Université de Montréal

Working memory in Alzheimer's disease and mild cognitive impairment (MCI): assessment and intervention

par

Lyssa Gagnon

Département de psychologie

Faculté des Arts et Sciences

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Cette thèse intitulée:

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Présentée par :

Lyssa Gagnon

a été évaluée par un jury composé des personnes suivantes :

Sven Joubert, président-rapporteur
Sylvie Belleville, directeur de recherche
Maryse Lassonde, membre du jury
Nicole Anderson, examinateur externe
Aude Dufresne, représentant du doyen de la FES

RÉSUMÉ

L’objectif principal de cette thèse est d’examiner et d’intervenir auprès des déficits de la mémoire de travail (MdeT) à l’intérieur de deux populations cliniques : la maladie d’Alzheimer (MA) et le trouble cognitif léger (TCL). La thèse se compose de trois articles empiriques. Le but de la première expérimentation était d’examiner les déficits de MdeT dans le vieillissement normal, le TCL et la MA à l’aide de deux versions de l’empan complexe : l’empan de phrases et l’empan arithmétique. De plus, l’effet de «l’oubli» (*forgetting*) a été mesuré en manipulant la longueur de l’intervalle de rétention. Les résultats aux tâches d’empan complexe indiquent que la MdeT est déficitaire chez les individus atteints de TCL et encore plus chez les gens ayant la MA. Les données recueillies supportent également le rôle de l’oubli à l’intérieur de la MdeT. L’augmentation de l’intervalle de rétention exacerbait le déficit dans la MA et permettait de prédire un pronostic négatif dans le TCL. L’objectif de la deuxième étude était d’examiner la faisabilité d’un programme d’entraînement cognitif à l’ordinateur pour la composante de contrôle attentionnel à l’intérieur de la MdeT. Cette étude a été réalisée auprès de personnes âgées saines et de personnes âgées avec TCL. Les données de cette expérimentation ont révélé des effets positifs de l’entraînement pour les deux groupes de personnes. Toutefois, l’absence d’un groupe contrôle a limité l’interprétation des résultats. Sur la base de ces données, la troisième expérimentation visait à implémenter une étude randomisée à double-insu avec groupe contrôle d’un entraînement du contrôle attentionnel chez des personnes TCL avec atteinte exécutive. Ce protocole impliquait un paradigme de double-tâche composé d’une tâche de détection visuelle et d’une tâche de jugement alpha-arithmétique. Alors que le groupe contrôle pratiquait simplement la double-tâche sur six périodes d’une heure chacune, le groupe expérimental recevait un entraînement de type priorité variable dans lequel les participants devaient gérer leur contrôle attentionnel en variant la proportion de ressources attentionnelles allouée à chaque tâche. Les résultats montrent un effet significatif de l’intervention sur une des deux tâches impliquées (précision à la tâche de détection visuelle) ainsi qu’une tendance au transfert à une autre tâche d’attention divisée, mais peu d’effets de généralisation à d’autres tâches d’attention. En résumé, les données originales rapportées dans la présente thèse démontrent un déficit de la MdeT dans les maladies neurodégénératives liées à l’âge, avec un gradient entre le TCL et la MA. Elles suggèrent également une préservation de la plasticité des capacités attentionnelles chez les personnes à risque de développer une démence.

Mots-clés: mémoire de travail, trouble cognitif léger, maladie d’Alzheimer, évaluation, intervention, empan complexe, entraînement cognitif, contrôle attentionnel

ABSTRACT

The principal aim of this dissertation is to investigate and intervene upon working memory (WM) impairments in two clinical populations: Alzheimer's disease (AD) and mild cognitive impairment (MCI). The dissertation is comprised of three empirical articles. The goal of the first study was to examine WM impairments in normal aging, MCI and AD using two versions of the complex span task: sentence span and operation span. In addition, the effect of forgetting was assessed by manipulating the length of the retention interval. Results indicate impaired WM on complex spans in MCI and, to a greater extent, in AD. Data also support a role for forgetting within WM. Increasing the retention interval augmented deficit in persons with AD, and showed potential in predicting a negative prognosis in those with MCI. The objective of the second article was to investigate the feasibility of a computerized cognitive training paradigm for the attentional control component of WM in healthy older individuals and those with MCI. Data from this experiment revealed positive effects of the intervention for both groups. However, the absence of a control group limited interpretation of results. Based on those data, the third article aimed to implement a double-blind randomized controlled study of training of attentional control in MCI with executive deficits. This involved a dual-task paradigm comprised of a visual detection task and a visual alpha-arithmetic judgment task. While the control group performed simple dual-task practice over six one-hour sessions, the experimental group received variable-priority training, in which participants managed their attentional control by varying the proportion of attentional resources allocated to each task. Results show a significant effect of intervention on one of the two tasks involved (accuracy on the visual detection task) and a trend for transfer to another task of divided attention, but little generalization to other tasks of attention. In summary, the original data reported in this thesis demonstrates WM impairment in age-related disorders, with a gradient between MCI and AD, and suggest preserved plasticity of attentional capacities in persons at risk of developing dementia.

Keywords: working memory, Mild Cognitive Impairment, Alzheimer's disease, assessment, intervention, complex span, cognitive training, attentional control

TABLE OF CONTENTS

LIST OF TABLES

List of Figures

List of abbreviations

AD: Alzheimer’s disease

ANOVA : analysis of variance

ApoE: Apolipoprotein E

APT: Attention Process Training

BP: Brown-Peterson

DAQ: Divided Attention Questionnaire

DSM-IV: Diagnostic and Statistical Manual

fMRI: functional magnetic resonance imaging

FP: fixed priority

GDS: Geriatric Depression Scale

MCI: mild cognitive impairment

MDRS: Mattis Dementia Rating Scale

MMSE: Mini-Mental State Examination

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association

PET: positron emission tomography

PI: proactive interference

PL: proportional loss

RL/RI-16: Rappel Libre/Rappel Indicé à 16 Items

RT: reaction time

SMAF: Functional Autonomy Measurement System

TEA: Test of Everyday Attention

VP: variable priority

WM: working memory

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Ask not what disease the person has, but rather what person the disease has.

attributed to Canadian physician William Osler (1849-1919)

preface of "An Anthropologist on Mars" by neurologist and author Oliver Sacks

CHAPTER 1: GENERAL INTRODUCTION

CONTEXT

The upcoming half century will witness dramatic population aging, which means a larger proportion of the population will be found in the elderly age groups. In fact, current estimates predict that the global fraction of the elderly population (aged 65 years or more) will more than double, rising from 7% in 2000 to 16% by 2050 (Cohen, 2003). Given that age is the biggest risk factor for dementia, it has been said that neurocognitive frailty is the biggest threat to successful aging in our society (Park & Reuter-Lorenz, 2009). Alzheimer's disease (AD), a degenerative disease with devastating repercussions on cognition, is the most common aetiology for dementia. In 2000, there were 4.5 million persons suffering from AD in the United States alone. By 2050, this number will increase by almost 3-fold, to 13.2 million individuals (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). In Canada, the economic burden of Alzheimer's disease and related dementias is projected to increase ten-fold, reaching 153 billion dollars in the year 2038, which makes the disease a substantial priority in terms of prevention and treatment research ("Rising Tide: The Impact of Dementia on Canadian Society," 2009).

An important setback that plagues treatment attempts is the early identification of AD. For this purpose, research has focused on characterizing the prodromal stage of the disease, in the hope that earlier identification of the disease will lead to earlier and more effective treatments and interventions. The term coined for this state is Mild Cognitive Impairment, or MCI. In general terms, persons with MCI (Petersen, 1999; Petersen et al., 2003) have a cognitive impairment but fail to meet criteria for dementia, yet they are at high risk of developing dementia, particularly AD, in the subsequent years. The principal aim of this dissertation is to investigate and intervene upon cognitive deficits of persons with MCI, in order to better characterize their profile and attempt to minimize their impairment. This thesis focuses on executive-type impairments, such as working memory and attentional control. The dissertation is comprised of three empirical articles. The objective of the first article is to examine working memory impairment in MCI and compare it to that of normal aging and AD using two versions of the complex span task. The goal of the second study is to investigate the feasibility of a computerized cognitive training paradigm for the attentional control component of WM in individuals with MCI. Based on those preliminary results, the third article aims to implement a double-blind randomized controlled study of training of attentional control in MCI with executive deficits.

The introduction section that follows will describe current research in assessment and intervention of working memory in AD and MCI, in order to put into context the subsequent three empirical articles composing this body of work. We will first present the clinical underpinnings of Alzheimer's disease and mild cognitive impairment as well as provide an overview of associated neuropsychological profiles. The second part will examine the theoretical concepts behind working memory, models of WM, tasks used to measure WM, and brain regions thought to be involved. Next, we will review specific impairments of WM and attentional control in normal ageing, AD and MCI. The third subsection of this introduction will address cognitive training of attentional control, both in healthy and clinical populations. The final part will present the objectives and hypotheses of the three empirical articles composing this dissertation.

1.1 Alzheimer's disease and mild cognitive impairment

1.1.1 Clinical description

Alzheimer's disease (AD) is the most common neurodegenerative disease in older adults (Kukull et al., 2002). Post-mortem examination of patients reveals a pathology including cortical atrophy, extracellular beta amyloid accumulation and intra-neuronal neurofibrillary tangles. The disease is thought to begin in the transentorhinal & entorhinal cortices, and to progress to the hippocampi before invading virtually all association areas (Braak & Braak, 1991). There is also mounting pathologic evidence that a significant portion of cases currently diagnosed as AD are actually of mixed aetiology and could include vascular pathology (infarcts and ischemic white matter lesions) and/or Lewy bodies (Gauthier & Poirier, 2008).

For over 15 years, the 1984 NINCDS–ADRDA research criteria for probable Alzheimer's disease (McKhann et al., 1984) along with the DSM-IV clinical criteria for dementia (APA, 1994) have been the gold standard for the diagnosis of dementia of the Alzheimer type in clinical research protocols. Recently, the National Institute on Aging and the Alzheimer's Association charged a workgroup with the revision of previous criteria. They have published new criteria for all-cause dementia as well as for AD dementia, to be used in both research and clinical settings. According to the new recommendations (McKhann et al., 2011), dementia at large is diagnosed when there are cognitive or behavioural symptoms that interfere with the ability to function as usual, that represent a decline from previous levels of functioning, and that are not explained by delirium or a major psychiatric disorder. The cognitive impairment is diagnosed through a combination of history-taking from the patient (confirmed by a knowledgeable informant) and objective cognitive assessment. In addition, the impairment involves at least two different domains among the following: memory; reasoning and judgment; visuospatial abilities; language; personality changes. Probable Alzheimer's disease is specifically diagnosed when the patient not only meets criteria for dementia, but also presents insidious onset of disease, significant history of worsening, and amnestic (memory) or nonamnestic (language, visuospatial, executive) presentation of cognitive deficits. Exclusion criteria for probable AD include substantial concomitant cerebrovascular disease and evidence or prominent features of another type of dementia, neurological disease or other medical comorbidity that could affect cognition.

In recent years, efforts have been deployed to define a pre-clinical phase of AD, particularly for intervention purposes. Although we cannot yet identify with certainty a prodromal stage of AD in individual patients, researchers agree on the existence of a cognitive syndrome which puts those affected at high-risk of progressing to dementia, most often dementia of the AD type or other types of dementia, such as vascular or frontotemporal dementia (Gauthier et al., 2006). One of the most frequent terminologies employed for this risk state for dementia is mild cognitive impairment (MCI) (Petersen et al., 1999). The criteria most often employed for MCI include a memory complaint (preferably corroborated by an informant), impaired memory function on neuropsychological tests (adjusted for age and educational level), preserved general cognitive function, intact activities of daily living and the absence of dementia (Petersen, 2003; Petersen et al., 2001). The core criteria recently established by the National Institute on Aging and the Alzheimer's Association workgroup are quite similar, and include cognitive concern reflecting a change in cognition reported by patient or informant or clinician, objective evidence of impairment in one or more cognitive domains (typically including memory), and preservation of independence in daily functional abilities. Although the criteria state that the differentiation of MCI from dementia rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities, they do specify that persons with MCI commonly have mild problems (slowness, errors) performing complex functional tasks, such as paying bills, or preparing a meal (Albert et al., 2011).

Older adults with MCI are thus identified as being at high-risk of progressing to AD (Gauthier et al., 2006; Petersen, 2003). Epidemiological studies suggest that the prevalence of MCI is around 5% of the general population. Incidence is estimated at 8 to 58 new cases per 1000 persons per year (Ritchie, 2004), with around 15% per year converting from MCI to dementia (Gauthier et al., 2006; Petersen et al., 2001). Multiple studies have found that persons with MCI develop dementia 10 times more often than persons not meeting criteria for MCI (Bowen et al., 1997; Petersen et al., 1999; Tierney et al., 1996).

