the executive tests administered in this study. Furthermore, clinically significant impairments were observed in each of the four domains of executive functioning (working memory, inhibitory

control, verbal fluency, and planning), and greater than 75% of MCI patients were impaired in each of the domains. These results indicate that, in addition to impairments in episodic memory, executive impairment is an important aspect of MCI. As such, tests of executive functioning, and particularly tests of inhibitory control, should be used in any neuropsychological test battery used to detect MCI. This will help with early and accurate diagnosis, improve case management, and potentially contribute to the identification of those with a particularly high risk of developing dementia.

Executive Functions in Frontotemporal Dementia and Lewy Body Dementia

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Abstract

Diagnosis of different types of dementia is often based on clinical symptomatology rather than underlying pathology, therefore accurate diagnosis depends on a thorough description of cognitive functioning in different dementias. Furthermore, direct comparison of cognitive functions between different types of dementia is necessary for differential diagnosis. Executive dysfunction is common in several types of dementia, including frontotemporal dementia (FTD) and Lewy body dementia (LBD), however FTD and LBD patients have never been directly compared on measures of executive functioning. The present study compared the performance of 24 FTD and 15 LBD patients on 6 measures of executive functioning in terms of statistical group differences, mean severity of clinical impairment in comparison to normal controls, and frequency of impairment. Results indicated a remarkably similar pattern of performance across all areas examined in terms of mean performance, as well as degree and frequency of impairment. Only the Stroop test produced results that could potentially differentiate patient groups. These findings suggest that both FTD and LBD should be considered to be disorders involving prominent executive dysfunction.

Keywords: dementia, frontotemporal dementia, Lewy body dementia, executive functioning, Brown-Peterson task, Letter-Number Sequencing, Stroop, Hayling test, verbal fluency, Tower of London, working memory, inhibitory control, planning

Executive Functions in Frontotemporal Dementia and Lewy Body Dementia

Dementia is a progressive neurodegenerative syndrome that becomes increasingly prevalent as one ages. It encompasses deficits in a wide variety of areas, including memory, speech and language, visuospatial abilities, executive functioning, personality, and behaviour. Dementia increases in prevalence with age, doubling approximately every five years, and ranging from 2% to 3% in individuals aged 65 to 74 to over 30% in individuals aged 85 and over. Alzheimer's disease (AD) is the most common and most studied form of dementia, accounting for approximately two thirds of all dementias (Hendrie, 1998). However, there are several other types of dementia that are less well-studied, including vascular dementia, frontotemporal dementia (FTD), and Lewy body dementia (LBD). One area of cognitive functioning that is commonly impaired in many dementias is executive functions (Knopman et al., 2003). However, executive deficits in multiple types of dementia are rarely studied together with the same measures, which makes it difficult to determine whether executive dysfunction is more severe or more prevalent in certain types of dementia in comparison to others. Thus, the aim of this study was to examine executive functioning deficits in two forms of dementia where this type of dysfunction is prominent, namely FTD and LBD.

FTD and LBD have distinctive underlying pathologies; however, diagnosis is based on clinical symptomatology rather than underlying pathology. Therefore, it is important to clearly differentiate the symptoms and cognitive deficits that present in these different forms of dementia. A thorough categorization of the executive deficits seen in FTD and LBD may contribute to an earlier and more accurate diagnosis, which could enable the implementation of preventative therapies and aid in the clinical management

of the disorders. To this end, the present study addressed executive functioning in FTD and LBD across four domains: working memory, inhibitory control, fluency, and planning. In addition, the degree and frequency of impairment in each domain was examined.

Executive Functioning

Executive functioning is a multidimensional construct that has been conceptualized as a high-level control over lower level cognitive functioning and higher-order cognitive capacities that subserve independent, goal-directed behaviour (Perry & Hodges, 1999; Royall et al., 2002; Stuss & Levine, 2002). Executive control is particularly important in novel situations in which automated, routine behaviours are inadequate and in which the individual must plan and carry out a sequence of actions while monitoring progress towards a goal and adjusting behaviour as necessary. Various subcomponents have been suggested to belong to the construct of executive functioning, including planning, initiation, organization, self-monitoring, cognitive flexibility, set shifting, inhibitory control, generative behaviour or fluency, abstraction, working memory, and divided attention (Alvarez & Emory, 2006; Royall et al., 2002; Spreen & Strauss, 1998; Stuss & Levine, 2002). Many of the components that have been suggested can be measured by tests that can be considered to tap into four overarching domains that are frequently cited in the literature: working memory, inhibitory control, verbal fluency, and planning. Many of the tests that cover these domains also tap into other subcomponents of executive functioning, as discussed below. As these four domains succinctly cover many aspects of executive functioning, we have chosen to focus on them in this study.

Working memory has been defined as the short-term maintenance and storage of task-relevant information while performing a cognitive task (Miyake & Shah, 1999). It has been argued that the manipulation of information held on-line, particularly when interference is present, represents the executive component of working memory (D'Esposito et al., 2000; Stuss & Levine, 2002). Thus, cognitive tasks that assess working memory typically require participants to continually maintain and update information held in mind. The Brown-Peterson task (BPT; Spreen & Strauss, 1998) and the Letter-Number Sequencing (LNS) subtest of the Wechsler Adult Intelligence Scale—III (WAIS-III; Wechsler, 1997) were the measures of working memory used in this study. These two tasks assess both manipulation and interference in working memory and are therefore particularly sensitive to the executive component of working memory (Stuss & Levine, 2002). Furthermore, both working memory tasks involve cognitive flexibility and set shifting in the form of switching between letters and numbers in the LNS and switching between the working memory task and interference task in the BPT.

Inhibitory control refers to the ability to suppress behaviour that is irrelevant to or impedes the task at hand, and is necessary in order to overcome prepotent, automated behaviours in novel situations (Shallice & Burgess, 1993). Inhibitory control is often tested by requiring participants to give a response other than the one that is most salient. The Hayling test (Bugess & Shallice, 1997) and the Victoria version of the Stroop test (Spreen & Strauss, 1998), which were used as measures of inhibitory control in this study, are examples of measures of inhibitory control.

The essence of verbal fluency is the ability to generate verbal material quickly and efficiently. Tests that measure fluency require individuals to produce material within

certain constraints during a specified time limit. These tasks require executive control for initiation (generation of words), organization of verbal retrieval, self-monitoring (tracking responses already given), and inhibition of responses that do not fit within the constraints (Henry & Crawford, 2004). Verbal fluency is often measured by requiring the patient to generate a list of words that begin with a specified letter (phonemic fluency) or that belong to certain semantic categories (e.g., animals; semantic fluency). Phonemic fluency has been generally accepted as a measure of executive function because generating words based on orthographic criteria is an unfamiliar task requiring novel search strategies. However, semantic fluency likely relies on well-established semantic knowledge, and therefore likely reflects semantic memory in addition to some aspects of executive functioning (Henry & Crawford, 2004; Stuss et al., 1998). Furthermore, clustering (production of words within subcategories) and switching (shifting between clusters) can be examined for both phonemic and semantic fluency. Switching has been argued to be more related to executive functioning than clustering, as the number of switches is more important than mean cluster size for optimal performance on phonemic fluency, whereas clustering and switching are equally important for performing well on semantic fluency (Troyer et al., 1997).

Planning a series of actions necessary to achieve a certain goal is a central aspect of executive functioning (Owen, 1997; Spreen & Strauss, 1998), and requires the ability to initiate and organize behaviour in time and space, monitor progress towards the goal, and adjust behaviour as necessary. Developing a plan of action is necessary when multiple steps must be coordinated to reach a goal (Owen, 1997). The measure of planning used in this study was the Tower of London (TOL; Shallice, 1982), in which

participants must move balls on pegs of varying heights in order to match a model configuration, within certain constraints. In this task, it is necessary to plan and execute the series of moves that is required to achieve the goal of matching the model.

Neural substrates of executive functions. Executive functions have been linked to the frontal lobes, and in particular, to dorsolateral prefrontal cortex (DLPFC). The prefrontal cortex is uniquely positioned to integrate information from multiple brain regions, as it is connected to more brain areas than any other cortical region and is a major target for both limbic and basal ganglia-thalamocortical circuits (Fuster, 2002; Royall et al., 2002). Therefore, the prefrontal cortex has been proposed to be primarily involved in unifying executive control over lower level functions (Gazzaley & D'Esposito, 2007). Lesion and functional imaging studies have linked the DLPFC to many aspects of executive functioning, including verbal fluency, working memory, attention (including attentional switching, selective attention, and sustained attention, inhibitory control, set-shifting, and planning (for reviews, see Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). However, several studies have found that some individuals with lesions to the frontal lobes perform within the normal range on tests of executive function and some patients with non-frontal lesions perform poorly on those tests (see Alvarez & Emory, 2006 for a review). The exact nature of the relationship between executive functioning and the frontal lobes is still under debate, but it is clear that some relationship exists. Some researchers have suggested that the control of executive functions is not localized exclusively within the frontal lobes, but rather within the system of circuits connected to the prefrontal cortex (Royall et al., 2002). As the prefrontal cortex and/or the networks connected to the prefrontal cortex are affected in

FTD and LBD (Grossman, 2002; Simard et al., 2000), executive dysfunction would be expected in both of these types of dementia.

Executive Function in Frontotemporal Dementia

FTD is a broad term that encompasses disorders such to as Pick's disease, frontal dementia, frontal lobe degeneration of the non-Alzheimer type, primary progressive aphasia, and semantic dementia (Chertkow et al., 2001). It is characterized by a decline in cognition, with disproportionate abnormalities in executive functioning, behavioural regulation, and expressive language. Patients often exhibit impairment in memory in daily activities similar to that seen in AD; however, it has been suggested that deficits related to executive functioning, such as inattention, inability to focus on one task, and easy distractibility may account for this impairment (Attix & Welsh-Bohmer, 2006; Heilman & Valenstein, 2003). Behavioural dysregulation often has a dramatic presentation, with patients demonstrating changes in personality, comportment, judgment, and social awareness. In addition, individuals with FTD may also demonstrate extrapyramidal features such as rigidity, gait instability, and other secondary signs of Parkinson's disease (PD; Attix & Welsh-Bohmer, 2006). Language difficulties are also common characteristics of FTD, in particular, progressive non-fluent aphasia (agrammatic speech), and semantic deficits (difficulty processing single words for meaning; Grossman, 2002). The average age of onset of FTD is approximately 10 years earlier than that of AD, with a mean age of onset of about 62 years and a range from as low as 21 years to as high as 80 years. In addition, FTD represents approximately 12% of all dementias that occur before the age of 65, and the risk of developing this form of dementia does not seem to increase with age (Grossman, 2002).