Mild cognitive impairment is a clinically heterogeneous label (Chertkow et al., 2008). Several distinct subtypes of MCI exist, depending on the cognitive domain(s) affected (Petersen, 2004). The amnestic MCI subtype refers to those with a memory impairment (amnestic single domain MCI), as well as to those with impairments in memory and in other cognitive domains such as language, executive function and visuospatial skills (amnestic multiple domain MCI). The non-amnestic subtype refers to those with impairments in domains other than memory and can affect only one cognitive domain (non-amnestic single domain MCI) or more than one cognitive domain (non-amnestic multiple domain MCI). Among the different clinical subtypes, the amnestic single and multiple domain subtypes have been found to be more likely to progress to AD (Petersen et al. 2001; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Ritchie & Tuokko, 2010). Neuropathologic features of MCI involve the medial temporal lobe structures and appear to be situated midway between the changes often observed in normal aging and the pathologic features of early AD, such as amyloid accumulation and neurofibrillary tangles (Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Petersen et al., 2006; Riley, Snowdon, & Markesbery, 2002), thus confirming the pre-clinical standing of MCI.

1.1.2 Neuropsychological profile

Episodic memory impairment, or amnesia, is one of the defining features of AD (Brandt & Rich, 1995) and, in an overwhelming majority of cases, the first cognitive deficit to present itself. Episodic memory was first defined in 1973 by Tulving & Thomson as a system "(…) concerned with storage and retrieval of temporally dated, spatially located, and personally experienced events or episodes, and temporal-spatial relations among such events.'' In other words, active retrieval from long-term memory is based on contextual information about the original learning experience (Smith, 2007). The episodic memory impairment in AD includes deficits in list recall of words, sentences or stories, and recognition memory for words, drawings or pictures. In particular, for the purposes of this dissertation, the issue of forgetting over time is of great importance. Indeed, it has been frequently shown that to-be-remembered information is rapidly lost in AD, as measured by significantly impaired delayed free recall tasks (Carlesimo, Fadda, Bonci, & Caltagirone, 1993; Greenaway et al., 2006; Welsh, Butters, Hughes, Mohs, & Heyman, 1991), even when encoding is maximized by inducing deep semantic processing (Grober & Kawas, 1997). Furthermore, studies consistently show an abnormal serial position effect, in which AD patients present impaired primacy with relatively preserved recency (Bayley et al. 2000; Burkart, Heun, & Benkert, 1998; Carlesimo, Fadda, Sabbadini, & Caltagirone, 1996; Gainotti & Marra, 1994), suggesting that information encoded at an earlier time is subject to greater forgetting than that presented more recently in time (Buschke et al., 2006; Morris & Baddeley, 1988; Simon, Leach, Winocur, & Moscovitch, 1994).

In addition to memory, deficits in other cognitive domains are present during the course of AD. Impairments of executive attention appear quite early on (Perry, Watson & Hodges, 2000), predominantly concerning speed of attentional switching and disengaging, response inhibition, divided attention, and working memory[1]. Semantic memory (verbal fluency, word finding, object naming) may also be affected, followed by deficits in language, visuoperceptual and visuospatial functions, verbal short-term memory, and comprehension. The abilities relating to sustained attention, remote and autobiographical memory, procedural skill learning, and emotional processing are generally preserved the longest within the neuropsychological profile of AD (Morris & Worsley, 2002).

In view of the fact that the very beginning of Alzheimer's disease is putatively represented by MCI, it follows that the first neuropsychological deficits to be detected in MCI affect verbal and visual episodic memory, at least for the majority of individuals with amnestic MCI who will develop dementia due to Alzheimer's disease. As mentioned in the previous section, this may include deficits in recalling lists of words or stories, as well as recognizing words, drawings or pictures. Like in AD, there is evidence showing that to-be-remembered information is rapidly lost over time in MCI, as demonstrated by poorer performance on longer retention intervals in the Brown-Peterson (BP) procedure (Belleville et al., 2007) and intertrial forgetting of items on a word list learning task (Moulin, James, Freeman, & Jones, 2004), although the extent of the deficit in MCI is not as extreme as in AD.

In addition to episodic memory deficits, there is evidence to suggest that persons with MCI may also experience impairments in other domains. In a meta-analysis of 47 studies published between 1985 and 2003, Bäckman, Jones, Berger, Laukka, & Small (2005) revealed that the preclinical phase of Alzheimer's (akin to MCI) is characterized by marked deficits of not only episodic memory, but also of global cognitive ability, perceptual processing speed, and executive functioning (cognitive flexibility, inhibition and manipulation in working memory). Somewhat smaller impairments were found in language (naming, vocabulary) and visuo-constructional abilities. Primary memory, or short-term memory, was relatively preserved. It is important to note that although cognitive deficits may be found across multiple domains in the MCI phase, the level of impairment is habitually less severe than in AD (Bäckman & Small, 1998; Collie & Maruff, 2000), indicating a gradient of severity across the disease.

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[1] The latter two will be described in depth in section 1.2.4 as they pertain directly to the subject of the empirical articles composing this dissertation.

To summarize, AD is a progressive neurodegeneration and there is increasing interest in trying to better understand the very beginning phase of the disease. Persons meeting criteria for MCI might be in a prodromal stage of AD. The epidemiological, clinical and neuropathological data suggest that the concept of MCI is valid and useful in research settings for the early identification of older adults at risk of progressing to dementia. The neuropsychological profile of those with MCI and AD is characterized by marked episodic memory deficit. Nevertheless, there is support for the presence of deficits in other domains of cognition. One of these major domains is working memory, the subject of the present thesis. Prior to reporting our data supporting the impact of AD and MCI on this domain, we will briefly define the concepts of working memory and present current models.

1.2 Assessment of working memory and attentional control in AD and MCI

1.2.1 Working memory: definition and measures

Working memory (WM) is classically conceived as a function that supports online manipulation and temporary storage of information. It is also increasingly viewed as a system that is involved in attentional control. Many tasks have been used to measure WM and their diversity reflects the complexity of this component and the range of processes that are encompassed by this concept. These tasks involve concurrent retention and processing (Daneman & Carpenter, 1980), divided attention (Morris, 1986), updating (Gevins & Cutillo, 1993; Sternberg, 1966), on-line manipulation of information (Craik, 1986), inhibition and selective attention (Burgess & Shallice, 1996; Stroop, 1935). They are extremely varied and only those that are more closely relevant to this thesis will be described here.

A large number of WM tasks include two components: processing and retention. One of the first such tasks used to measure WM in AD was the BP paradigm (Morris, 1986). In this task, consonant trigrams are maintained in memory for up to 30 seconds while a distractor task (for example, simple addition) is executed. The well-known n-back task (Gevins & Cutillo, 1993) entails viewing a continuous stream of items (for example, letters) and making a judgment of whether each item matches the stimulus presented ’’n’’ stimuli back, where n may be 1, 2 or 3. The n-back task is an example of continuous updating, whereas other tasks only involve discrete updating, such as the item recognition task (Sternberg, 1966). The latter involves retaining consecutive small memory sets (1-6 items) for up to 10 seconds and making a judgment on a probe item presented for each set. While the previously described paradigms necessitate storage as well as differing levels of processing, they do not require much online manipulation of information. In contrast, the alpha-span task (Craik, 1986) evaluates active manipulation of information by comparing recall of items in their alphabetical order to serial word recall.

In the same manner in which those tasks evaluate the coordination of two components (processing and retention), attentional control is also frequently measured with a paradigm requiring the coordination of two tasks: the dual-task. Like the BP procedure, dual tasks were among the fist used to demonstrate WM deficit in AD (Baddeley et al, 1986). This paradigm plays a chief role in the second and third studies included in this dissertation. In the dual-task, two tasks are first executed separately (single condition) and then simultaneously (dual condition). Comparison of the single and dual conditions produces a dual task decrement, a measure of divided attention. In other words, the decrement represents the cost associated with the executive control function responsible for multiple task coordination. As a result, dual task paradigms are perfect for isolating the executive component while appraising attention control functions, and hence, would be an ideal choice of measure in individuals with these types of deficits, such as AD and MCI.

Another set of tasks soliciting the coordination of two concurrent processes is the family of complex span tasks, typical and widely used measure of WM capacity. They include sentence span, operation span, reading span, listening span and counting span. The first two are the focus of the first study in this dissertation. In complex span tasks, a series of propositions is presented with the instruction to solve or make a judgement for each one while retaining the last element of each proposition, followed by free recall of the solution items (see Conway et al., 2005 for a methodological review). In other words, complex span tasks entail concurrent processing and short-term storage demands, a key feature in the assessment of WM.

The first study of measuring complex span, by Daneman & Carpenter (1980), consisted of a reading span task in which participants read a series of sentences for meaning while maintaining each last word in memory. Sentence span was defined as the maximum number of sentence-final words recalled in the correct order. Similarly, an operation span task developed by Turner and Engle (1989) involved arithmetical calculation (in lieu of sentence reading) for the processing component of the task and memory of the problem outcome. Empirical support for the validity of these tasks lies in their predictive power. Indeed, performance on these complex span tasks predicts performance on higher-order cognitive tasks (Engle, 2001), whereas performance on traditional simple span tasks (e.g. digit span) does not (Daneman & Carpenter, 1980). Sentence Span, for example, is highly correlated with a range of complex cognitive activities, including language comprehension (Daneman & Merikle, 1996), abstract reasoning (Engle, Tuholski, Laughlin, &

Conway, 1999) and general fluid intelligence (Engle, 2001). Therefore, this task is a very sensitive and valid measure of working memory, and thus, would be ideal for evaluating this capacity in clinical populations known to present WM deficits, such as AD and MCI.

In sum, numerous tasks have been proposed to evaluate WM, which is seen as a system involved in attentional control. Many of those tasks involve processing information while simultaneously retaining other relevant information in an active format. The range of processes involved reflects the complexity of this concept for which many models have been put forward, as will be described next.

1.2.2 Models

One of the most influential models of working memory has been that of Baddeley & Hitch (1974), which includes two peripheral slave systems for short-term storage of verbal and spatial information as well as the central executive, responsible for the coordination and monitoring of cognitive processes. More recent views of working memory describe it as an executive system of attentional control involved in the ability to control attention in order to maintain information in an active and quickly retrievable state (Engle, 2002).

Recently, researchers have begun to closely examine and disentangle different executive components of working memory. Baddeley (1996) separates the executive system into four main capacities: selection/inhibition of information, concurrent storage and manipulation of information, switching of retrieval strategies, and coordination of multiple activities (dual tasking). In a similar manner, Miyake, Emerson, & Friedman (2000) tackled the diversity of executive functioning using latent variable analysis and found three moderately correlated yet distinct functions: shifting of mental set, information updating and monitoring, and inhibition of prepotent responses. On the other hand, dual task coordination was found to be independent of these three functions. Finally, Belleville, Chertkow, & Gauthier (2007) have presented evidence supporting working memory being composed of information manipulation, inhibition, and dual task coordination. In sum, working memory is an executive system founded on multiple attentional control abilities and tasks used to measure it reflect this complexity.

One of these tasks is the complex span, or WM span, highlighted in the first experiment included in this thesis. Several views exist regarding the cognitive mechanisms underlying performance on complex span tasks. Individual differences research has shown that, over and above the storage and processing components, there emerges a control component which allows resistance to the interference between processing and storage (Jarrold & Towse, 2006). This potentially executive component, elicited in complex span tasks, can be differentially referred to in the literature as executive controlled attention (Kane et al. 2004), inhibitory attentional control (Hasher, Lustig, & Zacks, 2007), or central executive (Baddeley, 1986). Therefore, it appears that complex span tasks not only engage processing and retention, but may also elicit a higher-order function of attentional control.

Several models specifically striving to elucidate the interactions between storage and processing have been put forward. One of the first models, the cognitive space or resource-sharing account of working memory (Case, 1985), refers to the idea that a limited-capacity pool of cognitive resources can be flexibly allocated to either storage or processing. Accordingly, there is a trade-off between retention and processing. Thus, in a complex span task, a more demanding processing part (in terms of cognitive resources) will leave fewer resources for storage, resulting in poorer recall and a lower span (Case, Kurland, & Goldberg, 1982). An alternative explanation is the task-switching model, in which storage and processing are independent of each other, or are at least executed serially (Towse & Hitch, 1995). Thus, a lower working memory span would not be explained by storage competing with processing, but rather by memory decay over time. In other words, the only important factor is duration of processing, because memory traces of the to-be-recalled items decay as the concurrent processing task is being performed. In the face of this apparent dilemma opposing attentional trade-off versus task-switching, a third view has emerged to explain the interactive effects of storage and processing. Barrouillet, Bernadin, & Camos (2004) propose a time-based resource sharing account of working memory, a reconciliation of the two previously described models. According to this model, memory traces would suffer from time-related decay when a substantial amount of limited attentional resources is captured by processing. More recently, researchers have been revisiting the idea that duration of processing plays little to no role in performance on complex span tasks (Berman, Jonides, & Lewis, 2009; Lewandowsky & Oberauer, 2009). One such model proposes that representation-based interference causes deficits on complex span tasks (Saito & Miyake, 2004). By carrying out the processing part of the task, representations are generated that interfere with the storage of to-be-remembered representations, and thus forgetting occurs. In other words, a more demanding processing part causes more interference and poorer recall, virtually independently of duration of retention interval.