It has been suggested that there are three distinctive histopathological conditions underlying FTD. All three conditions are characterized by atrophy of the frontal and temporal lobes as well as neuronal loss and microvacuolation. The most common condition is *frontal lobe dementia of the non-Alzheimer's type*, alternatively called *dementia lacking distinctive histopathology*. This condition is so-named because of the lack of intracytoplasmic inclusions or swollen cells seen in other conditions underlying FTD. The other two underlying conditions of FTD are Pick's disease with both Pick bodies (agyrophilic inclusions) and Pick cells (swollen cells), and Pick's disease with swollen cells only. The former is classic Pick's disease, and the latter is also called *corticobasal degeneration*. The majority of the pathology of FTD is located in the neocortex of the frontal lobes and the anterior temporal lobes, however, lesions in subcortical regions such as the thalamus, neostriatum, or white matter pathways linking prefrontal and anterior temporal regions may be present (Grossman, 2002; Heilman & Valenstein, 2003).

Given the prominent frontal lobe pathology present in FTD, executive dysfunction would be expected in this disorder. Indeed, deficits in multiple domains of executive functioning have been reported in FTD (for a review, see Elderkin-Thompson et al., 2004). For example, deficits in working memory have been found on digit span backwards tasks (Kramer et al., 2003), although certain studies have found no impairment on digits backwards (Hodges et al., 1999; Perry & Hodges, 2000) and spatial working memory tasks (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999). Inhibitory control has been found to be impaired in FTD using the Stroop test and Elevator Counting with Distraction (Pachana, Boone, Miller, Cummings, & Berman,

1996; Perry & Hodges, 2000). Deficits in both phonemic and semantic fluency have also been reported (Hodges et al., 1999; Pachana et al., 1996; Pasquier, Lebert, Grymonprez, & Petit, 1995), and planning deficits have been found using the TOL in both moderate (Carlin et al., 2000) and mild (Rahman et al., 1999) FTD. In addition, impairments have been reported in set shifting and decision-making (Perry & Hodges, 2000; Rahman et al., 1999).

Executive Function in Lewy Body Dementia

LBD is a form of dementia characterized by parkinsonian motor disturbances, disturbances in arousal and sleep, and fluctuating cognitive symptoms. It is the second most common form of dementia after AD (Chertkow et al., 2001; Simard et al., 2000). The extrapyramidal features seen in LBD are similar to those seen in FTD, but are typically more severe (Heilman & Valenstein, 2003). The most common cognitive symptoms include deficits in executive functioning, visuospatial abilities, and attention, but the most prominent symptom is anterograde amnesia similar to that seen in AD (Knopman et al., 2003). Similar to FTD, it has been suggested that underlying deficits in attention or executive dysfunction are responsible for cognitive deficits seen in other areas, such as memory and speech (Attix & Welsh-Bohmer, 2006; Knopman et al., 2003).

As suggested by the name, the major neuropathological feature of LBD is Lewy body inclusions, which are abnormal protein aggregates present in the neurons of the limbic system and neocortical regions. In addition, pathology seen in AD (neurofibrillary tangles and amyloid plaques), microvacuolation, loss of synapses, and dysfunction of the dopamine system (as seen in Parkinson's disease) are also common (Heilman & Valenstein, 2003; Knopman et al., 2003; Simard et al., 2000). The brain areas most often

affected in LBD include the anterior frontal and temporal cortices, cingulate area, insula, substantia nigra, nucleus basalis of Meynert, locus ceruleus, nucleus raphe dorsalis, and amygdala (Simard et al., 2000).

The Lewy body pathology occurring in the frontal lobes and disruption of circuits linking the frontal cortex with subcortical structures both make it likely that executive dysfunction will be present in LBD (Dubois, Pillon, & McKeith, 2007). While fewer studies have examined executive functioning in LBD, as with FTD, studies have shown that patients with LBD are impaired in several domains of executive functioning (for a review, see Simard et al., 2000). For example, deficits have been reported for LBD patients on working memory tasks such as digit span (Crowell, Luis, Cox, & Mullan, 2007) and digits backwards (Calderon et al., 2001). In one study, LBD patients were impaired on tests of inhibitory control such as the Stroop test (which some patients were unable to complete) and Elevator Counting with Distraction (Calderon et al., 2001), as well as on an experimental task requiring set shifting and response inhibition (Bradshaw, Saling, Anderson, Hopwood, & Brodtmann, 2006). Deficits in both phonemic and semantic fluency have also been reported, as well as impairments in cognitive flexibility and set shifting, as measured by trail-making and the Wisconsin Card Sorting test (Calderon et al., 2001; Crowell et al., 2007; Ferman et al., 2006). To date, no studies have examined planning abilities in patients with LBD. Given that many of the deficits reported in certain domains of executive functioning have not been replicated in other studies, the executive dysfunction in LBD is not as well established as it is in FTD.

FTD vs. LBD

The deficits in memory and executive function seen in FTD and LBD overlap considerably with each other and with those found in AD (Attix & Welsh-Bohmer, 2006; Heilman & Valenstein, 2003). There is some evidence that executive functions are more impaired in FTD than AD (for a review, see Harciarek & Jodzio, 2005), with this being found for a composite measure of executive functioning (Walker, Meares, Sachdev, & Brodaty, 2005), working memory (digits backwards - Kramer et al., 2003; dual task - Perry & Hodges, 2000), inhibitory control (Stroop - Pachana et al., 1996; Elevator Counting with Distraction - Perry & Hodges, 2000), phonemic fluency (Hodges et al., 1999; Lindau, Almkvist, Johansson, & Wahlund, 1998; Pachana et al., 1996), and cognitive flexibility (WCST - Perry & Hodges, 2000). However, several studies have found no differences between AD and FTD on executive measures, such as working memory (digits backwards - Perry & Hodges, 2000), inhibitory control (Stroop - Pachana et al., 1996; Perry & Hodges, 2000), phonemic and semantic fluency (Diehl & Kurz, 2002; Hodges et al., 1999; Kramer et al., 2003; Nedjam, Devouche, & Dalla Barba, 2004; Pasquier et al., 1995; Perry & Hodges, 2000), and cognitive flexibility (trail making - Kramer et al., 2003; card sorting - Nedjam et al., 2004).

A recent literature review has concluded that the most consistent difference between the cognitive profiles of LBD and AD is a greater deficit in spatial working memory in LBD (Simard et al., 2000), however some studies have shown that patients with LBD perform worse than AD patients on other measures of executive functioning, including other types of working memory (digits backwards - Calderon et al., 2001; digit span - Crowell et al., 2007), inhibitory control (experimental response inhibition task -

Bradshaw et al., 2006; Stroop errors - Guidi, Paciaroni, Paolini, De Padova, & Scarpino, 2006), phonemic fluency (Calderon et al., 2001; Crowell, Luis, Cox, & Mullan, 2006; Ferman et al., 2006; Galasko, Katzman, Salmon, & Hansen, 1996), and set-shifting (Trails B - Crowell et al., 2007; Ferman et al., 2006; Kraybill et al., 2005; Salmon et al., 1996; WCST - Preobrazhenskaya, Mkhitaryan, & Yakhno, 2006). In addition, a recent meta-analysis combined various measures of executive functioning using effect sizes and found that LBD patients were more impaired on executive functioning than both controls and AD patients (Collerton, Burn, McKeith, & O'Brien, 2003). However, as with FTD, several other studies have found no differences between LBD and AD on measures of executive functioning, such as working memory (digit span and digits backwards - Gnanalingham, Byrne, & Thornton, 1997; Johnson, Morris, & Galvin, 2005; Salmon et al., 1996), inhibitory control (Elevator Counting with Distraction - Calderon et al., 2001), phonemic and semantic fluency (Crowell et al., 2007; Galasko et al., 1996; Gnanalingham et al., 1997; Guidi et al., 2006; Noe et al., 2004; Salmon et al., 1996), and cognitive flexibility (card sorting - Gnanalingham et al., 1997).

Both FTD and LBD patients have prominent executive dysfunction, which is consistent with the neuropathologies underlying the two syndromes. FTD and LBD may present with similar types of cognitive deficits, such as executive dysfunction, and there may be similarities in other areas as well, such as motor disturbance (Chertkow et al., 2001). When individually compared to AD on measures of executive functioning, both FTD and LBD patients have been found to be equally or more severely impaired than AD patients. However, FTD and LBD patients have never been directly compared on

measures of executive functioning, therefore it is very important to characterize the executive dysfunction in these two groups using the same tests.

It is currently unknown whether there is a difference in the severity or frequency of executive dysfunction in FTD and LBD. In addition, there may be differences between the two groups in the relative degree of impairment in one domain of executive functioning in comparison to other domains. Differentiating the two groups based on performance on tests of executive function could aid in earlier and more accurate diagnosis. Therefore, we compared executive functioning in FTD and LBD patients in several different ways. First, we conducted an analysis to determine whether there were statistical differences between the two groups. We then compared clinical impairment on each of the different measures by computing standardized scores of each of the groups using data collected from normal elderly controls and comparing the groups on the average degree of impairment as well as the frequency of impairment. Examining both statistical differences and differences in clinical impairment is important, as statistical comparisons can only provide information regarding reliable differences between the groups, not whether those differences are clinically significant. Given that both FTD and LBD patients performed worse than AD patients on measures of executive function, we predicted that both groups would be impaired on each of the tests of executive functioning administered in this study. However, as FTD is more typically thought of as a disorder involving prominent executive dysfunction, we predicted that FTD patients would perform more poorly than LBD patients across the different measures.

Method

Participants

FTD and LBD are far more rare than AD, and it is often difficult to accumulate a large enough sample to study. Therefore, the Consortium on Cognition and Aging (CCA) of the Quebec Research Network on Aging pooled resources from memory clinics and academic centres across the province of Quebec by developing a registry of patients with some of the more rare forms of dementia. The CCA chose to include FTD and LBD patients in the registry, and common diagnostic tools and protocols for clinical, neuropsychological, and brain imaging testing were developed for the assessment of these patients. Twenty-four FTD patients and 15 LBD patients were recruited who met the inclusion criteria for this study. In addition, 27 normal elderly controls (NECs) were recruited to serve as a control group for the calculation of clinical impairment. Patients were initially seen by one of the participating physicians as part of their normal clinical work. Informed consent was obtained from all the participants or their family members as appropriate, and ethical approval for the study was obtained from all institutions involved. NECs were recruited from the same community as the patients through posters advertising the study and visits to senior centres and residences.

During the initial examination with the physicians, patients completed a mental status assessment and a physical evaluation to confirm the diagnosis of FTD or LBD. FTD was diagnosed according to the consensus criteria by Neary and colleagues (2005), and LBD was diagnosed according to the consensus criteria by McKeith and colleagues (2004). Participants in the control group were excluded if they scored below the cutoff on the Mini Mental State Examination (MMSE; Folstein et al., 1975). In order to qualify for

the study, patients had to be free of serious health problems and possible systemic causes of their illness. Patients were also excluded if there was evidence of another brain diseases or a chronic psychiatric disorder (other than mild depression), such as cerebrovascular disease, head trauma, cerebral infection, metabolic dysfunction, thyroid dysfunction, B_{12} / folic acid, epilepsy, psychosis, schizophrenia, intoxication, or alcohol abuse. For FTD and LBD patients, this information was obtained through the physical examination, and for controls, through a self-report questionnaire.

FTD, LBD, and NEC groups were compared in terms of age, education, gender distribution, and, as Quebec is a bilingual province and participants were tested in their primary language (either French or English), the groups were also compared on language distribution. There were significant group differences in age, $F(2, 63) = 5.87$, $p = .005$, with FTD patients being younger than both LBD patients and NECs, $p < .05$, which is consistent with the general finding that FTD typically has an earlier age of onset (Grossman, 2002). As age was not significantly correlated with any of the variables in this study, it was not included as a covariate in any group comparisons. The groups also differed in education, $F(2, 63) = 4.15$, $p = .020$, with LBD patients having fewer years of education than NECs. In terms of gender distribution, FTD and LBD patients were comparable, $\chi^2(1, N = 39) = .028$, $p = .866$, and NECs had a smaller proportion of males than both the FTD and LBD groups, $\chi^2(1, N = 42) = 7.46$, $p = .006$; $\chi^2(1, N = 51) = 8.63$, $p = .003$, respectively. In addition, the three groups were comparable in language distribution, $\chi^2(2, N = 66) = .918$, $p = .632$ (see Table 3 for means and proportions).

FTD and LBD patients were also compared on a number of clinical measures, as summarized in Table 4. The two groups did not have a significantly different level of

overall cognitive impairment, as measured by the MMSE, and did not report significantly different levels of subjective memory impairment, as measured by the Subjective Memory Complaints Scale (SMCS; Schmand et al., 1996). LBD patients did have a significantly lower score on the Barthel Index (BI; Mahoney & Barthel, 1965), a measure of functional independence in basic activities of daily living (e.g., feeding, bathing, and grooming), which is expected, given the nature of physical impairment in LBD. There were no group differences on the Functional Activities Questionnaire (FAQ; Pfeffer et al., 1982), a measure of higher-level activities of daily living (e.g., paying bills, shopping, and cooking). Both FTD and LBD patients were impaired on this measure. Finally, there were no differences on the Geriatric Depression Scale (GDS; Yesavage et al., 1982), a measure of recent depressive symptoms, on which scores were indicative of mild depression in both FTD and LBD.

Materials and Procedure

The two patient groups were tested at each of the individual clinics, and control participants were tested at Concordia University and the Institut Universitaire de Gériatrie de Montréal. Common evaluation tools and standardized procedures were provided to each of the testing centres, in order to ensure a standardized method of testing. In addition, the neuropsychologists, nurses, and graduate students who completed the testing were trained on the administration of the tests, and all tests were administered according to standardized procedures. As Quebec is a bilingual province, participants were tested in their primary language (either French or English), and equivalent French and English versions of each of the tests were employed.

Six tests of executive functioning were administered as part of a longer battery of neuropsychological tests administered in standardized order, which included tests of learning and memory, language, visual-spatial function, attention, and motor praxis. The six measures of executive functioning were: the BPT, the LNS, the Hayling test, the Stroop test (Victoria version), phonemic and semantic fluency, and the TOL.

Adapted Brown-Peterson Task. The version of the BPT used in this study was taken from the computerized Memoria Battery (Belleville, Chatelois et al., 2003; Bherer et al., 2001). Participants were presented with sets of three consonants that were randomly sampled from the alphabet, but which were not phonologically similar and did not form any known acronyms. These consonant trigrams were to be kept in mind for delay periods of 0, 10, 20, or 30 seconds, during which an arithmetic interference task was performed (adding one to a series of randomly generated numbers presented orally). The delay periods were randomly ordered, and an auditory cue signaled the end of the delay and the commencement of recall. During the recall phase, participants were required to write down the letters they could remember from the consonant trigram in the order in which they were presented. There were three practice trials and 12 test trials (3 trials of each of the 4 delay periods). The number of correct letters recalled for each delay period was recorded.

Letter-Number Sequencing. The LNS is a subtest of the WAIS—III (Wechsler, 1997), in which a sequence of intermixed digits and letters is presented orally to the participant, and the participant must recall the digits first in ascending order followed by the letters in alphabetical order. The test consists of seven blocks of increasing length,

with three trials per block. One point is awarded for every correct trial, and the total number of correct trials was recorded.

Hayling test. The Hayling test is a measure of inhibitory control with two separate sections, each containing 15 sentences with the last word missing. In each section, the examiner reads the sentences aloud, and the participant is required to complete the sentence as quickly as possible. In Section 1, the participant must give a response that sensibly completes the section, and in Section 2, the participant must give a response that is unconnected to the sentence in every way. In other words, the participant must inhibit the automated response that sensibly completes the sentence and generate an alternative response. For example, in the sentence "Most cats see very well at _____" the participant must suppress the response "night" and generate an unrelated response, such as "banana". The response latencies for both sections were recorded, as well as the number of connected errors (words that sensibly complete the sentence, e.g., "night"), and somewhat connected errors (words that are related to the sentence in some way, e.g., "dog") for Section 2. An inhibition time score was calculated in order to control for differences in response initiation time by subtracting the mean response latency of Section 1 from the mean response latency of Section 2. In addition, a weighted error score was calculated by assigning 3 points to connected errors and 1 point to somewhat connected errors, as per the protocol outlined by Belleville and colleagues (2006). Finally, an overall scaled score was calculated according to the procedure outlined in Burgess and Shallice (1997). The English version of this test was published by Burgess and Shallice (1997), and the French version was published by Belleville and colleagues (2006).

Stroop Victoria. The Victoria version of the Stroop test (Spreen & Strauss, 1998) consists of three parts, in which stimuli in blue, red, green, and yellow ink are presented in 6 rows of 4 items. The first section consists of 24 coloured dots, and the second section consists of common words (and, when, hard, over) printed in coloured ink. In the third part, colour names are printed in each of the different colours except the colour that corresponds with the word (i.e., the word 'blue' is never printed in blue ink). In each section, participants are required to name the colour of the ink and to disregard any verbal content. Thus, in the colour condition, the participant must inhibit the prepotent response of reading the colour word, and instead name the colour of the ink in which the word is printed. The time to complete each section and the number of errors for each section were recorded. Interference scores were calculated by subtracting the dot condition from the colour condition for both time and errors, in order to control for colour naming speed.

Verbal fluency. Participants completed both a phonemic fluency task and a semantic fluency task (Spreen & Strauss, 1998). In the phonemic task, participants must generate as many words as possible that begin with a certain letter within certain parameters. English-speaking participants were given the letters *F, A,* and *S,* with 60 seconds to generate words, and French-speaking participants were given the letters *P, L,* and *T,* with 90 seconds to generate words, according to standardized administration procedures. For semantic fluency, participants were asked to generate as many words as possible from a given category (animals). The total numbers of correct words generated for both phonemic and semantic fluency were recorded. In addition, both phonemic and semantic fluency were scored for clustering and switching, as per the procedure outlined by Troyer, Moscovitch, and Wincour (1997). Clusters are groups of words produced

consecutively that belong to the same phonemic or semantic subcategory. For phonemic fluency, clusters are defined as groups of words that begin with the same two letters (e.g., *aim, air*), differ only by a vowel sound (e.g., *sale, sole*), rhyme (e.g., *fair, flair*), or are homonyms (e.g., *son, sun*). For semantic fluency, clusters are defined as a group of words that are part of the same semantic subcategory, such as farm animals, pets, African animals, and various zoological categories (for complete scoring rules, refer to the Appendix of Troyer et al., 1997). A switch is defined as a transition between clusters and is a measure of the ability to shift between categories. The total number of switches and the mean cluster size were recorded.

Tower of London. The version of the TOL used in this study was an abridged version (Shallice, 1982), in which there are two boards, each with three pegs of progressive lengths. Each board has a red, yellow, and blue ball arranged on the pegs in a certain way. One ball fits on the shortest peg, two balls on the medium peg, and three balls on the longest peg. The balls on the examiner's board are arranged in a model configuration, and the balls on the participant's board are arranged in a starting configuration. The participant must move the balls on his or her board to match the model configuration in as few moves as possible, moving only one ball at a time, and never placing the ball anywhere except on another peg. There are 12 trials, 3 of which require a minimum of 3 moves to complete, and 9 of which require a minimum of 5 moves to complete. Of the 5-move trials, 6 contain a trigger, which is an instance where one of the balls can be moved directly into its final position from the first move. Three of those trials contain a positive trigger, where moving the ball directly into its final position helps

with the resolution of the problem, and the other 3 trials contain a negative trigger, where moving the ball directly into its final position hinders the resolution of the problem.

Results

Group Comparison

Performance on the tests of executive functioning was compared between FTD and LBD patients to determine if the two patient groups could be differentiated on the basis of these tests. Each neuropsychological measure was treated as a separate family of comparisons, and Bonferroni corrections were used for multiple comparisons within the same neuropsychological measure and for follow-up comparisons where appropriate. Not all patients completed all of the tasks, and missing data were primarily due to difficulties performing the task, or discontinuation due to fatigue. The number of patients that completed each task is indicated below. Mean scores for FTD and LBD groups on each of the measures are presented in Table 5.

Working memory. Fourteen FTD patients and 12 LBD patients completed the BPT, which was analyzed using a mixed analysis of variance (ANOVA) with group (FTD, LBD) as the between-subjects factor, and delay (0 s, 10 s, 20 s, 30 s) as the within-subjects factor. There was no main effect of Group, $F(1, 24) = 2.30$, $p = .142$, and no Group × Delay interaction, $F(3, 72) = .796$, $p = .500$. There was a significant main effect of Delay, $F(3, 72) = 37.35$, $p < .001$, $\eta^2 = .609$, where both groups demonstrated a substantial drop in the number of letters recalled in the 10 second, 20 second, and 30 second delay conditions relative to the 0 second delay condition, $p < .001$, but there were no differences in the number of letters recalled between the 10 second, 20 second, or 30 second delay periods. Twenty-three FTD patients and 15 LBD patients completed the

LNS, which was analyzed using a univariate ANOVA. There was no difference in performance on this task, $F(1, 36) = .108, p = .745$.

Inhibitory control. Twenty-one FTD patients and 14 LBD patients completed the Stroop test. This test was analyzed with a multivariate ANOVA, which revealed a group difference approaching significance, $\lambda(2, 32) = .831, p = .052$. Follow-up comparisons revealed that this effect was driven by a difference approaching significance in the number of errors, $F(1, 33) = 3.90, p = .057, \eta^2 = .106$, with LBD patients making more errors than FTD patients. It is likely that the group difference in number of errors on the Stroop represents a true effect, but that we lacked sufficient power to obtain a significant result, due to the small sample size. There was no difference in inhibition time on the Stroop, $F(1, 33) = 2.76, p = .106$. Fifteen FTD patients and 13 LBD patients completed the Hayling test, which was analyzed with a multivariate ANOVA. There was no significant group difference on this measure, $\lambda(2, 24) = .903, p = .473$.

Verbal fluency. Twenty-three FTD patients and 13 LBD patients completed the verbal fluency tasks. Phonemic and semantic fluency were analyzed together using a multivariate ANOVA. Results indicated no significant group differences on these measures, $\lambda(2, 33) = .959, p = .500$. Furthermore, clustering and switching for phonemic and semantic fluency were analyzed together using a multivariate ANOVA, and no group differences were observed, $\lambda(4, 29) = .856, p = .323$.