A growing number of studies are attempting to shed light on the mechanism by which the processing component of the complex span task disrupts storage of items in memory and causes forgetting. The classic stimulus order effect (Hitch et al. 2001) refers to the fact that when cognitive load is kept stable, span scores are better when retention intervals, as determined by duration of processing, are shorter. Towse, Hitch, & Hutton (1998) showed this by examining the role of temporal factors in working memory spans of children and adults. They developed an experimental paradigm in which overall task difficulty (processing phase) remained constant while retention requirements varied. This was done by altering the length of the stimuli to be processed. As predicted by the task-switching model, augmenting retention intervals - but not processing difficulty - reduced working memory spans. The authors attribute this to the influence of forgetting over time, an issue often neglected in current conceptions of complex working memory tasks. Thus, the stimulus order effect retains our interest as a tool allowing us to tease apart processing and storage within working memory, thereby contributing to models of WM.

1.2.3 Brain regions involved

Another tool used to elucidate the components of WM is brain imaging, which has shown exponential growth in the field of cognitive neuroscience over the past few decades. Given that WM is a complex system involved in attentional control and that it encompasses many processes, it follows that widely distributed brain regions may be activated depending on the task and methodology employed. Cerebral activity is most often focused in the parietal, prefrontal and anterior cingulate cortices (Cabeza & Nyberg, 2000; Kane & Engle, 2002; Salmon et al., 1996; Smith, 2000). In particular, it appears that parietal regions are especially involved in the sustained and selective attention processes necessary for task execution, while prefrontal regions are solicited for executive-type processes. As for the anterior cingulate, it is involved in attentional control processes in relation to task difficulty (Bush, Luu, & Posner, 2000), acting in concert with prefrontal regions (Markela-Lerenc et al., 2004).

To obtain an evidence-based, integrated view of the neural correlates of tasks evaluating WM, meta-analyses of 60 neuroimaging (PET and fMRI) studies of WM in healthy adults were performed by Wager & Smith (2003). The two most common tasks reviewed consisted of the n-back and item recognition tasks (described earlier), but other paradigms, such as the complex span task, were also included. Beyond the expected material-specific dissociations, effects of executive processes were found in the superior parietal cortex for all tasks. With respect to the prefrontal regions, tasks entailing executive processes generally produced more dorsal frontal activations. In addition, the superior frontal cortex responded more frequently in WM tasks entailing continuous updating and in those requiring memory for temporal order. As for WM tasks engaging manipulation (including dual-task requirements or mental operations), the inferior frontal cortex appeared involved. These results provide neuroanatomical evidence supporting the cognitive viewpoint of executive functions being fractionated into different component processes, as described previously.

Although meta-analyses possess the advantage of pooling large amounts of data to draw general conclusions, they may mask results from individual paradigms. Imaging studies have shown that the coordination of two concurrent tasks activates parietal, anterior cingulate and lateral prefrontal regions, such as the dorsolateral area (D'Esposito et al., 1995; 1998), the inferior frontal gyrus (Herath, Klingberg, Young, Amunts, & Roland, 2001), the middle frontal gyrus (Szameitat, Schubert, Muller, & Von Cramon, 2002) and cortical areas along the inferior frontal sulcus (Schubert & Szameitat, 2003). These regions all appear to be involved in managing the interference effects embedded in various types of dual-task paradigms.

One task playing a central role in the present thesis is the family of complex spans tasks, which include both processing and retention components and thus, can be considered as a subtype of dual task. A few studies have been conducted on the neural correlates of WM spans. Consistent with the hypothesis that executive control processes within WM are primarily prefrontal cortex-mediated while mnemonic processes involved in storage are more posteriorly mediated (Postle, Berger, & D'Esposito, 1999), complex span tasks have been shown to activate both prefrontal and medial temporal regions, respectively. More specifically, the lateral prefrontal, anterior cingulate and parietal regions have been solicited in reading span (Osaka et al., 2004), listening span (Osaka et al., 2003) as well as in verbal and spatial adaptations of complex span (Chein, Moore, & Conway, 2011). With respect to the storage demands, medial temporal activations have been shown during recall from verbal and spatial WM span (Chein et al., 2011), as well as during encoding and maintenance in operation span (Faraco et al., 2011). Hence, the neural substrates of WM span involve interconnections between areas subserving attentional, executive and retention demands. Thus, it appears that dual-tasks and complex span tasks engage similar regions of the brain, with the notable exception of storage-related hippocampal activations exclusive to WM spans.

As the previously reported findings attest, many studies have examined the neural correlates of WM in normal adults. However, only a handful of studies have done the same with MCI and AD populations. Overall, these individuals tend to show changes in cortical activity in the regions classically associated with WM. Relative to healthy controls, persons with MCI have shown atypical activations of: frontal, parietal and anterior cingulate regions during a visuospatial WM task (Kochan et al., 2010); frontal and medial temporal regions during a visual WM task (Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006); as well as prefrontal regions during a divided attention task (Dannhauser et al., 2005). Individuals with AD tend to exhibit a similar pattern. They have been found to have increased activity in parietal networks and decreased activations of lateral prefrontal regions, both in verbal (Lim et al., 2008) and visuospatial (Lipton et al., 2003) working memory tasks. In summary, findings from brain imaging studies in MCI and AD confirm the presence of dysfunctional cortical activity in regions typically engaged during WM tasks.

1.2.4 Working memory and control of attention in AD and MCI

Given current cognitive and neuroanatomical models which designate WM and attentional control as a central component of complex cognitive activities, it is not surprising to note the increasing amount of research focusing on these constructs. It is equally important to study these chief cognitive components in degenerative disease in order to better understand how they are affected. Indeed, although episodic memory is habitually the first cognitive domain affected in AD, working memory and attentional control impairments are also well documented in AD (for reviews, see Bherer, Belleville, & Hudon, 2004; Collette & Van der Linden, 2005; Huntley & Howard, 2010; Morris, 1994), and are present quite early in the disease (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Perry & Hodges, 1999). Moreover, it has been suggested that they underlie difficulties with everyday activities present in AD (Perry & Hodges, 1999), for example, walking while talking (Cocchini et al., 2004).

Individuals with AD show deficits on many attentional control tasks; for example, impairments in latency and accuracy in spatial switching abilities (Belleville, Bherer, Lepage, Chertkow, & Gauthier, 2008), as well as in inhibition capacities on the Stroop (Belanger, Belleville, & Gauthier, 2010) and Hayling tasks (Bélanger, 2009; Belleville, Chertkow, & Gauthier, 2007), all considered to rely heavily on executive or attentional control functions. In addition, there are many findings suggesting a deficit in WM requiring concurrent storage and processing in AD. For example, individuals with AD perform consistently worse than controls on such tasks as the Brown-Peterson, whether the distractor task is verbal (counting, articulation) (Belleville, Chertkow, & Gauthier, 2007) or non verbal (tapping) (Belleville, Peretz, & Malenfant, 1996; Morris, 1986). Likewise, they are impaired on the alphabetical serial word recall task (alpha-span) (Belleville, Rouleau, Van der Linden, & Collette, 2003). Furthermore, AD produces deficits in non-verbal working memory, both visuo-spatial (Toepper, Beblo, Thomas, & Driessen, 2008; Vecchi, Saveriano & Paciaroni, 1998) and auditory (White & Murphy, 1998).

When tested with tasks of divided attention, persons with AD show a larger dual task decrement than in normal aging. In other words, they perform similarly to controls in the single condition but decline disproportionately in the dual condition (Perry & Hodges, 1999). This robust finding has been replicated with different task combinations, such as a simple judgement task combined with a digit span task (Grober & Sliwinski, 1991), a visuo-motor task combined with an individually-adjusted digit span task (Baddeley et al., 2001; Collette, Van der Linden, & Salmon, 1999; Greene, Hodges, & Baddeley, 1995; Perry, Watson, & Hodges, 2000), and a pursuit tracking task combined with counting, tone detection or digit recall (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Logie, Cocchini, Della Sala, & Baddeley, 2004).

It has been proposed that this attentional deficit in AD is due to impairment of a specific executive function for dual task coordination. In fact, Logie et al. (2004) found that even a dual task paradigm with very low cognitive demand produced a dual task decrement in AD. Furthermore, in varying the level of difficulty of one task while simultaneously keeping that of the other constant, they found no evidence of interaction between difficulty and performance, as measured by the dual task decrement. This suggests that the divided attention impairment observed in AD is not due to limited attentional resources. This impairment is found even when the difficulty of individual tasks is adjusted to the person's level suggesting that it does not arise from diminished speed of processing in AD. In addition, Baddeley et al. (2001) found that focal attention was not impaired in individuals with AD compared to controls, even though they presented a significant dual task decrement in two distinct dual task paradigms. Taken together, these results point towards the existence of an identifiable cognitive component for multiple task coordination which is impaired in AD.

The complex span task is widely used in neuropsychological practice to measure coordination of concurrent storage and processing, but has only been explored by very few studies in AD. This is surprising because the task has been shown to be reliable and sensitive to the integrity of higher-order cognitive constructs. Rochon, Waters, & Caplan (2000) have demonstrated impaired performance in mild-to-moderate AD patients on the dot span task, a visual WM span involving counting series of dots and reporting the totals. Two studies have investigated sentence span in AD. First, in an experiment relating prospective memory to retrospective memory, Maylor, Smith, Della Sala, & Logie (2002) found significantly lower spans in two groups of possible/probable AD patients. However, they employed auditory presentation of sentences and did not require any processing task to prevent rehearsal of sentence-final words. Second, Waters and Caplan (2002) administered WM spans within a study examining the relationship between WM and sentence comprehension. Their task involved visual presentation and a validity judgment of sentences to sustain processing during storage. Two separate conditions were employed: syntactically simple, one-proposition sentences and syntactically complex, two-proposition sentences. For both conditions, they showed impaired WM spans in their group of mild-to-moderate AD patients. As for operation span, to our knowledge, no studies have attempted to employ this version of complex span in this population, leaving open the question of whether AD affects WM span with numerical stimuli.

Given these deficits in AD, a small but growing number of studies have investigated facets of WM and attentional control in persons with MCI. Missonnier et al. (2005) and Yetkin, Rosenberg, Weiner, Purdy, & Cullum (2006) demonstrated normal performance on 2-back and 3-back working memory tasks in MCI. Similarly, Dannhauser et al. (2005) showed normal performance on a divided attention task involving concurrent visual and auditory detection tasks. Of note is the fact that performance levels in the two previously described studies were quite high, indicating a possible ceiling effect. In other words, the tasks may simply have been too easy to detect subtle working memory impairment in MCI. In contrast, other studies have reported definite attentional control deficits in persons with MCI. With respect to the n-back working memory task, Borkowska, Drożdż, Jurkowski, & Rybakowski (2009) showed impaired performance and latency for older adults with MCI on a visual 1-back version. Belleville, Chertkow, & Gauthier (2007) evaluated attentional control in older persons MCI and found that performance of individuals with MCI was impaired compared to controls in the Brown-Peterson paradigm. In addition, their results showed that impairment in active manipulation of information during an alphabetical serial recall task predicted future progression from MCI to AD. Further evidence of impaired WM and attentional control can be inferred from recent studies describing spatial switching deficits (Belleville, Bherer, Lepage, Chertkow & Gauthier, 2008; Sinai, Phillips, Chertkow, & Kabani, 2010); reduced latency of inhibition on the Stroop task (Belanger, Belleville, & Gauthier, 2010); semantic inhibition impairment on the Hayling task (Bélanger et al. 2009); visuo-spatial working memory deficits (Alescio-Lautier et al., 2007).

In summary, there exists some evidence that WM and attentional control capacities can be impaired in MCI in the same manner as they are in AD. Thus, the same identifiable cognitive component for multiple task coordination which appears affected by the pathology of Alzheimer's disease could also be affected in MCI, but to a lesser extent. However, these constructs have not yet been evaluated in MCI with the most widely used measures of WM capacity: complex span tasks (Conway et al., 2005).

1.2.4.1 Role of forgetting within WM deficits in AD and MCI

As mentioned previously, many WM tasks include both processing demands and short-term storage, as measured by complex span tasks. These two components are solicited concurrently and both contribute to performance obtained at recall. One interesting hypothesis pertaining specifically to the storage component of WM is that retention rates, or ''forgetting'', may contribute to performance. In other words, it is possible that difficulty in storing information could play a unique role in exacerbating WM deficits on complex span tasks. This is particularly relevant when trying to understand the processes that underlie WM deficits in AD and when trying to devise tasks sensitive to the early phase of the disease. Indeed, AD is a clinical population known for its well-documented retention deficit (Grober & Kawas, 1997), as described earlier. Notably, delayed recall deficits and impaired primacy effects suggest that to-be-remembered information is subjected to greater forgetting when it is encoded earlier, rather than later, in time. It has been proposed that retention is impaired in MCI as well, which might contribute to their impairment on WM tasks. For example, the fact that persons with MCI decline significantly when the retention interval is lengthened to 30s in the Brown-Peterson paradigm suggests that storage duration may play a role in their WM performance (Belleville et al., 2007). A better understanding of the role of retention within WM is important because it may shed light on a common mechanism in both WM and long term memory, in addition to helping in the development of tests sensitive to the disease. Yet it remains to be seen if the hypothesis that forgetting contributes to performance is valid in typical WM tasks, which are habitually very short in duration and only require temporary retention. To our knowledge, no experiment has attempted to test this hypothesis directly in AD and MCI. This could be done using the previously mentioned stimulus order effect, a tool that allows us to temporally isolate the duration of storage within WM span.