Planning. This task was very difficult for both the FTD and the LBD patients, and many patients were unable to complete the task. Eventually, the task was dropped from the testing protocol. However, the fact that both groups demonstrated difficulty with this task clearly indicates that there is an impairment in planning in both FTD and LBD. Only

5 FTD patients and 4 LBD patients completed the TOL. The resulting sample size is too small to include in any analyses, therefore, these results cannot quantify whether or not FTD and LBD patients differ in their planning abilities. However, it is instructive to note that the majority of patients in both groups were unable to do the task.

Profile of Executive Functioning

Comparisons of group means are useful for determining whether reliable differences exist between groups, but they do not provide information as to whether these differences are large enough to be detectable in clinical practice. Therefore, we calculated standardized scores for each of the FTD and LBD patients based on the means and standard deviations of the control group. As can be seen in Figure 5, mean standardized scores for FTD and LBD patients revealed that both groups were clinically impaired on all of the tasks of executive functioning in comparison to the normal controls, with impairment defined as greater than 1.5 standard deviations below the mean. Furthermore, FTD and LBD patients exhibited a similar profile of executive functioning, with both groups performing comparatively worse on the tests of inhibitory control (Stroop and Hayling tests), than the verbal fluency tasks and the working memory tasks (BPT and LNS). Both FTD and LBD patients exhibited severe impairment on the Stroop and the Hayling test, with a relatively greater impairment on errors on the Hayling test. The only tests on which FTD and LBD patients were substantially different in terms of degree of impairment were the Stroop test and the Hayling test. On the Stroop, LBD patients performed 2.78 standard deviations below FTD patients on inhibition time, and 2.99 standard deviations below FTD patients on number of errors. On the Hayling test, LBD

patients performed 1.86 standard deviations below FTD patients on inhibition time, and 1.44 standard deviations below FTD patients on errors score.

Frequency of Impairment

A complimentary way to look at differences in executive function in FTD and LBD is to determine if impairment on any of the measures is more frequent in one of the groups. Therefore, we determined how many patients in each group were impaired on each of the measures, and then calculated the percentage of patients impaired in each group. As can be seen in Figure 6, impairment was highly prevalent, with more than 70% of patients being impaired on each of the tests of executive functioning in both FTD and LBD groups. Furthermore, where differences existed between groups, impairment was more frequent in the LBD group, with a difference of 29% on the BPT and 24% on the Stroop. Very similar frequencies of impairment were found for the LNS, the Hayling test, and verbal fluency. However, due to the fact that several FTD patients did not complete the BPT and the Hayling test, frequencies were computed again assuming that patients who did not complete the task were impaired. In comparison to the previous calculation, the only difference that was greater than 3 percentage points was for the BPT for FTD patients, which yielded a frequency of impairment of 83.3%. This is a difference of 11.9 percentage points in comparison to the first analysis. LBD patients were still more frequently impaired on the BPT, with 100% of patients in this group being impaired.

Discussion

This was the first study to directly compare FTD and LBD patients on measures of executive functioning. We examined both statistical group differences and differences in clinical impairment. In terms of clinical impairment, we compared both the average

degree of impairment and the frequency of impairment. Overall, we found that the two groups performed remarkably similarly across the different measures employed, which is interesting and somewhat surprising, given that FTD is more typically considered to be a disorder with prominent executive dysfunction. In comparison to normal controls, both groups were clinically impaired on all of the measures of executive functioning administered. Furthermore, the analysis of individual performance in comparison to normal controls on each of the tests of executive functioning revealed that executive dysfunction was highly prevalent in both FTD and LBD, with over 70% of patients were impaired on each of the tests. Where differences between patient groups in frequency of impairment existed (BPT and Stroop), impairment was more prevalent in LBD patients. This does not appear to be due to fewer FTD patients completing some of the tasks, as LBD patients were still more frequently impaired when patients who did not complete the task were counted as impaired in the analysis.

The mean standardized scores calculated in comparison to the normal controls revealed that the two groups had a similar pattern of impairment across the tests of executive functioning. Both FTD and LBD patients were more severely impaired on the measures of inhibitory control than on tests of working memory or verbal fluency, with a particularly severe impairment on errors on the Hayling test. It is very striking that both groups showed severe deficits on the Hayling test (Figure 5), and that all patients showed this deficit (Figure 6). For both the Stroop and the Hayling test, impairment was greatest for error scores. This may be due to the fact that errors on these tests are uncommon in normal controls (Bielak et al., 2006; Spreen & Strauss, 1998), making error scores particularly sensitive to detecting deficits. Consistent with a higher prevalence of

impairment on some of the executive functioning tests in LBD patients, where differences existed in the mean severity of impairment, it was the LBD group that was more impaired. LBD patients were consistently more severely impaired across the different measures, but the differences were only substantial for the Stroop test and the Haying test. The greater severity of impairment on the Stroop in LBD patients is consistent with the higher prevalence of impairment on this test in LBD patients.

Statistical comparisons of mean performance on each of the tests also revealed that FTD and LBD patients performed very similarly overall. However, consistent with the higher prevalence and severity of impairment in LBD patients, the mean scores of the LBD group were consistently poorer than those of the FTD group across the different measures. Furthermore, once again, the Stroop test was the only measure that revealed potential group differences, with error scores on this test approaching significance. Considering that the differences on the Stroop test emerged in the frequency analysis, the mean standardized scores, and the statistical analysis, it is likely that this is a true effect but that we lacked sufficient power to obtain a statistically significant result. Previous studies have found deficits on the Stroop in both LBD (Calderon et al., 2001) and FTD (Pachana et al., 1996), with both groups performing more poorly than AD patients (Guidi et al., 2006; Pachana et al., 1996)

The consistently poorer performance of LBD patients in all of the different types of analyses conducted is contrary to what would be expected, given that FTD is more typically considered to be a disorder involving disproportionate deficits in executive control. This suggests that LBD should be reconceptualized as a disorder with executive deficits that are as severe (if not more so) than those seen in FTD. However, it is

important to consider the number of FTD patients who were not able to complete some of the tasks. The behavioural disturbance that is common in FTD patients is known to cause difficulty assessing these patients and to lead to a high proportion of missing data (Smeding & de Koning, 2000). The resulting data may be an overestimation of the abilities of FTD patients, as they include only those patients who were able to complete the task. The two tasks that a disproportionate number of FTD patients failed to complete were the BPT and the Hayling test. The performance of the two groups on the BPT was very similar; however, only 58% of the FTD patients completed this task, whereas 80% of the LBD patients completed the task. This suggests a bimodal distribution, in which FTD patients are either able to complete the task and perform similarly to LBD patients (though both are impaired relative to controls), or they are so impaired that they cannot complete the task. However, 96% of FTD patients and 100% of LBD patients were able to complete the other task of working memory, the LNS, and there were no group differences on this test. Therefore, the BPT may be more sensitive than the LNS in detecting differences between FTD and LBD patients, but it is too difficult for many FTD patients to complete when deficits exist. Thus, another version of the BPT, perhaps with a simpler interference task, may be useful in differentiating FTD from LBD.

There were also substantially fewer FTD patients than LBD patients who completed the Hayling test (63% and 87%, respectively). Analysis of the data from those who did complete the Hayling test revealed no significant differences between the patient groups. As with the working memory tasks, the proportion of patients completing the other test of inhibitory control was more similar, with 83% of FTD patients and 93% of LBD patients having completed the Stroop test, and no differences between groups on

that test. However, the Stroop test was the only test on which there was a difference approaching significance, with LBD patients making more errors than FTD patients. Therefore, there is some evidence that, despite greater difficulties in completing the Hayling test in FTD patients, LBD patients may have a greater deficit in inhibitory control. This was confirmed by examining differences between standardized scores, which revealed that the Stroop test was the only test for which there was a difference of more than two standard deviations between the patient groups.

A widespread impairment on tasks of executive functioning in both LBD and FTD is consistent with what has previously been reported in the literature (e.g., Elderkin-Thompson et al., 2004; Simard et al., 2000). However, this is the first study to directly compare FTD and LBD patients, allowing us to determine whether these two patient groups can be distinguished on the basis of different measures of executive functioning. The results of this study suggest that executive functioning in FTD and LBD is very similar in terms of mean scores, relative degree of deficit as assessed by standardized scores, and frequency of impairment, with the Stroop test being the only measure with the potential to differentiate the two groups. Thus, while executive dysfunction has more typically been considered to be characteristic of FTD, the results of this study suggest that LBD should also be considered to be a disorder strongly characterized by executive dysfunction. Indeed, these two types of dementia cannot be differentiated on the basis of tests of executive functioning alone (with the possible exception of the Stroop test), though LBD patients actually performed consistently more poorly than FTD patients on the measures used in this study. Therefore, more studies are needed comparing FTD and

LBD patients in different cognitive domains in order to help with the differential diagnosis of these two dementias.

General Discussion

The two studies presented here were designed to evaluate executive functioning in three different patient groups: two groups with dementia (FTD and LBD), and one group at risk of developing dementia (MCI). When taken together, the results of the two studies suggest that tests of executive functioning may be useful for aiding in the early identification of those at risk of developing dementia (MCI), but not in differentiating FTD and LBD. Specifically, MCI patients differed significantly from controls on all of the measures of executive functioning administered, exhibited clinically significant deficits in all four executive domains tested, and more than 75% were impaired in each of the domains. In contrast, FTD and LBD patients did not differ on any of the measures administered, and had a similar profile of severity and prevalence of impairment across the different tests. However, an interesting trend emerged across the two studies. In both cases, when the profile of the degree of impairment on the different tests was examined, it was evident that the greatest deficit was on measures of inhibitory control. In the case of MCI patients, there was a strikingly severe impairment on the Hayling test in comparison to the other tests administered. FTD and LBD patients were also most impaired on the Hayling test, but the other test of inhibitory control, the Stroop, was also quite profoundly impaired, particularly in LBD patients. This suggests that the ability to inhibit prepotent responses is an area that is particularly affected in both preclinical dementia (MCI) and later in the progression of the syndrome (i.e., in FTD and LBD).