1.3 Cognitive Intervention

Thus far, it has been demonstrated that WM represents a core component of complex cognition as well as a vital construct in understanding some of the deficits observed in AD and MCI. Furthermore, deficits in this domain appear quite early in the disease and may underlie difficulties in everyday complex activities. It follows that they must also be considered an important therapeutic target for intervention, the subject of the present section. Most notably, the MCI phase appears to be a key period for providing such interventions. Therein lays the possibility of promoting brain plasticity and delaying cognitive decline in adults at high risk of developing dementia. This is especially crucial in view of the fact that current pharmacological treatments are not effective in halting disease progression. Thus, cognitive interventions properly designed to target impairments exhibit potential in improving cognitive functioning.

1.3.1 Definition

Taken broadly, cognitive interventions for individuals with dementia may encompass cognitive rehabilitation, remediation, training, stimulation, practice, orientation, exercise, etc. (Clare, 2007). In an attempt to clarify the terminology employed, Clare, Woods, Moniz Cook, Orrell, & Spector (2003) have developed the following definitions of intervention types. *Cognitive stimulation*, most often applied in cases of moderate-to-severe dementia, encompasses non-specific group activities and discussions that endeavour to enhance cognitive and social functioning at large; for example, reality orientation. In contrast, *cognitive rehabilitation* is habitually employed in the early-stages of dementia and entails individualised interventions which address specific practical difficulties encountered in activities of daily living. As for *cognitive training*, it is utilized with a broad range of individuals, from healthy older adults to MCI and persons with dementia, and differs from the two previous interventions in that it aims to improve specific neuropsychological functions, such as memory, language, or attention.

The present dissertation focuses on cognitive training. This approach uses a theoretically-based, standardized protocol and is most amenable to quantitative research in group settings. Given that working memory is an executive system founded on multiple attentional control abilities, it follows that training programs elaborated by different research groups have focused on one or more of these components. As a result, the cognitive training literature is greatly heterogeneous, with varied methodology, including content, intensity, frequency, outcome measures, etc. For this reason, synthesizing and extracting general conclusions becomes a complex matter. Nonetheless, the following sections will endeavour to describe published studies examining training of attentional control and working memory; first from a general perspective, then in MCI. Subsequently, two key issues in training will be discussed: meta-cognition and transfer effects.

1.3.2 Working memory training programs

Attentional control training has been studied in traumatic brain injury (TBI) patients for over 25 years. For example, Attention Process Training (APT) (McKay Moore Sohlberg & Mateer, 1987) is a theoretically based multilevel intervention which targets sustained, selective, and divided attention. It has been shown to be efficacious in case studies (Palmese & Raskin, 2000). Moreover, Sohlberg, McLaughlin, Pavese, Heidrich, & Posner (2000) found larger improvement on neuropsychological measures after APT training than following traditional therapeutic support. However, others have failed to find a positive effect of APT in TBI that surpasses that of simple practice effects (Park, Proulx & Towers, 1999). APT has also been employed with a post-stroke population (Barker-Collo et al., 2009), with beneficial effects demonstrated on a primary attention measure, but no generalization of effects to broader outcomes. Cognitive training for attention has thus been studied in certain clinical populations for many years already.

As the population advances in age, cognitive training for attentional control that was once reserved for brain-injured patients has now expanded to healthy elderly adults. Here, there exists more evidence that highlights the feasibility and beneficial impact of cognitive intervention on attention control capacities. McDowd (1986) first showed that extended practice involving two perceptual-motor tasks (visual pursuit tracking and auditory choice reaction time) could ameliorate divided attention capacities for dual tasking in healthy older adults. More recently, the ACTIVE study, a large, multi-centre, randomized controlled trial of three distinct training interventions (memory, reasoning, and speed of processing) was conducted with older adults (Ball et al., 2002; Willis et al., 2006) . Participants receiving the speed of processing intervention were trained on a computerized divided attention task of visual search with distracters. The vast majority (87%) of these individuals significantly improved their searching abilities following training, and these cognitive effects were mostly maintained at the 2- and 5-year follow-ups, especially for those who had received booster training. Finally, a particularly important study in the context of this dissertation is that of Kramer, Larish, & Straye (1995). These authors demonstrated the benefits of variable priority (VP) training on attentional control in a dual task comprised of a visual monitoring task and an alphabet-arithmetic task. The objective of VP training is to promote control of attentional abilities and enhance dual task coordination by emphasizing one task more or less than the other task across different blocks. Their VP training resulted in attentional control enhancement, including superior performance on another new dual task, indicating an acquired dual task coordination ability that is generalizable. Contrasting results were obtained by Bherer et al. (2005; 2008), who found no advantage for a modified VP training over simple, rote dual-task practice (fixed priority training, or FP). Nevertheless, both FP and VP trained groups of older adults improved not only on the trained task, but also on new task combinations involving new stimuli; again demonstrating transfer of training effects. Consequently, there is converging evidence supporting cognitive training for attentional control in healthy elderly adults, which begs the question: could this training also be beneficial in older adults with cognitive deficits?

1.3.3 Training in AD & MCI

Recently, researchers have developed cognitive training for older persons with cognitive deficits resulting from Alzheimer's disease (AD) (Buschert, Bokde, & Hampel, 2010). Given that episodic memory is the most affected cognitive domain in AD, intervention has mainly focused on memory, with success for task-specific improvements (Grandmaison & Simard, 2003). However, it has been shown that cognitive interventions are not superior to global stimulation in AD, in terms of behavioural and functional improvements (Farina et al., 2006). Moreover, multiple methodological problems arise when intervening with this clinical population, due to their relatively advanced cognitive deficits. For example, difficulty in grasping complex instructions, remembering lessons, sustaining attention, etc. (Van der Linden, Juillerat, & Delbeuck, 2004). For the above-mentioned reasons, intervention with an MCI population is much more feasible, because their cognitive deficits are not such that everyday functioning is impaired. It is also hypothesized that intervening in the MCI phase could possibly prevent or slow down future cognitive impairment associated with AD (Petersen et al., 1997). Thus, MCI is an ideal stage for intervention, which is why a growing number of cognitive intervention studies have been conducted with the MCI population. In view of the fact that episodic memory impairment is generally the first deficit to emerge, most of these interventions concern the effectiveness of memory training (for reviews, see Belleville, 2008; Miotto, Serrao, Guerra, Lúcia, & Scaff, 2008). It appears that memory intervention in MCI has shown at least mild beneficial effects (Li et al., 2011). In view of these positive findings, it is a valid and important endeavour to verify if individuals with MCI may also benefit from training of other cognitive domains affected, such as attentional control.

There is support in the literature for control of attention to be targeted in intervention studies in MCI. Although there have been no interventions with this specific purpose, there exist studies showing effects of training focusing on a broad range of cognitive functions including, but not limited to, attentional components. One pilot study, testing a computer-assisted cognitive training program focusing mainly on memory, but also on processing speed, found benefits for older individuals with age-associated memory impairment (analogous to MCI) (Gunther, Schafer, Holzner, & Kemmler, 2003). In another study, Olazarán et al. (2004) built a global, cognitive-motor stimulation program (including attention training) for a mixed-patient group of MCI and mild-to-moderate AD. Following the intervention, trained participants retained their general cognitive performance levels, whereas the control group declined. A third study, focusing on educational and multidimensional cognitive training, found enhanced attention and everyday executive function (in finances and shopping) in individuals with MCI (Brum, Forlenza & Yassuda, 2009). Interestingly, a pilot study (n=12) using the commercially-available Nintendo Brain Age game was recently conducted in MCI (Hsiung, Kupferschmidt, Naus, Feldman, & Jacova, 2009). The authors reported evidence of improvement in psychomotor speed, but not on clinical outcomes. Thus, multidimensional training protocols have shown promise in ameliorating attentional functions in MCI. However, there is no way of knowing which ingredients or components included in these interventions produced effects specific to attentional capacities, as they trained multiple cognitive domains at once.

Further support for attention training in MCI can be found in other executive-type practice and training paradigms. For one, Belleville et al. (2008) have reported improved spatial switching capacities in MCI following practice. Furthermore, Unverzagt et al. (2007) showed that “memory-impaired” older adults (as defined by low performance on a verbal memory test) benefited as much as healthy older adults did from training on the computerized divided attention search task described previously in the ACTIVE study. Another study has focused exclusively on auditory processing speed and accuracy in MCI (Barnes et al., 2009). Their intervention group showed a non-significant trend towards better general cognitive status as compared to the active control group. Hence there exists evidence that training executive attention functions may benefit individuals with MCI, although it has not yet been directly investigated with dual-task paradigms. Our experiments thus aimed to fill this void by studying cognitive training focusing solely on attentional control in MCI. This will be done whilst considering two factors highlighted as relevant in the scientific literature on cognitive intervention: meta-cognition and transfer effects.

1.3.4 Meta-cognition

One of these factors is the development of awareness during cognitive training. Indeed, an increase in meta-cognition has been highlighted as a vital factor in a successful intervention (Clare, Wilson, Carter, Roth, & Hodges, 2004). Certainly, control beliefs and goal setting have been shown to augment performance, even in older adults (West & Yassuda, 2004). Thus, awareness regarding cognitive potential and performance could trigger participants to realize that they can exert a certain amount of control over their own cognition. This could be particularly crucial in an intervention study focusing on attentional control, in which the control or coordination component may be influenced by the participants themselves. Accordingly, by including a self-regulatory strategy designed to enhance meta-cognition in an attention control protocol, such as the variable priority (VP) training regimen (Kramer et al., 1995) described earlier, it is possible that trainees may learn to regulate their attentional resources through goal-setting and enhanced awareness. Improvements in meta-cognitive skills may also optimize generalization of training effects, given their higher order, overarching position in cognition.

1.3.5 Transfer effects

Another important factor that has emerged from the general cognitive training literature is transfer, a central concept in the field of learning. Much debate has surrounded this construct during the past century, dating as far back as work by Thorndike & Woodworth in 1901. Although no consensus has been reached, in general terms, transfer can be defined as “the ability to extend what has been learned in one context to new contexts” (Bransford, Brown, & Cocking, 1999, p. 51). As research on cognitive training is expanding, the importance of studying the degree of transfer of newly acquired skills has intensified (Willis & Schaie, 2009).

From a practical standpoint, it is vital that intervention studies be able to accurately measure to what extent, if any, training benefits generalize to other tasks, other stimuli and, eventually, to functional activities (Zelinski, 2009). If the ultimate goal of training older adults is to reverse cognitive deficits and/or prevent further decline, it follows that the usefulness of various training protocols will be judged on the criteria of transfer. A few comprehensive taxonomies have been proposed to precisely appraise transfer effects (Barnett & Ceci, 2002; Haskell, 2001). One often-employed dichotomised concept distinguishes near transfer (proximal or primary outcome) from far transfer (distal or secondary outcome). Unfortunately, transfer (notably, far transfer) effects following training have often proven quite narrow or elusive (Noack et al., 2009), and improvements are often domain-specific (Li et al., 2011). However, as described previously, one particular type of training, VP training of attentional control, has shown relatively successful transfer of acquired skills, at least within the laboratory environment (Bherer et al. 2005; 2008; Kramer et al., 1995). Perhaps this approach of focusing training on a higher-order cognitive skill involved in multiple cognitive processes, such as attentional control, enhances the probability of transfer to novel tasks, as executive-type functions are solicited in a whole range of cognitive activities, including everyday problem-solving and decision-making.

1.4 Summary, Objectives and Hypotheses

1.4.1 Summary

Although it is well established that the neuropsychological profiles of individuals with AD and MCI are characterized by marked episodic memory deficit, there is extensive support for the presence of deficits in other domains of cognition. One of these major domains and the subject matter of the present thesis is working memory, an executive system of attentional control. The focus of our first experiment is to better understand WM deficits in AD and MCI by relying on complex span tasks, the most widely used measures of WM capacity. These WM span tasks have been explored by only very few studies and modalities in AD and, to our knowledge, not at all in MCI. Furthermore, as WM includes both processing and storage components, it is not known to what extent the well-documented retention deficit of AD contributes to WM performance. The stimulus order effect, which allows us to tease apart processing and storage within WM, has not been exploited in AD or in MCI. In summary, no study has yet attempted to assess WM performance and evaluate the contribution of forgetting in AD and MCI using complex span tasks. This data could provide critical insight into the impact of this progressive neurodegenerative disease on WM integrity and the precise nature of WM deficits in AD and its prodromal phase, MCI.

Since WM and attentional control deficits can underlie difficulties in everyday complex activities, it is a worthy endeavour to target them in cognitive intervention studies, the subject of our second and third experiments. In view of the fact that current pharmacological treatments are not effective in halting the progression of AD, the MCI phase appears to be a key period for providing such interventions. Computerized training protocols, notably variable-priority training, have shown promise in ameliorating attentional functions in healthy adults and thus, could benefit individuals with cognitive deficits, such as in MCI. In particular, dual task paradigms allow isolation of the executive component while appraising attention control functions, and could constitute the ideal training task to promote brain plasticity in persons at a high risk of developing dementia. No data has yet been reported concerning the training of attentional control using dual-tasks in MCI and, to our knowledge, no intervention studies have focused on MCI with executive deficits. Thus, examining the feasibility and efficacy of variable-priority training in MCI could offer valuable insight into the remaining cerebral plasticity of this population, as well as important clinical implications for individuals at a high risk of developing dementia.

1.4.2 First experiment

The objectives of the first experiment were: 1) to demonstrate WM impairment in performance of MCI on complex span tasks, which measure concurrent processing and storage, 2) to contrast this impairment to that found in AD, and 3) to appraise the contribution of forgetting with the stimulus order effect.

We hypothesized that participants with AD and MCI would be impaired on complex span tasks and that the MCI group would be situated midway between the AD group and healthy controls. In addition, AD, and perhaps MCI, were expected to be more sensitive to the duration constraints of the retention phase and, in other words, to present an exacerbated stimulus order effect. This was assessed with complex span tasks in which we manipulated storage requirements while keeping processing demands equivalent, as executed in Towse et al. (1998). To ensure that these effects were not material-specific, they were measured with Operation and Sentence complex span tasks. Finally, we considered the prognostic value of Sentence and Operation Span by comparing the performance of individuals with MCI who remained stable over the subsequent year or two to that of MCI who subsequently declined or progressed to AD.

1.4.3 Second experiment

The goal of the second study was to investigate the feasibility of a computerized cognitive training paradigm for attentional control in a convenience sample of healthy older individuals and those with MCI. This was achieved with a dual-task training paradigm in which task priority is manipulated (VP training). We predicted that the VP training intervention would significantly improve attentional control capacities for both older adults and MCI, as evaluated by the main outcome measure.

1.4.4 THIRD EXPERIMENT

Based on the positive findings of the second experiment, this study sought to implement a double-blind randomized controlled study of the same VP training paradigm, but with MCI selected for their executive deficits. This was deemed crucial because variability exists within the cognitive profiles of different MCI subtypes. We chose to target only individuals with executive deficits, in order to focus on those in need of improvement. Second, we compared VP training to an active control condition, in which task priority does not vary across trials (FP training) in order to rule out the possibility that improvement is simply due to practice effects. Training duration was also extended and a meta-cognition enhancement step was added, based on research showing the importance of awareness in cognitive interventions (Clare et al., 2004). This third experiment also aimed to verify if the benefits of training generalized to primary (experimental dual-task) and secondary (ecological dual-tasks; subjective divided attention capacities; perceived well-being) outcome measures.

We hypothesized that VP training would prove superior to FP training, given that the former necessitates a greater level of attentional control and that previous research has shown VP training to be superior in healthy older adults (Kramer et al., 1995). In addition, benefits were expected to transfer to the primary outcome measure and, perhaps, generalize to secondary outcome measures.

CHAPTER 2: EXPERIMENT 1

Working memory in Mild Cognitive Impairment and Alzheimer's disease: contribution of forgetting and predictive value of complex span tasks

Lyssa G. Gagnon [1,2], Sylvie Belleville [1,2]

[1] Research Centre, Institut universitaire de gériatrie de Montréal

[2] Dept of Psychology, University of Montreal

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Abstract

Objective: This study examines working memory (WM) in mild cognitive impairment (MCI) and Alzheimer's disease (AD). **Method**: Performances on Sentence Span and Operation Span were measured in individuals meeting criteria for MCI (n=20) and AD (n=16) as well as in healthy older adults (n=20). In addition, the effect of retention interval was assessed by manipulating the length of first and last items of trials (long-short versus short-long), as forgetting might contribute to impaired performance in AD and MCI. **Results**: Results show a Group effect ($p<.001$, $\eta^2=.47$): in both conditions and for both material types, WM span is lower in AD than in MCI ($p<.001$), which in turn is lower than in healthy aging ($p<.05$). An effect of retention interval on complex span was found for all groups ($p<.001$, $\eta^2=.57$), supporting a role for forgetting within WM. When computing a proportional interval effect ($p<.05$, $\eta^2=.12$), it was found that persons with AD were more sensitive to retention interval than healthy older adults ($p<.05$). Among persons with MCI, those who later showed significant clinical deterioration or progression to AD were more affected by retention interval ($p<.05$, $\eta^2=.28$) than those who remained stable. Furthermore, deficits in AD are associated with a higher proportion of intrusion errors, particularly those from the current trial ($p<.05$, $\eta^2=.15$), which could reflect inhibitory processes. **Conclusions**: Overall, these results indicate impaired WM in age-related disorders with a gradient between MCI and AD. Retention interval increases deficit in persons with AD. It also shows potential in predicting a negative prognosis in those with MCI.

Keywords: working memory, Mild Cognitive Impairment, Alzheimer's disease, complex span

Introduction

Working memory (WM) is classically conceived as a function that supports online manipulation and temporary storage of information (Baddeley & Hitch, 1974). Complex span tasks (Daneman & Carpenter, 1980), in which participants are required to process (read or solve) a series of problems, following which they must recall problem-final items in correct serial order, are the most widely used measures of WM. Very few studies have evaluated WM in persons meeting criteria for mild cognitive impairment (MCI) and, to our knowledge, none have yet utilized complex span tasks to do so. As evidence supports impaired WM and attentional control early on in Alzheimer's disease (AD) (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Belleville, Peretz and Malenfant, 1996; Belleville, Chertkow, & Gauthier, 2007; Perry & Hodges, 1999), it is essential to characterize the time course of this executive impairment by evaluating it in MCI, the very earliest phase of AD. Also imperative is to document these WM deficits with the complex span, a tool that is widely used in clinical settings. Finally, as forgetting forms the hallmark of AD, it is fundamental to determine its role within the WM deficits reported, as it might contribute to a new theoretical account of WM deficit in MCI and AD (Hitch, Towse, & Hutton, 2001). Accordingly, the objectives of the present original study are to demonstrate and characterize WM deficits on complex span tasks in MCI; compare them to those found in AD; investigate the impact of forgetting on the WM capacities of persons with AD and MCI; and verify the predictive value of these tasks for progression from MCI to AD. The resulting data should provide critical insight into the nature and progression of working memory impairment from healthy aging to degenerative disease.

Complex span tasks

Amongst the most commonly employed measures of WM capacity is the family of complex span tasks (see Conway et al., 2005 for a methodological review). Daneman and Carpenter (1980) were the first to propose a Sentence Span task in which participants read a series of sentences for meaning while maintaining each last word in memory. Sentence Span was defined as the maximum number of sentence-final words recalled.

A recent latent-variable analysis of these components in WM spans demonstrated unique and shared variance among processing and representational (storage) constructs in relationship with higher-order cognition (Unsworth, Redick, Heitz, Broadway, & Engle, 2009). Hence, complex span tasks entail concurrent processing and short-term storage demands, a key feature in the assessment of WM. In addition, individual differences research has shown that, over and beyond these domain-general processing and domain-specific representational systems, there emerges a control component which allows resistance to the interference between processing and storage (Jarrold & Towse, 2006). This potentially executive component is differentially referred to as executive controlled attention (Kane et al. 2004), inhibitory attentionnal control (Hascher, Lustig & Zacks, 2007), or central executive (Baddeley, 1986). This control component elicited in complex span tasks (Jarrold & Towse, 2006) helps in explaining data showing that complex span tasks constitute highly valid and reliable predictors of higher-order cognitive functions (Engle & Kane, 2004). Hence, and contrary to traditional simple span tasks (e.g. Digit Span, Daneman & Carpenter, 1980), Sentence Span, for example, is highly correlated with a range of complex cognitive activities, including language comprehension (Daneman & Merikle, 1996), abstract reasoning (Engle, Tuholski, Laughlin, & Conway, 1999) and general fluid intelligence (Engle, 2001).

WM in MCI and AD

Working memory impairments are well documented in AD (for reviews, see Bherer, Belleville, & Hudon, 2004; Collette & Van der Linden, 2005; Morris, 1994). For example, individuals with AD are impaired on the Brown-Peterson paradigm, in which consonant trigrams are retained in memory for up to 30 seconds while a distracter task is executed (Belleville, Peretz, & Malenfant, 1996; Morris, 1986; Kalpouzos et al. (2005); Sebastian, Menor, & Elosua, 2006). Persons with AD are equally impaired on the alpha-span task, which evaluates active manipulation of information by comparing recall of items in their alphabetical order to serial word recall (Baddeley, Della Sala, & Spinnler, 1991; Belleville, Rouleau, Van der Linden, & Collette, 2003). Additionally, AD produces deficits in non-verbal working memory, both visuo-spatial (Toepper, Beblo, Thomas, & Driessen, 2008; Vecchi, Saveriano & Paciaroni, 1998) and auditory (White & Murphy, 1998). Very few studies have previously explored complex spans in AD. Rochon, Waters & Caplan (2000) found impaired performance on the Dot Span task, a visual WM span that involves counting series of dots and reporting the totals. Maylor, Smith, Della Sala, & Logie (2002) as well as Waters & Caplan (2002) also demonstrated WM deficits in AD on Sentence Span.

In general terms, persons with MCI (Petersen, 2003) have a cognitive impairment but fail to meet criteria for dementia. The amnestic MCI subtype refers to those with a memory impairment (amnestic *single* domain MCI), as well as to those with impairments in memory and other cognitive domains such as language, executive function and visuospatial skills (amnestic *multiple* domain MCI). The non-amnestic subtype refers to those with impairments in domains other than memory. A large proportion of MCI will progress to dementia and, among the different clinical subtypes proposed by Petersen, the amnestic single and multiple domain subtypes are those more likely to progress to AD (Petersen et al. 2001, 2004). MCI persons might stand in a prodromal stage of the disease (Gauthier et al. 2006) and therefore they should present evidence, albeit milder than in AD, of WM deficits. Few studies have examined WM deficit in detail in persons with MCI. Belleville et al. (2007) have demonstrated attentional control and WM impairments in persons with MCI and showed that the impairment predicts future progression to AD. Although no studies to date have attempted to evaluate WM spans in MCI, Rosen, Bergeson, Putnam, Harwell, & Sunderland (2002) have compared performance on Operation Span — a WM task similar to Sentence Span which uses arithmetic operations as stimuli — between two groups of middle-aged individuals who differed with respect to genetic risk for AD based on their apolipoprotein E (APOE) genotype. Despite displaying no symptoms of dementia or cognitive deficits, ε4 carriers demonstrated significantly lower WM spans - but not simple spans - than ε4 non-carriers. Consequently, the authors suggest this task may hold promise for early detection of degenerative disease, a proposition which we shall attempt to substantiate.

Forgetting in Complex Span tasks

An additional chief and innovative component of this study was to assess the contribution of forgetting in complex span performance of persons with AD and MCI. A number of studies have attempted to shed light on how the processing component of the complex span task disrupts storage of items in memory and causes forgetting. The classic stimulus order effect (Hitch et al. 2001) refers to the fact that when cognitive load is kept constant, span scores are higher when retention intervals, as determined by duration of processing, are shorter. This well-known effect indicates that forgetting contributes to performance on complex span tasks. Towse, Hitch and Hutton showed this by investigating the role of temporal factors in working memory spans of children and adults (Towse, Hitch, & Hutton, 1998, 2000). They adapted the standard Sentence Span task in such a way that overall task difficulty (load) remained constant while retention duration varied. This was accomplished by varying the length of the stimuli to be processed. By using mixed lists of short and long sentences, they produced two matched conditions: a long-final condition - in which a short sentence is in first position in the list while a long sentence ends the list - and its opposite: a short-final-condition (see Figure 1). This paradigm ensures that total duration and processing load are equivalent between conditions. Yet, because storage demands begin after the first sentence is processed, to-be-remembered words are held in memory longer when the first sentence is short, rather than long. Hence, retention interval is shorter in the short-final than in the long-final condition. Results from Towse and collaborators showed that spans were indeed higher in the short-final than long-final condition. This effect is attributed to the influence of forgetting over time, and thus will be used in an innovative fashion to measure the effect of forgetting on the WM deficit of AD and MCI.

Forgetting in MCI and AD

The issue of forgetting over time is of utmost importance in the context of AD. Indeed, it has been frequently shown that to-be-remembered information is rapidly lost in AD, as measured by significantly impaired delayed free recall tasks (Carlesimo, Fadda, Bonci, & Caltagirone, 1993; Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Furthermore, studies with AD patients consistently show impaired primacy with relatively preserved recency (Bayley et al. 2000; Burkart, Heun, & Benkert, 1998; Carlesimo, Fadda, Sabbadini, & Caltagirone, 1996; Gainotti & Marra, 1994). As memory items encoded at an earlier time are subject to greater forgetting than those presented more recently in time, this is supportive of impaired forgetting in AD. Increased forgetting would also be coherent with findings of impairment in MCI and AD patients on the longer intervals of the Brown-Peterson task (Belleville et al. 2007; 1996).