It is unclear why inhibitory control should be more greatly affected than other measures of executive functioning. With regards to the neural correlates of the different domains of executive functioning, all four domains examined in this study have been

associated with the DLPFC; however, inhibitory control appears to involve some additional areas of the frontal cortex, including the superior medial gyrus, ventrolateral prefrontal cortex, right frontopolar regions, and the anterior cingulate cortex (Bench et al., 1993; Floden & Stuss, 2006; Liddle et al., 2001; Menon et al., 2001). In particular, both the Hayling test and the Stroop have been shown to activate the anterior cingulate in addition to the DLPFC (Bench et al., 1993; Collette et al., 2001; Nathaniel-James et al., 1997; Pardo et al., 1990). The neuropathologies of FTD and LBD have clearly been shown to affect the frontal lobes, both directly through pathology in the frontal lobes and indirectly through pathology affecting circuits connecting the frontal lobes to posterior brain regions (Dubois et al., 2007; Grossman, 2002). In contrast, the neuropathology of MCI has been less clearly linked to the frontal lobes, with the most consistent finding being atrophy in the medial and inferior temporal lobes (Pennanen et al., 2005; Whitwell et al., 2007). However, there is some emerging evidence that suggests that there may be a disruption of long distance corticocortical connectivity affecting the frontal lobes in MCI (Tao & Tian, 2005). Furthermore, some studies have reported atrophy in the inferior prefrontal cortex in mild AD and MCI (Duarte et al., 2006; Salat et al., 2001). Thus, there is evidence that frontal lobe functioning is affected in MCI, FTD, and LBD, but the lack of strong evidence for frontal lobe pathology in MCI is also suggestive of the fragility of executive functioning. Executive functions may depend on distributed neuronal networks (Royall et al., 2002), and therefore may be easily disrupted by damage to non-frontal brain regions. But the question remains: Is there evidence that the neuropathologies of these disorders may underlie the disproportionate deficit in inhibitory control in comparison to other domains of executive functioning?

The atrophy seen in FTD is often variable, sometimes affecting frontal areas more than temporal regions, and sometimes the other way around. Both the DLPFC and the anterior cingulate cortex have been implicated in the pathology of FTD, particularly when executive dysfunction is present (Grossman, 2002). Therefore, it is possible that the atrophy of the anterior cingulate in addition to the DLPFC contributes to the greater deficit in inhibitory control, as the anterior cingulate has been uniquely implicated in this domain of executive functioning. In LBD, pathology in the DLPFC is not typically reported, with the frontal pathology more typically involving the anterior frontal regions and the cingulate cortex (Simard et al., 2000). The pathology in the cingulate cortex in LBD may account for the greater relative impairment on measures of inhibitory control in comparison to other domains of executive functioning. In MCI, the frontal regions most often implicated are the inferior prefrontal cortex and medial frontal lobes, including the left anterior cingulate (Duarte et al., 2006; Leube et al., 2008; Pennanen et al., 2005; Whitwell et al., 2007). As in the case of LBD, the pathology present in the anterior cingulate and not the DLPFC may explain the greater deficit in inhibitory control. However, in all three of these disorders, pathways connecting the frontal lobes to posterior regions are also affected, making it difficult to say with any degree of certainty which parts of the frontal lobes are more affected by the pathologies of these disorders. For example, as the subcortical regions involved in the different frontal basal ganglia-thalamocortical circuits are located closely together, a single subcortical lesion may affect multiple more distally located regions of the prefrontal cortex, such as the DLPFC and the anterior cingulate (Royall et al., 2002). Furthermore, the extent to which anterior cingulate involvement reflects inhibitory control processes remains unclear. Some studies

have found activation of the anterior cingulate in the non-inhibition conditions of the Stroop and the Hayling test, such as the congruent colour-word condition of the Stroop (Bench et al., 1993), and Section 1 of the Hayling test (Nathaniel-James et al., 1997). Thus, at this point, it is premature to relate the disproportionate deficits in inhibitory control to neuropathology in the anterior cingulate in FTD, LBD, and MCI. Future research should be aimed at addressing the issue of the neural correlates of executive functioning in these three patient groups, and particularly in MCI, as frontal lobe dysfunction is not typical of this group. A promising area of emerging research is the examination of long distance connectivity in MCI and its relationship to executive functioning by examining coherence in brain activation between different regions (measured by electroencephalography) and its relationship to performance on tests of executive functioning (van der Hiele et al., 2006). Further research should also be aimed at elucidating the role of the anterior cingulate in inhibitory control, and the relationship between pathology in the anterior cingulate in MCI, FTD, and LBD and executive functioning.

Another possible reason for a disproportionate deficit in inhibitory control is the relative sensitivity of tests of inhibitory control in comparison to tests tapping in to other domains of executive functioning. There is some evidence that tests of inhibitory control are particularly sensitive to detecting other forms of brain pathology, such as traumatic brain injury. For example, one study found that the inhibition condition of the Stroop tests was one of only two measures that was best able to discriminate between patients with traumatic brain injury and control participants (Bate, Mathias, & Crawford, 2001). The sensitivity of the tests used to measure inhibition (Stroop and Hayling test) does not

seem to be due to a higher level of difficulty, as these tests are not particularly difficult to understand or complete, especially in comparison to some of the other tests administered in this study, such as the measures of working memory (BPT and LNS). However in normal controls, errors on the inhibition conditions of the Stroop and the Hayling tests are uncommon (Bielak et al., 2006; Spreen & Strauss, 1998), which may make these tests particularly sensitive to changes in functioning.

While it may not be clear at this point why a disproportionate deficit in inhibitory control is present in MCI, FTD, and LBD, another interesting question is what the practical implications of such a deficit are. Previous research has shown that both the Hayling test and the Stroop have moderate correlations with measures of everyday functioning such as the Dysexecutive Questionnaire, Community Integration Questionnaire, and the Brock Adaptive Functioning Questionnaire (Chaytor, Schmitter-Edgecombe, & Burr, 2006; Odhuba, van den Broek, & Johns, 2005). Furthermore, other studies have found that impairment on various measures of executive functioning, such as the Allen Cognitive Levels and the Executive Interview predicted functional impairment (for a review, see Royall et al., 2002). However, executive impairment in the present study was not consistently related to the measures of functional impairment that were employed (BI and FAQ). In MCI patients, only longer planning time on the N5 condition of the TOL was significantly correlated with poorer scores on the BI, and only fewer words on phonemic fluency was correlated with poorer scores on the FAQ. In LBD patients, a poorer score on the BI was associated with increased time to complete all three conditions of the Stroop test, more errors on the words condition of the Stroop, fewer words on semantic fluency, and fewer switches on semantic fluency. A poorer FAQ score

was associated with increased time on the dots and words conditions of the Stroop, increased time on Section 2 of the Hayling test, and fewer switches on semantic fluency. In FTD patients, the correlations were in the opposite direction than what would be expected, with lower scores on the LNS and fewer letters recalled for the BPT 10 second and 20 second delay conditions being associated with better scores on the BI and the FAQ ($p < .05$ in all cases). Thus, while the executive measures employed in this study did not produce consistent correlations with the BI and FAQ, it is possible that the executive deficits that were observed would be correlated with other measures of everyday functioning, as suggested by previous research. The results of the present study do not directly support the practical significance of executive dysfunction in everyday life, but previous studies do suggest that deficits on tests of executive functioning can translate into difficulties in daily activities such as medication compliance, housekeeping, and working (Royall et al., 2002).

Another interesting finding that emerged in the MCI study was the differences in severity of clinical impairment that emerged when impairment was calculated using our normal controls as a comparison group versus using published normative data. In general, clinically significant impairment was observed more frequently when our normal controls were used for the calculation of impairment, with an impairment greater than 1.0 standard deviations below the mean of the normal controls on the LNS, Hayling errors and scaled score, phonemic and semantic fluency, and TOL total time for N3, T+, and T- trial types. The only tests that did not produce a clinically significant deficit were the BPT and the Stroop. When impairment was calculated using published norms, the impairments on the LNS, fluency tasks, and TOL total time were no longer significant, but impairment on

TOL number of moves for N3, N5, and T- trial types reached clinical significance. The practical implication of this finding is that the use of normative data collected from participants who are from the same community as the patients being tested, and who were administered the same battery of tests, is a more accurate and sensitive means to detect clinical impairment. In addition, the use of the same sample of participants as a comparison group for each of the different tests in the battery allows for a more accurate comparison of clinically significant impairments across tests. Therefore, although it may not be practically feasible to collect "in-house" normative data at every clinic that conducts neuropsychological testing, it is clear that this is the preferred method, where possible, as important differences in results emerge when published norms are used.

One of the limitations of the present studies is the relatively small sample size of FTD and LBD patients. The small sample size for these patient groups translates into limited power to detect differences in performance between the two groups. Furthermore, the small sample size of FTD patients makes it impossible to investigate the various subtypes of FTD, such as progressive nonfluent aphasia and semantic dementia. However, both FTD and LBD are rare forms of dementia, and the final sample size arrived at in this study is the result of the joint efforts of eight memory clinics across the province of Quebec recruiting patients over a number of years. Furthermore, the sample size obtained for this study is comparable to previous studies examining these patient groups (Collerton et al., 2003; Hutchinson & Mathias, 2007). Another limitation is the inability of FTD and LBD patients to complete the TOL, and the large number of FTD patients missing data for the Hayling test and BPT. The TOL is a difficult task, even for normal controls, and it was simply too difficult for FTD and LBD patients to complete.

Future studies should examine planning abilities in FTD and LBD patients using a task that the majority of patients are able to complete, such as a maze task, perhaps. Regarding the missing data for the Hayling test and BPT in FTD patients, this is a problem that has frequently been reported, and is likely due to the behavioural dysfunction that is common in FTD (Smeding & de Koning, 2000). In order to combat this problem, more information is needed to determine which neuropsychological measures the majority of FTD patients are able to complete, and which statistical procedures should be used to produce the most accurate picture of the performance of FTD patients when missing data is present.

In terms of methodology, it would have been ideal if all of the testing were done at one location to ensure the highest degree of accuracy possible. However, several steps were taken to ensure accuracy in testing procedures, including providing training sessions and testing manuals, as well as site visits from the project coordinator to ensure that proper testing procedures were being followed. Another potential limitation is that LBD patients were recruited exclusively from memory clinics, as opposed to motor disorder clinics, which could possibly have created a selection bias in which our group of LBD patients had a higher frequency and/or severity of cognitive deficits. Furthermore, it would have been better if the control group was more closely matched to the patient groups on demographic variables (language distribution for MCI patients, age and gender distribution for FTD patients, and education and gender distribution for LBD patients), in order to allow for a more accurate calculation of clinical significance. Finally, it would also have been ideal to conduct a follow-up with MCI patients after a number of years to

determine if performance on any of the tests of executive functioning could predict conversion to dementia.

The present studies also have several strengths. One major strength of both studies is the systematic examination of multiple tests of executive functioning covering several different domains. This is important in any study of executive functions, as executive functioning is not a unitary construct, but rather represents multiple cognitive functions that are grouped together under one umbrella term. Thus any study of executive functioning that does not examine multiple domains is incomplete, and unfortunately, this is all too common. By examining several different domains in the present study, we were able to compare performance across the different domains both within and between groups and to determine a pattern of impairment for each of the patient groups examined, enabling us to determine which domains are more or less severely affected in each of the groups. Another strength of both studies is the inclusion of both a statistical and clinical analysis of the data. The statistical analysis provided information about the presence of reliable differences between the groups, and the clinical analysis provided information about the severity and frequency of impairments in the different groups using methodology that is used in clinical practice. The inclusion of the clinical analysis provides invaluable information about the neuropsychological test performance of these groups in clinical practice.

The examination of executive functioning in MCI is important, as it contributes to our understanding of the cognitive profile of individuals who are at a high risk of developing dementia, and provides information that is useful for early and accurate diagnosis. Furthermore, the direct comparison of executive functioning in FTD and LBD

is an important strength, as this study was the first to directly compare the two groups in this area of cognitive functioning. The direct comparison of different patient groups is essential to advancing our understanding of the different disorders and is important for potentially aiding in differential diagnosis.

The findings of the two studies presented herein have several important implications. First of all, the high frequency of impairment on the neuropsychological tests of executive functioning administered in this study in MCI, FTD, and LBD patients suggests that these tests are likely to be useful in the early diagnosis of those at risk of developing dementia as well as in the diagnosis of individuals who already have dementia. Tests of inhibitory control and particularly the Hayling test may be most useful in this regard, given the particularly high frequency and severity of impairment on this test in all three patient groups. In addition, as these tests appear to be sensitive to detecting changes in cognitive functioning, they may be useful in monitoring the progression of the disease and the effectiveness of treatment interventions. Furthermore, previous studies have shown that impairment in an additional non-memory domain is indicative of a greater likelihood of developing dementia in MCI patients (Bozoki et al., 2001). Therefore, the Hayling test may also be useful in establishing impairment in a non-memory domain, thereby helping to improve prognostic accuracy. However, the tests of executive functioning did not differentiate FTD from LBD (with the possible exception of the Stroop test), therefore future studies should compare FTD and LBD on other tests and in other cognitive domains to help with differential diagnosis. The similar profile and prevalence of executive impairment in FTD and LBD is interesting, though, as FTD has more typically been considered to be a disorder involving disproportionate

deficits in executive functioning. The results of the second study indicate that LBD should be reconceptualized as a disorder involving substantial executive deficits that are equal to, or even more severe than, those seen in FTD.

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Table 1

Demographic and Clinical Variables in Mild Cognitive Impairment and Normal Controls

	MCI		NEC				
Variable	*M*	*SD*	*M*	*SD*	$F(\chi^2)$	df	*p*
Age	72.4	8.6	71.8	5.0	.15	1, 69	.703
Education	13.1	3.1	14.4	3.2	3.15	1, 70	.080
Sex[a]	45.0	-	40.6	-	(.139)	1, $N = 72$	.709
Language[b]	87.5	-	62.5	-	(6.16)	1, $N = 72$	.013*
MMSE	28.1	1.4	28.9	1.1	8.23	1, 69	.005**
GDS	5.8	3.5	2.4	2.8	19.54	1, 68	< .001**
SMCS	7.4	2.7	4.4	2.5	21.89	1, 69	< .001**

Note. MCI = mild cognitive impairment; NEC = normal elderly controls; MMSE = Mini-mental State Examination; GDS = Geriatric Depression Scale; SMCS = Subjective Memory Complaints Scale. [a]Sex is given as percent male. [b]Language is given as percent French.

*$p < .05$. ** $p < .01$.

Table 2

Performance of MCI Patients and Normal Elderly Controls on Tests of Executive Function

	MCI		NEC			
Variable	*M*	*SD*	*M*	*SD*	Sig	η^2
Brown-Peterson Task (No. Correct Letters)[a]	6.26	.23	7.49	.24	*	.17
0 s Delay	8.51	.77	8.66	.75		
10 s Delay	6.22	2.36	7.44	1.61	*	.08
20 s Delay	4.62	2.62	6.44	2.29	*	.12
30 s Delay	5.68	2.29	7.44	1.81	*	.16
Letter-Number Sequencing						
Total Score	8.22	2.39	10.81	2.49	*	.23
Stroop Test						
Interference Time Ratio (sec)	2.53	1.01	2.25	0.72		
Interference Errors	1.84	2.32	0.59	1.29	*	.10
Hayling Test						
Inhibition Time Ratio (sec)	5.53	5.12	5.34	2.25		
Errors Score	19.19	7.69	3.13	2.17	*	.58
Overall Scaled Score	2.78	1.44	5.63	0.98	*	.48
Phonemic Fluency						
Total Words	35.06	12.91	46.56	11.24	*	.11
Mean Cluster Size	1.34	.39	1.76	.62	*	.13
Number of Switches	23.89	9.33	28.81	8.48	*	.07

Semantic Fluency						
Total Words	13.31	3.06	18.13	3.83	*	.26
Mean Cluster Size	2.38	1.47	2.30	.72		
Number of Switches	5.42	1.76	6.65	2.15	*	.09
Tower of London						
Total Time (sec)[a]	34.00	1.94	23.30	1.94	*	.20
3 Move Trials	16.57	11.60	10.86	3.31		
5 Move Trials, +ve Trigger	33.29	20.02	21.42	8.76		
5 Move Trials, No Trigger	38.45	20.36	29.73	17.24		
5 Move Trials, -ve Trigger	47.71	24.57	31.20	11.90		
Planning Time (sec)[a]	6.88	.68	5.60	.68		
3 Move Trials	6.03	4.48	4.58	1.79		
5 Move Trials, +ve Trigger	6.78	4.59	5.47	3.57		
5 Move Trials, No Trigger	8.00	7.12	6.70	4.43		
5 Move Trials, -ve Trigger	6.71	4.33	5.65	4.56		
Number of Moves[a]	7.19	.28	6.30	.28		
3 Move Trials	3.35	.61	3.13	.49		
5 Move Trials, +ve Trigger	7.52	2.87	6.18	1.68		
5 Move Trials, No Trigger	8.45	3.75	7.68	2.94		
5 Move Trials, -ve Trigger	9.45	4.03	8.22	1.92		

Note. MCI = mild cognitive impairment; NEC = normal elderly controls. [a]Results are reported as mean (SE).

* $p < .05$

Table 3

Participant Demographics: Frontotemporal Dementia (FTD), Lewy Body Dementia (LBD), and Controls (NEC)

	FTD		LBD		NEC		Group Differences
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	($p < .05$)
Age	67.6	8.3	73.3	5.7	73.4	5.1	FTD < LBD, Controls
Education	11.5	3.8	10.1	3.8	13.0	2.3	LBD < Controls
Sex[a]	70.8	--	73.3	--	29.6	--	Controls < FTD, LBD
Language[b]	79.2	--	86.7	--	74.1	--	n.s.

Note. [a]Sex is given as percent male. [b]Language is given as percent French.

Table 4

Clinical Characteristics in Frontotemporal Dementia (FTD) and Lewy Body Dementia (LBD)

	FTD		LBD				
Variable	*M*	*SD*	*M*	*SD*	df	*F*	*p*
MMSE	24.22	4.40	23.83	4.59	1, 33	.058	.811
SMCS	6.00	4.67	7.07	4.03	1, 35	.519	.476
BI	97.87	9.43	85.27	2.21	1, 36	6.29	.011*
FAQ	15.78	8.96	17.80	10.14	1, 36	.415	.523
GDS	5.37	4.51	8.07	6.81	1, 32	1.92	.175

Note. MMSE = Mini-mental State Examination; SMCS = Subjective Memory Complaints Scale; BI = Barthel Index; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale.

*$p < .05$.

Table 5

Performance of Frontotemporal Dementia (FTD) and Lewy Body Dementia (LBD) Patients on Tests of Executive Functioning

	FTD		LBD	
Variable	*M*	*SD*	*M*	*SD*
Brown-Peterson Task (No. Correct Letters)[a]	4.41	.59	3.08	.64
0 s Delay	7.36	2.76	6.42	2.54
10 s Delay	3.43	3.06	2.50	2.47
20 s Delay	3.21	3.19	2.00	1.71
30 s Delay	3.64	2.95	1.42	2.31
Letter-Number Sequencing				
Total Score	4.17	3.71	3.80	2.93
Stroop Test				
Interference Time (sec)	33.00	36.97	62.71	68.75
Interference Errors	6.52	6.62	10.79	5.65
Hayling Test				
Inhibition Time (sec)	82.37	85.48	127.02	168.43
Errors Score	26.67	11.47	30.46	7.64
Overall Scaled Score	1.53	.92	1.15	.56
Phonemic Fluency				
Total Words	20.70	17.09	14.62	8.43
Mean Cluster Size	1.29	.60	1.02	.67
Number of Switches	14.57	13.97	10.31	6.05

Semantic Fluency				
Total Words	8.43	4.53	7.54	3.89
Mean Cluster Size	1.61	.98	2.21	1.51
Number of Switches	3.90	2.30	2.62	1.80

Note. [a]Results are reported as mean (SE).

Figure Captions

Figure 1. Performance on the Brown-Peterson Task across delay conditions in mild cognitive impairment (MCI) and normal elderly controls (NEC).

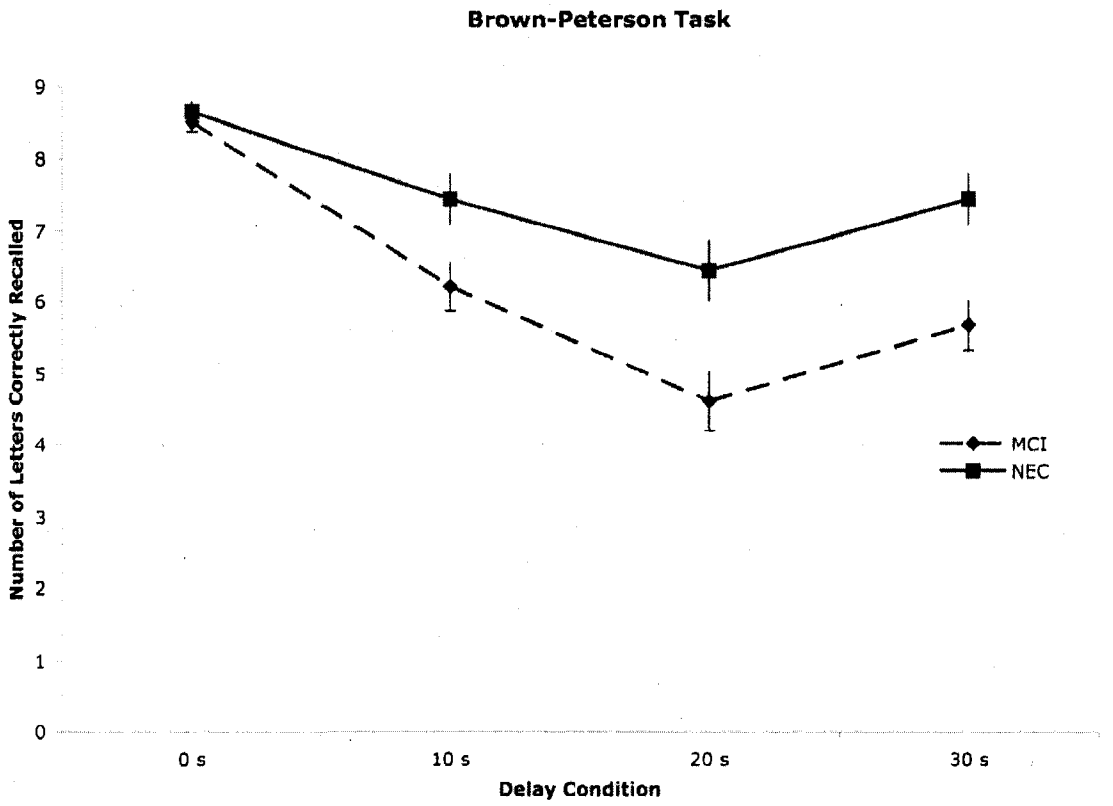
Figure 2. Average degree of impairment across tests of executive functioning in mild cognitive impairment in comparison to our sample of normal elderly controls. Tot = total score; LNS = Letter-Number Sequencing; Err = errors scaled score; ScSc = Overall Scaled Score; Ph = phonemic; Sem = semantic; N3 = 3-move trial; T+ = 5-move trial, positive trigger; N5 = 5-move trial, no trigger; T- = 5-move trial, negative trigger.