Consequently, evidence suggests that forgetting may play a critical role in determining the magnitude and nature of the WM deficit in AD, and as well as in MCI. However, to date, no study has yet attempted to assess whether forgetting contributes to WM in this population. This highlights the importance of examining the contribution of forgetting over time in WM span tasks and the implications for theories of WM deficit in degenerative disease such as AD. Accordingly, the goals of the present study were 1) to demonstrate WM deficits in performance on complex span tasks in MCI, 2) to compare them to those found in AD, and 3) to evaluate the contribution of forgetting with the stimulus order effect. We hypothesized that participants with AD and MCI would be impaired on complex span tasks and that the impairment would be larger in the former group than in the latter. In addition, AD, and perhaps MCI, were expected to be more sensitive to the duration constraints of the storage phase and, in other words, to present an exacerbated stimulus order effect. This was assessed with complex span tasks in which we manipulated retention requirements while keeping processing demands equivalent, as executed in Towse et al. (1998) (see Figure 1). As previously described, mixed lists of items varying in length constituted two matching conditions which differed only in duration of storage. Thus, if forgetting is greater in AD and MCI, their span should be proportionately lower than that of controls in the condition in which retention intervals are longer (long-final).

To ensure that these effects were not material-specific, they were measured with Operation and Sentence complex span tasks. We also looked at serial position effect in view of the fact that impaired forgetting should have a more detrimental effect on the primacy portion of the serial position curve than on the recency portion. As error type typically reflects the nature of the memory process, we also examined error types. Error types were examined for Sentence Span only, as responses on Operation Span come from a limited set of stimuli (numbers zero through nine). We hypothesized that AD, and perhaps MCI, would show primacy deficits but preserved recency. As for types of errors, we expected that lower spans would be mostly due to omissions, if memory mechanisms were in play, but to intrusions, if they were due to reduced resistance to interference. Finally, we investigated the prognostic value of Sentence and Operation Span by comparing the performance of individuals with MCI who remained stable over the subsequent year or two to that of MCI who subsequently declined or progressed to AD.

Method

Participants

In total, 60 elderly adults participated in the study: twenty patients had a diagnosis of AD, twenty persons met criteria for MCI and twenty were healthy older adults. However, four participants with AD were excluded from the study, either due to their incapacity to maintain task goal or to floor effects. Consequently, sixteen individuals with AD were retained for analyses. Their characteristics and clinical results are presented in Table I.

Both AD and MCI patients were recruited from memory clinics in Montreal. They were diagnosed by experienced geriatricians or neurologists on the basis of an extensive clinical and neuropsychological assessment. Persons with AD met NINCDS-ADRDA research criteria for probable AD (McKhann et al. 1984) and the DSM-IV clinical criteria for dementia of the Alzheimer type (APA, 1994). As for adults with MCI, they all met criteria for amnestic single domain (n=13) or multiple-domain MCI (n=7) (Gauthier et al. 2006). Accordingly, all participants with MCI: (a) had a memory complaint (b) performed at least 1.5 standard deviation below age normative values on the standardized memory test (single domain amestic MCI) or on memory and other cognitive tasks (multiple domain amnestic MCI) (c) scored above the cut-off for dementia on the MMSE, relative to age and educational level (d) did not have problems with functional independence due to their cognitive deficits (e) did not fulfill criteria for dementia. Normal older adults were recruited from a list of volunteers who had previously agreed to be contacted in order to participate in research projects such as the present study. They were evaluated with the same clinical and neuropsychological batteries as the patients and performed within normal range.

All participants were characterized with the following standardized neuropsychological battery. Dementia severity and global functioning were assessed using the MMSE (Folstein, Folstein, & McHugh, 1975) and the Mattis dementia rating scale (MDSR: Mattis, 1976). Memory was measured with a word free and cued recall test (RL/RI16 free and cued recall task: Van der Linden et al. 2004). Executive functions (Stroop-Victoria: Regard, 1981), constructional praxis (copy of the Rey figure: Rey, 1959) and language (Boston Naming Test: Kaplan, Goodglass, & Weintraub, 1983) were also evaluated.

All participants were French-speaking and possessed normal or corrected-to-normal hearing and vision. They were all community-dwelling, living in the Montreal area. Exclusion criteria consisted of alcoholism, general anaesthesia in the past 6 months, presence or history of severe psychiatric disorders, neurological disorders, cerebrovascular disorders or stroke, and any form of dementia other than AD.

MCI Decliners/Converters

Participants with MCI were followed yearly for clinical assessments. It was possible to determine the severity of cognitive impairment, between one and two years later, for 19 out of the 20 MCI participants. They were classified as having remained stable (MCI-stable), declined significantly (MCI-decliners) or progressed to AD (MCI-converters). MCI-converters were identified as meeting criteria for dementia on the basis of aforementioned clinical criteria. MCI-decliners did not yet meet criteria for dementia at follow-up, but showed a decrease in performance greater than one SD of the control group on at least two of the neuropsychological measures used for clinical description. This quantitative criterion was used for performance decline given that it is more than one order of magnitude greater than what is reported as the yearly decline amongst healthy older adults (approximately 0.02 SD for memory and 0.08 SD for processing speed; Bennett et al. (2002). According to these criteria, a subgroup of 7 MCI-decliners/converters was identified and compared to the group of 12 MCI-stable. Among the seven MCI-decliners/converters, four initially met criteria for multiple-domain MCI, whereas three met criteria for single domain MCI. Furthermore, among the initial group of multiple-domain MCI (n=7), three remained stable (about 43%), two significantly declined (about 29%), and two others progressed to AD (about 29%). As for the initial group of single-domain MCI (n=13), nine stayed stable (about 69%), two individuals declined (about 15%), and one progressed to AD (about 8%). It is important to note that at baseline, MCI-stable and MCI-decliners/converters groups did not statistically differ in terms of age, educational level and performance on clinical measures.

Material

Stimuli were constructed in the same manner as those contained in Towse, Hamilton, Graham, & Hutton (2000) and Hutton, Towse, & Hitch (1997)[2].

Sentence Span stimuli

Stimuli items for the Sentence Span task consisted of 162 French sentences in which the final word was missing. The strong context of the sentence made this word highly predetermined. Pilot data ensured that these sentences were correctly completed by most participants. They were constructed to be of one of three lengths: short (4-5 words), intermediate (7-8 words) and long (10-12 words). For example, an intermediate item was ‘‘I eat my dinner with a knife and…’’ where the expected response was ‘‘fork’’. Each short item was matched to a long item which differed by extra words that maintained the constraint on the missing word. For example, the short sentence ‘‘The dog wagged its…’’ was matched to the longer sentence ‘‘The dog was very happy and so it wagged its…’’. Both sentences had the same answer (‘‘tail’’). Thus both retention interval conditions produced the same words to be remembered, but necessitated different processing times due to sentence length. To avoid undue processing, syntactic complexity was kept to a minimum. Final words were always concrete monosyllable words. Frequency was controlled by distributing equally frequent words throughout matching trials of each condition.

Operation Span stimuli

Stimuli items for the Operation Span task consisted of 162 arithmetic operations requiring addition or subtraction of single-digit numbers. Similarly to Sentence Span, three possible forms existed: short, intermediate and long. Short operation lengths contained two terms (i.e. $A \pm B = \ldots$); intermediate items included three terms (i.e. $A \pm B \pm C = \ldots$); long items included 4 terms (i.e. $A \pm B \pm C \pm D = \ldots$). In all cases, A was a one-digit number from 1 to 9 and B, C, and D were either 1 or 0. Answers were always single-digit numbers. Examples include ‘‘7 + 1 = …’’ for short items and ‘‘5 + 1 + 1 + 1= …’’ for long stimuli. As in Sentence Span, each short operation was matched to a long operation which differed by extra numbers, but still generated the same answer to be remembered. In the above examples, both operations produced the same answer (‘‘8’’). As a result, the same numbers were to be remembered in both retention interval conditions, but they differed in processing time due to operation length.

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[2] We would like to thank John N. Towse for providing us with these Technical Reports.

Procedure

The method employed was that of Towse et al. (1998) and Cowan, Day, Saults, Keller & Johnson (1992). The items (sentences or operations) were presented one after another on a computer screen. A practice session consisting of three trials containing two items each preceded both sentence and Operation Span tasks. Practice trials were sometimes repeated in order to ensure full grasp of task rules. More often than not, this was necessary for the AD participants. Testing began at span level of two. Three trials were provided at each span level. For each trial, the participant was instructed to silently read the incomplete stimulus item (operation or sentence) and say aloud the answer (number or word) to each item as rapidly as possible. As soon as a response was given, the experimenter would press a button to cue the next sentence or operation. Unexpected or wrong answers were noted, although participants were instructed not to correct themselves or give alternate answers. At the end of the trial, a green dot appeared on-screen which signaled to the participant to recall aloud answers to all items in the correct serial order (i.e. the memory set). Participants were instructed to say ‘‘pass’’ when a word was forgotten, in order to maintain the correct serial positions of subsequent recalled items. If the first two trials at any given level were perfectly performed, the third trial was omitted. Every time the participant correctly remembered all their answers on any two trials out of a possible three, they proceeded to the next span level in which the number of items in the trial was increased by one. Testing either proceeded until span level of seven or was terminated when more than one out of three trials at a given span level was incorrectly recalled.

There were two conditions in each span task: short-final and long-final, as was shown in Figure 2. In the short-final condition, the first item was always long, the last item was short, and the intervening items (if needed) were of intermediate length. In the long-final condition, the opposite was true, that is the first item was always short, whereas the last item was long. Short- and long-final items were matched, in the sense that they produced the same answers. Accordingly, combining items of intermediate length with matched short- and long-final items produced equivalent memory sets, i.e. sets of answers (numbers/words) to be remembered. Since the set of answers held in memory during the span task was equivalent for both conditions (short- or long-final), differences in performance between conditions could not be attributed to memory content. Rather, it was the retention interval, as determined by item length, which varied between conditions: long items contained 5 to 8 more words, or 2 more arithmetic terms, than short items. Both Sentence and Operation Span tasks were performed by every participant. Order of material condition (operation and sentence) was counter-balanced. Within each task, order of retention interval condition (short-final vs long-final) was also counter-balanced across participants.

Scoring

Span scores

The correction criterion was correspondence between supplied item and recalled item, in the correct position (Towse et al. 1998). Therefore, if a participant made a mistake in calculating the sum of an arithmetic operation but correctly recalled the supplied number at the end of the trial, it was counted as a correct response. To increase the sensitivity of the measure, a modified scoring method was used to compute span scores (Conway et al. 2005). First, a span level was determined. It corresponded to the length of the longest series for which recall was accurate on at least two out of three trials. Subsequently, the proportion of correct items for trials above span level was added to the span level achieved. For example, a participant achieving span level 4 and correctly recalling 6 individual items out of a possible 15 on the 3 trials of span level 5 would obtain the following span score : 3+(6/15)=3.4.

Cost scores

In light of the fact that working memory capacities, and thus baseline performance on span tasks, differ greatly between groups, a cost score was computed to determine the magnitude of the stimulus order effect. The following equation was used to compute a stimulus order effect “cost score” for each participant: (short-final – long-final) / short final * 100. A group effect on that score would indicate that groups differ in their sensitivity to the retention interval.

Primacy and recency effects

We examined serial position effects by calculating a primacy score on the last span level attempted. This was determined by totaling the number of sets in which the first item of the set was omitted during recall. Only the first item was employed for primacy in view of the small set sizes typical of WM tasks (2-7). Recency scores were computed in a similar manner using the final word of each set.

Errors in Sentence Span

Whereas Operation Span responses came from a limited set of stimuli (numbers zero through nine), answers in Sentence Span were all unique and thus afforded us the possibility to examine more closely the nature of errors committed. The type and frequency of verbal recall errors produced can yield additional information about the mechanisms involved in forgetting (Henson, 1998). Typically, errors are of two types: items errors and Order errors. While the latter consist of correct words placed in the incorrect serial position, item errors include Omissions and Intrusions (Unsworth & Engle, 2007b). Intrusions were of particular interest in this task, for they reflect interference from previously presented material, and thus were further subdivided into words intrusions from a previous trial (Previous), or words intrusions from the current trial (Current). The percentage of other types of intrusion errors that were Repetitions, Phonological Intrusions or Extraneous Intrusions (unrelated to any trial) was negligible and such errors were not included in analyses.

Results

Clinical data and preliminary analyses

Participants were first compared on their socio-demographic and clinical characteristics[3] using ANOVAs with Group (three levels: healthy older adults, MCI, AD) as a between-subject factor. Results are presented in Table I. All groups were comparable on age, $F(2,53) = 1.26$, $p > .05$ and educational level, $F(2,53) = 1.17$, $p > .05$. As expected, the only significant difference between individuals with MCI and controls was on the immediate and delayed recall of the RL/RI16 recall task, which confirms memory impairment in MCI. As for participants with AD, they differed from healthy controls and from MCI on measures of global functioning (MMSE, MDRS) as well as on measures of memory (immediate and delayed recall of the RL/RI16 recall task) and inhibition (Stroop). They also differed from controls on a measure of language (Boston Naming).