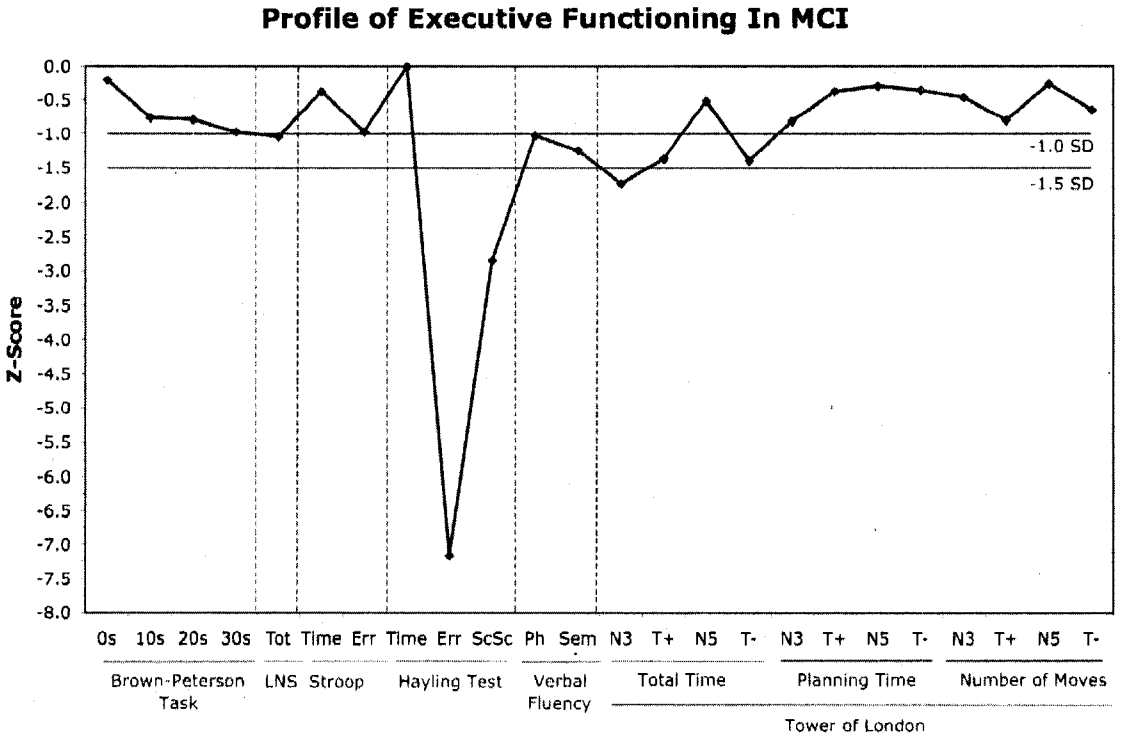
Figure 3. Average degree of impairment across tests of executive functioning in mild cognitive impairment in comparison to normal elderly controls and published norms. Tot = total score; LNS = Letter-Number Sequencing; Err = errors scaled score; ScSc = Overall Scaled Score; Ph = phonemic; Sem = semantic; N3 = 3-move trial; T+ = 5-move trial, positive trigger; N5 = 5-move trial, no trigger; T- = 5-move trial, negative trigger.

Figure 4. Frequency of executive impairment in mild cognitive impairment, (A) on each test of executive functioning, and (B) in each domain of executive functioning. BPT = Brown-Peterson Task; LNS = Letter-Number Sequencing; TOL = Tower of London.

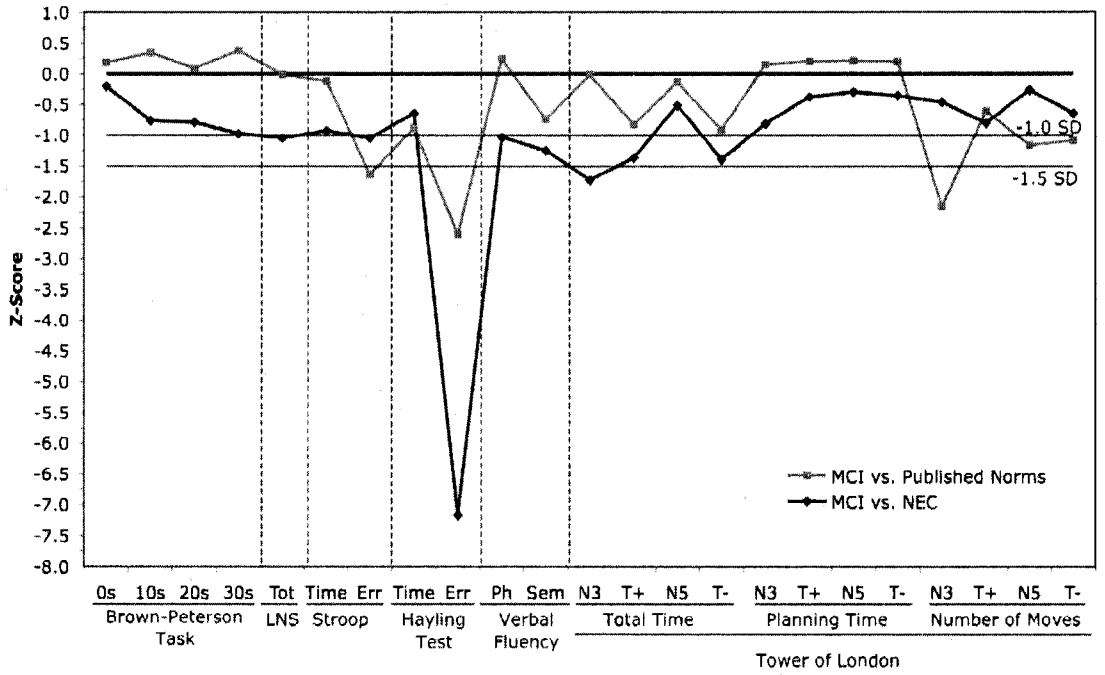
Figure 5. Average degree of impairment expressed as standardized scores across tests of executive functioning in frontotemporal dementia (FTD) and Lewy body dementia (LBD) in comparison to normal elderly controls. Sc Score = Overall Scaled Score; Phon = phonemic; Sem = semantic.

Figure 6. Frequency of executive impairment in frontotemporal dementia (FTD) and Lewy body dementia (LBD) on each test of executive functioning. BPT = Brown-Peterson Task; LNS = Letter-Number Sequencing.

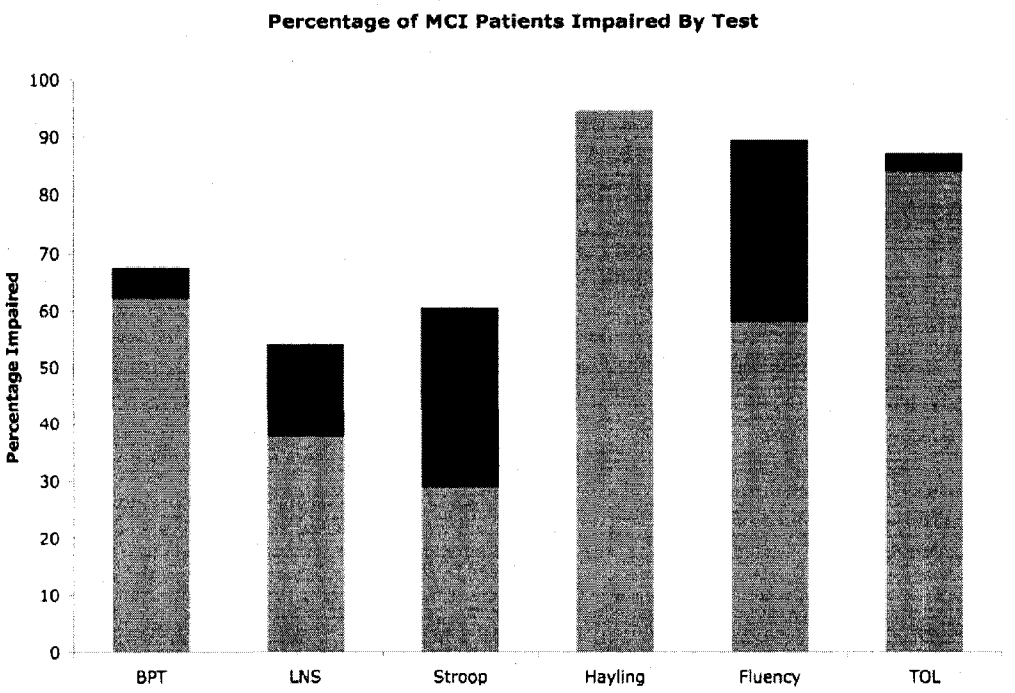

Brown-Peterson Task
Number of Letters Correctly Recalled
9
8
7
6
5
4
3
2
1
0
0 s
10 s
20 s
30 s
Delay Condition
MCI
NEC


Profile of Executive Functioning In MCI
Z-Score
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
-8.0
-1.0 SD
-1.5 SD
0s 10s 20s 30s Tot Time Err Time Err ScSc Ph Sem N3 T+ N5 T- N3 T+ N5 T- N3 T+ N5 T-
Brown-Peterson Task
LNS
Stroop
Hayling Test
Verbal Fluency
Total Time
Planning Time
Number of Moves
Tower of London

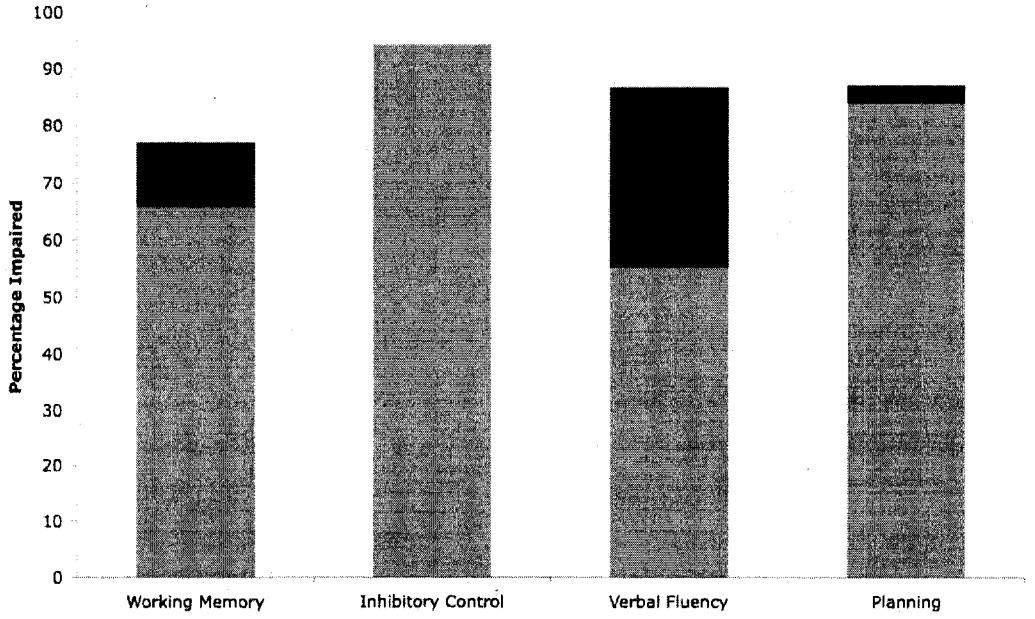
Profile of Executive Function - Normative Data Versus Normal Elderly Controls



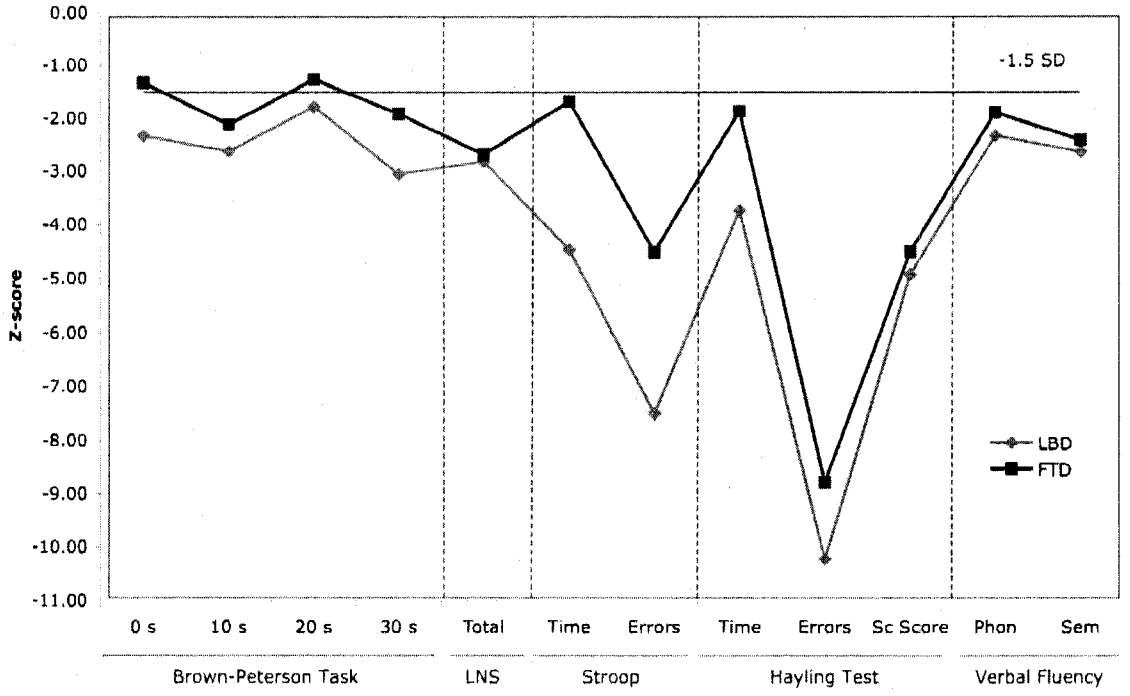
A)


Percentage of MCI Patients Impaired By Test
Percentage Impaired
100
90
80
70
60
50
40
30
20
10
0
BPT
LNS
Stroop
Hayling
Fluency
TOL

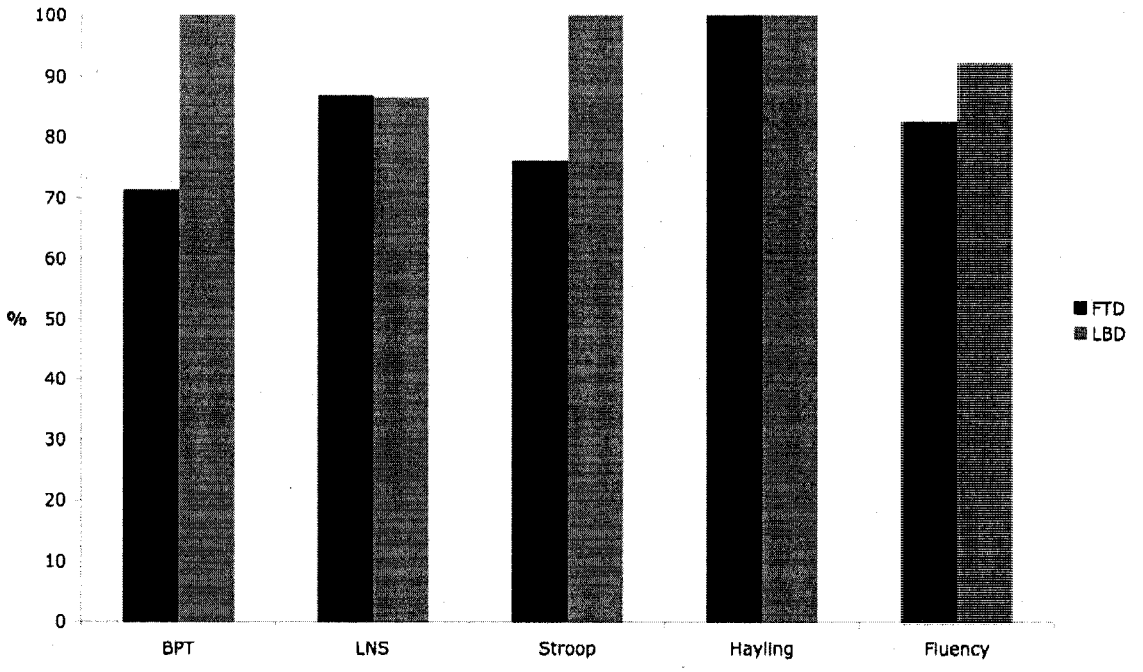
B)


Percentage of MCI Patients Impaired By Domain
Percentage Impaired
100
90
80
70
60
50
40
30
20
10
0
Working Memory
Inhibitory Control
Verbal Fluency
Planning

Profile of Executive Functioning in FTD and LBD



Percentage of FTD and LBD Patients Impaired on Tests of Executive Functioning



Appendix A

Diagnostic Criteria

Mild Cognitive Impairment

1. Mild Impairment (Check all of A)

- ☐ Decline from a previous normal level of function
- ☐ Complaints from subject or family
- ☐ Demonstrable abnormality on mental status testing
- ☐ Impairment is not sufficient to meet clinical criteria for dementia

2. Domain of impairment (may be more than one)

- ☐ Short term memory
- ☐ Long term memory
- ☐ Picture naming / object identification
- ☐ Personality
- ☐ Judgment/ executive function
- ☐ Visuo-spatial processing / construction
- ☐ Praxis
- ☐ Other, specify: _____

Frontotemporal Dementia

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental function of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

1. Core diagnostic features

- ☐ Insidious onset and gradual progression

- ☐ Early decline in social interpersonal conduct
- ☐ Early impairment in regulation of personal conduct
- ☐ Early emotional blunting
- ☐ Early loss of insight

2. Supportive diagnostic features

A. Behavioural disorder

- ☐ Decline in personal hygiene and grooming
- ☐ Mental rigidity and inflexibility
- ☐ Distractibility and impersistence
- ☐ Hyperorality and dietary changes
- ☐ Perseverative and stereotyped behaviour
- ☐ Utilization behaviour

B. Speech and language

- ☐ Altered speech output
    - o Aspontaneity and economic speech
    - o Press of Speech
- ☐ Stereotypy of speech
- ☐ Ecolalia
- ☐ Perseveration
- ☐ Mutism

C. Physical signs

- ☐ Primitive reflexes
- ☐ Incontinence

- ☐ Akinesia, rigidity, and tremor
- ☐ Low and labile blood pressure

D. Investigations

- ☐ Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
- ☐ Electroencephalography: normal on conventional EEG despite clinically evident dementia
- ☐ Brain imaging (structural or functional): predominant frontal and/or anterior temporal abnormality

Lewy Body Dementia

1. The central feature required for a diagnosis of LBD is

- ☐ progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.

2. Two of the following core features are essential for a diagnosis of probable LBD, and one is essential for possible LBD:

- ☐ Fluctuating cognition with pronounced variations in attention and alertness
- ☐ Recurrent visual hallucinations that are typically will formed and detailed
- ☐ Spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are:

- ☐ Repeated falls

- ☐ Syncope
- ☐ Transient loss of consciousness
- ☐ Neuroleptic sensitivity
- ☐ Systematized delusions
- ☐ Hallucinations in other modalities

4. A diagnosis of LBD is less likely in the presence of

- ☐ Stroke disease, evident as focal neurologic signs or on brain imaging
- ☐ Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for clinical picture

Appendix B

Participating Investigators

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Ska, Bernadette, Centre de Recherche, Institut Universitaire de Gériatrie de Montréal/ Université de Montréal

Database:

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Imaging:

Kabani, Noor, Dept. of Experimental Medicine Jewish General Hospital/ McGill University

Appendix C

Clinics

1. Jewish General Hospital (Memory Clinic)
2. Institut Universitaire de Gériatrie de Sherbrooke (Memory Clinic)
3. Centre Hospitalier de l'Université de Montréal (Geriatric Department, Memory Clinic)
4. Clinique Neuro Rive Sud (Neurology Clinic)
5. Hospital Enfant Jesus Quebec (Memory Clinic)
6. McGill Center for Aging (Memory Clinic)
7. Institut Universitaire de Gériatrie de Montréal (Cognition Clinic)
8. Hôpital Maisonneuve-Rosemont (Neurology Department)

Appendix D

Order of Testing

First Assessment:	time
- Reaction Time Simple & Choice X 2	10'
- Selective Reminding Test	10'
- Visual Reproduction subtest of WMS-III	10'
- Letter-Number Sequencing subtest of WMS-III	5'
- Stroop Test (Victoria version)	5'
- Tower of London	20'
- Delayed Recall & Copy of Visual Reproduction	10'
- Block Design subtest of WAIS-III	10'
- Digit Symbol (Coding) subtest of WAIS-III	10'
- Delayed Recall of Selective Reminding Test	5'
- Boston Naming Test	5'
- Birmingham Object Recognition Battery: Orientation Match Task, Position of Gap Match Task, Object Decision Task	10'
TOTAL:	110 MIN
Second Assessment:	
- Reaction Time Simple & Choice X 2	10'
- False Recognition Test	15'
- Brown-Peterson Task	15'
- Bell's Test	5'
- Semantic Knowledge	10'

- Gestural Praxis 5'
- Dictation of Croisile 10'
- Hayling Test 10'
- Verbal fluency [4 categories: Animals, tools, clothing, vegetables; 3 letters: PLT (French), FAS (English)] 20'

TOTAL: 100 MIN.