Complex span performance

None of the participants performed at ceiling level on the tasks. Span scores are displayed in Figure 3. A mixed analysis of variance (ANOVA) was computed on absolute complex span scores. The within-subject factors included were Material (Sentence Span; Operation Span) and Retention interval (short-final; long-final), and the between-subject factor was Group (healthy older adults; MCI; AD). The ANOVA indicated a significant effect of Material, $F(1,53) = 75.26$, $p < .001$, $\eta^2=.59$, an effect of Retention interval, $F(1,53) = 70.39$, $p < .001$, $\eta^2=.57$, and an effect of Group $F(2,53) = 23.48$, $p < .001$, $\eta^2=.47$. None of the interactions reached significance, including the Group x Material, $F(2, 53)= 1.37$, N.S., $\eta^2=.05$, Group x Retention, $F(2, 53)= 0.51$, N.S., $\eta^2=.02$, Material x Retention, $F(1, 53)= 2.62$, N.S., $\eta^2=.05$, and Group x Material x Retention, $F(2, 53)= 1.18$, N.S.,

[3] Clinical data on a few tests (Stroop, Rey Figure, Boston Naming) were missing for one or two participants per group.

η^2=.04, interaction effects. Inspection of Figure 3 indicates that performance on Operation Span was higher than that on Sentence Span. In addition, scores were higher in the short-final condition in which retention interval is shorter. As for the main group effect, inspection of Figure 3 and Tukey post-hoc mean comparisons indicated that WM performance of individuals with AD was significantly worse than that of aged controls ($p < .001$) as well as that of persons with MCI ($p < .001$), which in turn was lower that that of controls ($p < .05$). Since Material did not interact with other variables (Group or Retention interval), there was no need to further analyze the data for Operation and Sentence spans separately.

Stimulus Order cost score

The stimulus order “cost score” reflects the percentage of loss incurred by increasing the retention interval (i.e. long-final condition relative to the short-final condition). A mixed ANOVA, with Material (Sentence Span; Operation Span) as a within-subject factor and Group (healthy older adults; MCI; AD) as a between-subject factor, revealed a main effect of Group only, $F(2,53) = 3.48$, $p < .05$, η^2=.12. Post-hoc Tukey mean comparisons indicated that only the performance of persons with AD (mean: 13.08, S.E.: 2.34) was significantly different ($p<.05$) from that of healthy older adults (mean: 5.93, S.E.: 2.48). Performance of persons with MCI was not statistically different (mean: 10.53, S.E.: 2.44). Therefore, it appears that persons with AD are more vulnerable to retention interval manipulation than normal aged controls.

Serial Position Effects in WM

The effect of serial position was assessed by computing the number of omissions on the first and last items of the longest span level attempted. Results are displayed in Table II. Given that the range of scores was small (0-3), non-parametric analyses were employed. For Sentence Span, a Kruskall-Wallis test indicated Group differences solely in primacy scores, for both short-final, $H(2, N=56) = 12.31$, $p= .002$, and long-final, $H(2, N = 56) = 17.50$, $p = .000$, conditions. To determine which group(s) differed, pairwise comparisons were computed on primacy scores for both intervals. For the short-final condition, a Mann-Whitney test indicated that individuals with AD omitted more first items, and thus had diminished primacy, as compared to healthy controls, $U = 62.5$, $p = .001$. Primacy of persons with MCI also differed from that of controls, $U = 130.0$, $p =.03$, and was not different from that found in AD ($p =.10$). As for the long-final condition, in which retention interval was augmented, a Mann-Whitney test indicated that individuals with AD omitted more first items than did both MCI, $U = 51.5$, $p = .000$, and healthy older adults, $U = 51.5$, $p = .000$, who in turn did not differ one from another ($p = 1.0$). As for Operation Span, a Kruskall-Wallis test indicated Group differences solely in primacy scores for the long-final condition only, H(3, N=56) = 9.36, $p = .009$. A Mann-Whitney test indicated that individuals with AD omitted more first items than did older controls, U = 77.5, $p = .003$. Primacy of MCI did not differ from that of AD ($p = .089$) or older adults ($p = 1.0$). No group differences on recency were found.

Error analysis

Percentages of Omissions, Order errors as well as Previous and Current intrusions were computed for each participant from total number of items attempted in that condition. Results are displayed in Table III. Separate two-way ANOVA's, with Retention interval (short-final; long-final) as a within-subject factor and Group as a between-subject factor (healthy controls; MCI; AD) were performed on dependant variables. Analysis of the data showed no differences between groups for Omissions and Order errors. For Previous Intrusions, only a significant main effect of Interval, $F(1,53) = 6.44$, $p < .05$, $\eta^2=.11$, was found. All participants made more Previous Intrusions in the long-final condition (mean = 6.63; SD = 9.3) than in the short-final condition (mean = 3.18; SD = 5.4). For current Intrusions, a significant main effect of Group, $F(2,53) = 4.68$, $p < .05$, $\eta^2=.15$, was found. Post-hoc mean comparisons indicated that persons with AD produced a larger percentage of current intrusion errors than did persons with MCI ($p < .05$) and controls ($p < .05$).

Examination of MCI Decliners/Converters

In order to investigate longitudinal evolution amongst the group of MCI, complex span performance and stimulus order effects from MCI who remained stable were compared to those of decliners/converters MCI. An ANOVA using Material (Sentence Span; Operation Span) and Retention interval (short-final; long-final) as within-subject factors and Group (MCI-stable; MCI-decliners/converters) as a between-subject factor revealed a significant Group by Retention interval interaction, $F(1,17) = 6.50$, $p < .05$, $\eta^2=.28$, which indicated that MCI-decliners/converters were not as successful as MCI-stable in the long-final condition only. This finding was confirmed by analyses of stimulus order effect cost scores which isolate retention interval manipulation. Indeed, a mixed ANOVA with Material (Sentence Span; Operation Span) as a within-subject factor and Group (MCI-stable; MCI-decliners/converters) as a between-subject factor revealed a main effect of Group only, $F(1,17) = 5.07$, $p < .05$, $\eta^2=.23$, indicating higher cost scores for MCI-decliners/converters (mean: 16.51, S.E.:3.55) than for MCI-stable (mean: 7.68, S.E.: 3.18). This confirms that their performance was affected to a greater extent by retention interval manipulation.

Discussion

The goal of the present study was to quantify and characterize WM deficits in performance on complex span tasks in MCI and compare them to those found in normal aging and AD. In addition, we wished to evaluate the impact of degenerative disease on forgetting within WM and, conversely, verify if this measure possessed predictive value for progression to AD. Results establish impaired WM in Sentence and Operation Span tasks for both patient groups as compared to healthy older adults. Moreover, WM impairment in MCI was situated midway between that of controls and that of AD. This is the first time that deficits of this type have been shown for MCI. This important finding not only confirms the prodromal status of MCI, but is also consistent with well documented attentional control and working memory impairments in AD (Bherer et al. 2004; Collette & Van der Linden, 2005; Morris, 1994; Belleville et al, 2001), which are present quite early in the disease (Baddeley et al. 2001).

The other important goal of our study was to investigate the role of forgetting within WM. Thus, the lengths of first and last trial items were manipulated in order to create two matched conditions differing only in retention interval, or duration of storage. Clearly, our results support a role for forgetting in WM across both complex span tasks. All groups were sensitive to the interval length manipulation with worst performance obtained when the last item was longer and, thus, retention duration increased. Hence, the classical stimulus order effect was confirmed here in normal aging, MCI and AD.

Retention duration showed a unique contribution to the magnitude of deficit in AD and MCI. As expected, AD individuals as well as MCI decliners were shown to be significantly more sensitive to the duration constraints of the storage phase. Our interpretation is that forgetting plays a greater role for AD than for normal aging in the Sentence and Operation Span deficits observed. Note that this result pertaining to forgetting was found when examining retention cost scores that take into account baseline performance. Our initial analysis of raw data failed to find a Group x Retention interaction. We believe this is because it did not take into account baseline performance levels, which are significantly lower in MCI and AD. For instance, one less word recalled following retention interval manipulation carries more weight in a span level of three than in a span level of six. It might also be due to the fact that the initial analysis included decliners and non decliners, the latter not showing as much of a forgetting effect, thereby contributing to variability in the analysis.

The effect forgetting was further confirmed by examining serial position effects. Individuals with AD recalled significantly less primacy items than did healthy older adults in Sentence Span (both conditions) and Operation Span (long-final condition). As for individuals with MCI, they displayed impaired primacy in Sentence Span (short-final condition). These results are the first to establish impaired primacy in MCI and concur with those of Rosen et al. (2002) who demonstrated primacy deficits in Operation Span (using words as to-be-remembered items) for ε4 carriers at higher risk for AD. Our results concur with Buschke et al. (2006) who proposed that, as WM deficits documented in AD disrupt the ability to simultaneously encode and process information, rehearsal of earlier words is hampered by interference of subsequent words and thus, the primacy effect is abolished. As expected, no group differences in recency were found.

Of remarkable interest is the found prognostic value of Sentence and Operation Span tasks. Indeed, both the Group by Interval interaction and the cost scores on the WM span tasks allowed us to distinguish persons with MCI who declined or progressed to AD from those who remained stable over the following one to two years. It could be interpreted that MCI decliners and converters are most affected by retention interval manipulation because they are closer to conversion to dementia, and that our paradigm is sufficiently sensitive to detect this subtle impairment. Alternatively, it is well known that not all persons with MCI will show subsequent cognitive decline, and manipulating the retention interval may allow us to distinguish among MCI those who will not progress to dementia. The fact that these groups were initially undistinguishable on clinical neuropsychological measures makes this novel finding all the more striking. Precise clinical characterization, along with specific biomarkers, are becoming vital for profiling subgroups of MCI at highest risk for progression to AD, given that trials for potential disease modifying agents are multiplying and necessitate early identification of patients.

In addition, as it has been suggested that attentional control and WM deficits underlie difficulties with everyday activities present in AD (Perry & Hodges, 1999), it is crucial to develop clinical tools that can precisely evaluate and identify early impairments. Our results further support a key idea: complex span tasks, already widely utilized in clinical settings, can be employed in individuals with MCI in order to distinguish them from healthy aging, particularly when it includes long interval durations.

The exact nature of forgetting within WM span tasks is subject to great debate. Some have proposed the passage of time to be the main factor in play (Hitch et al. 2001). Others have proposed that duration of processing does not play a direct role (Berman, Jonides, & Lewis, 2009; Lewandowsky & Oberauer, 2009). Instead, the stimulus order effect could be explained by greater interference from previous items on the list, since the long-final condition exposes the participant to more words during the retention interval, despite interval length being equal (Saito & Miyake, 2004). Consequently, forgetting would be the result of representation-based interference. Although not the main objective of this study, analysis of errors produced during the recall phase of Sentence Span may shed light on the mechanism involved in forgetting. Our data reproduces results by Unsworth & Engle (2007b) who report that, in complex span, Omissions errors are the most frequent, followed by Order errors and Intrusions. Concerning persons with AD, significantly more Current than Previous Intrusion errors were produced in both conditions. This could reflect the "executive" control component elicited in complex span tasks (Jarrold & Towse, 2006), sometimes referred to as executive controlled attention (Kane et al. 2004), inhibitory attentional control (Hascher, Lustig & Zacks, 2007), or the central executive (Baddeley, 1986). For example, in an attentional control view, individuals with AD may have deficits in strategic control at encoding sentence-final words and inhibiting non-sentence-final words. This concurs with recent data from Castel, Balota, & McCabe (2009) who demonstrated impaired value-directed remembering in AD. Our data could also be interpreted in line with inhibitory control accounts (Hascher et al. 2007), which posit that WM spans measure inhibitory aspects of attention regulation, such as the ability to "delete" irrelevant items. We interpret these irrelevant items to be those of the current trial (current intrusion errors), since previous trial items will most likely have already been forgotten by persons with AD, given their episodic memory impairment.

A strong methodological aspect of this study was to ensure that active maintenance of the to-be-remembered stimuli was efficiently blocked (Saito, Jarrold, & Riby, 2009). This was accomplished by making participants process items and generate final to-be-remembered answers, rather than simply read them as was done in previous studies of Sentence Span in AD (Maylor et al. 2002; Waters & Caplan, 2002). Furthermore, material was counter-balanced across conditions to ensure that any differences found were related to our experimental manipulation. Conversely, it is important to address some limitations in this study. First, reaction times were not recorded for completion of sentences and arithmetic operations. It is possible that severity of cognitive impairment may have caused longer delays in responding, consequently elongating retention interval. It could be argued that the task was thus more difficult for AD participants. However, as conditions were matched, particular response characteristics relating to timing would have been present in both the short-final and long-final conditions, thus canceling out their effect. Similarly, we concede that it is not possible to tell if sentence and operation stimuli were perfectly matched in terms of length and solving time. However, as mentioned above, any differences would be present in both the short-final and long-final conditions of each task version. Furthermore, the lack of a Material x Retention interval interaction effect is comforting and suggests that that both tasks reacted similarly to the manipulation. An additional limitation of this study concerns the complexity of task instructions. Individuals with AD had more difficulty integrating the steps and objective of Sentence and Operation Span tasks. In consequence, we cannot posit this type of task to be of much use in severely impaired AD individuals. Nonetheless, our main goal of establishing it as a tool sensitive to MCI was attained.

In sum, our overall results fit with the idea of progressive working memory (WM) impairment from healthy aging to degenerative disease. Indeed, WM in complex span tasks is impaired in MCI and, to an even greater extent, in AD. Forgetting plays an important, often overlooked role within WM and is exacerbated by degenerative disease such as AD and MCI. Forgetting appears to play an even greater role in MCI who will show subsequent cognitive decline and progress to AD, relative to MCI remaining stable over a 1 to 2 year period. These group differences need to be replicated on an individual basis, as sensitivity to retention interval may hold promise as a useful marker in distinguishing persons with MCI who will decline or progress to AD from those who remain stable in the short-term.

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Table I

Mean scores for age, education, and clinical measures in healthy controls, MCI and AD participants (S.D. in parentheses)

	Controls (n=20)	MCI (n=20)	AD (n=16)
Age	69.90 (7.93)	73.40 (6.89)	71.63 (7.27)
Education	14.70 (2.87)	15.90 (4.10)	14.19 (3.35)
MDRS	138.90 (2.95)	135.55 (5.03)	120.31 (10.04)**
MMSE	28.80 (1.06)	27.95 (1.50)	23.94 (2.29)**
Stroop color (time for plate 3)	27.00 (7.0)	33.11 (11.94)	61.94 (40.37)**
Rey Figure copy (score)	31.60 (3.16)	30.98 (3.07)	29.68 (5.12)
RL/RI-16 immediate recall	9.16 (1.61)	6.50 (1.99)**	2.81 (1.42)**
RL/RI-16 delayed free recall	12.67 (1.81)	9.60 (3.23)**	3.31 (3.30)**
Boston naming	13.16 (1.30)	12.58 (1.64)	11.46 (2.26)*

Compared to healthy controls: * $p < 0.05$. ** $p < 0.01$.

Figure 1

Illustration of how retention interval was manipulated. The boxes represent sentences or arithmetic operations and their differing sizes illustrate the different sentence/operation lengths (short, intermediate, long). In the short-final condition (a), the longer item is presented first and the shorter item is presented last. As storage of memory items begins after completion of the first item, retention interval is shorter. In the long-final condition (b), the shorter item is presented first and the longer one last. As a result, condition (b) involves additional retention time (represented by dotted line) even though overall task length is equivalent to that of condition (a).

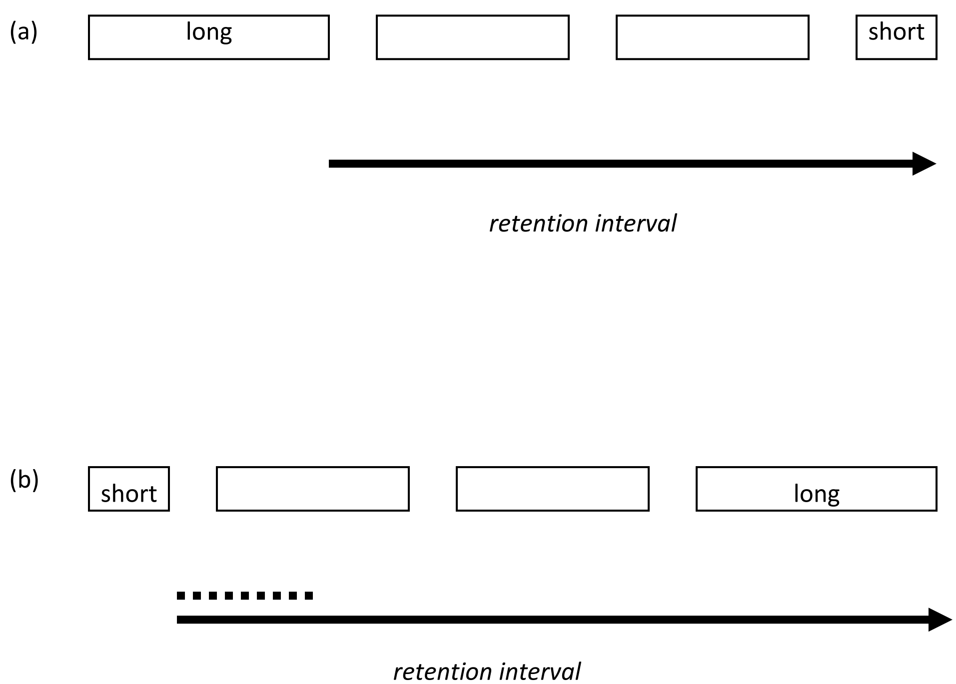

Figure 2

Examples of Sentence Span trials. Notice that the same memory set is used in long-final condition for participant 1 as well as in short-final condition for participant 2, and vice versa. Final items are shown in italic and are produced by the participant. Thus, memory set 1 would be: *tail, wand, ring, hands*, while memory set 2 would be: *fork, cavities, asleep, grass*.

Participant 1

1) Long-final condition

The dog wagged its….. *tail*

The magician waved his magic….. *wand*

I think I can hear the telephone….. *ring*

At the end of the show, she stood up and clapped her….. *hands*

2) Short-final condition

I sit down and eat my dinner with a knife and….. *fork*

Brushing your teeth prevents….. *cavities*

She was tired and so she fell….. *asleep*

A cow eats….. *grass*

Participant 2

1) Short-final condition

The dog was very happy and so it wagged its….. *tail*

The magician waved his magic…. *wand*

I think I can hear the telephone…. *ring*

She clapped her….. *hands*

2) Long-final condition

I eat with a knife and….. *fork*

Brushing your teeth prevents….. *cavities*

She was tired and so she fell….. *asleep*

The cow trotted across the pasture and ate some….. *grass*

Figure 3

Mean span scores for long-final and short-final conditions in AD, MCI and healthy controls (HC) in Sentence Span (first graph) and Operation Span (second graph) conditions. (Error bars represent S.E.)

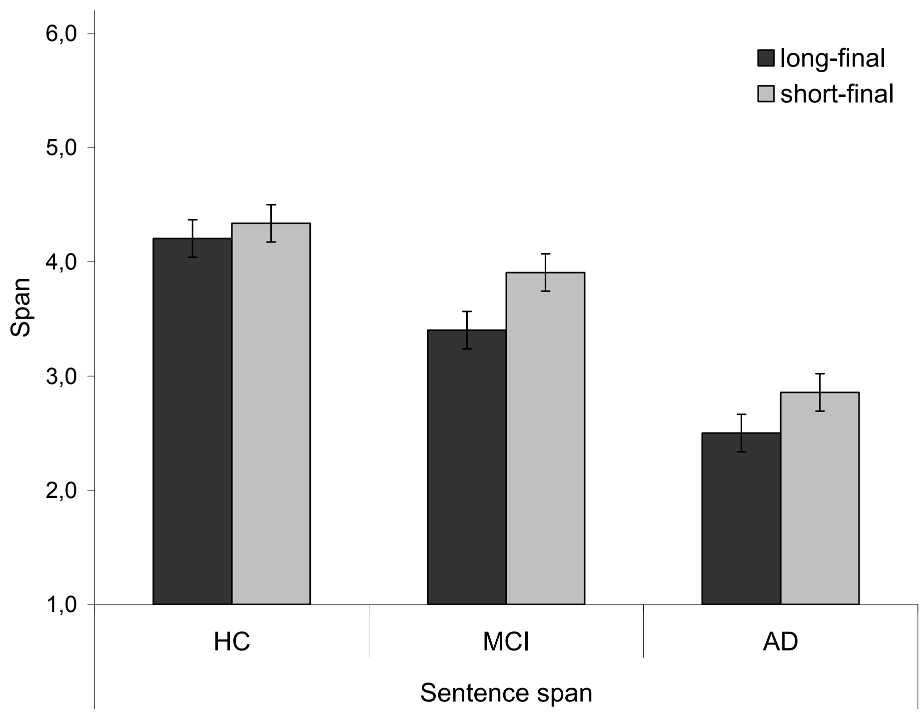

Figure 3 (Continued)

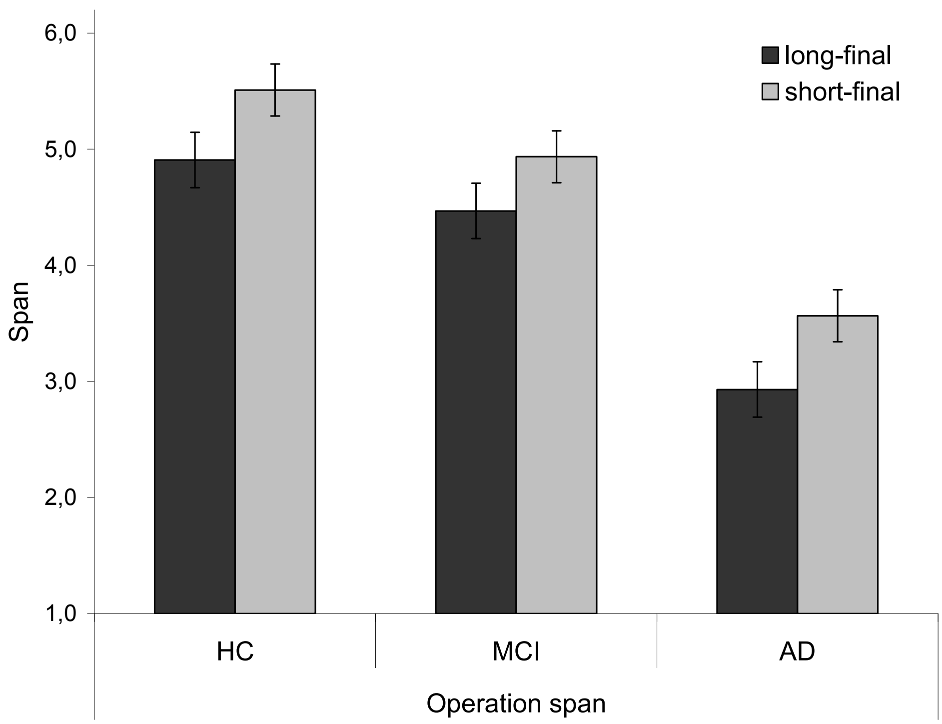

Table II

Primacy (number of first items omitted) (S.D. in parentheses)

		Controls	MCI	AD
Sentence Span	Short-final	0.25 (.44)	0.80 (.89)*	1.38 (1.1)**
	Long-final	0.85 (.67)	0.85 (.67)	2.06 (.92)**
Operation Span	Short-final	0.20 (.41)	0.25 (.44)	0.44 (.51)
	Long-final	0.25 (.55)	0.55 (.69)	1.00 (.82)**

Different from controls at * $p < 0.05$ ** $p < 0.01$

Table III

Proportion of error types in Sentence Span (S.D. in parentheses)

		Controls	MCI	AD
Omissions	Short-final	20.22 (13.6)	20.80 (9.8)	31.59 (20.4)
	Long-final	22.62 (13.3)	19.50 (10.6)	25.35 (21.3)
Order errors	Short-final	10.50 (12.3)	13.43 (14.0)	19.62 (21.5)
	Long-final	13.92 (14.0)	14.67 (14.2)	13.19 (15.6)
Intrusions	Short-final	3.38 (5.2)	3.24 (6.3)	2.86 (4.5)
(Previous)	Long-final	5.03 (7.2)	7.56 (10.2)	7.47 (10.7)
Intrusions	Short-final	1.17 (2.9)	1.31 (3.3)	3.65 (6.8)*
(Current)	Long-final	2.69 (4.5)	2.42 (4.7)	6.42 (7.0)*

Different from controls and MCI at * $p < 0.05$.

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CHAPTER 3: EXPERIMENT 2

Training of attentional control in mild cognitive impairment

Lyssa G. Gagnon [1,2], Sylvie Belleville [1,2]

[1] Research Center, Institut universitaire de gériatrie de Montréal

[2] Centre de recherche en neuropsychologie et cognition, Dept of Psychology, University of Montreal

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Abstract

This study evaluated the efficacy of a cognitive intervention for attentional control in older adults with mild cognitive impairment (MCI). Sixteen individuals with MCI and 9 healthy controls were trained with a dual-task paradigm comprised of a visual detection task and a visual alpha-arithmetic judgement task. A variable-priority training strategy was employed, in which participants had to manage their attentional control by varying the proportion of attentional resources allocated to each task. The outcome measure was a dual-task similar to that used in training. Analyses combining accuracy scores and reaction times revealed a significant effect of intervention on one of the two tasks involved (visual detection task). Moreover, there was a positive effect of intervention on the combined *mu* score, which represents the overall dual task decrement of the divided attention measure. There were no group differences. These results indicate that older persons with MCI can improve their attentional control when provided with appropriate cognitive training, despite the fact that they suffer from memory deficits. This suggests preserved plasticity of attentional capacities in persons at risk of developing dementia.

Introduction

For several decades, cognitive intervention has been attempted in populations with cognitive deficits resulting from traumatic brain injury. These studies have often proven successful, notably strategy training for remediation of mild memory impairment and post acute attention deficits, as well as interventions for functional communication deficits (Cicerone et al., 2000; Cicerone et al., 2005). A large number of studies have also shown that normal older adults can improve their cognition when provided with cognitive training (Ball et al., 2002; Stigsdotter & Backman, 1989; Yesavage, Sheikh, Friedman, & Tanke, 1990). Recent efforts have been directed toward developing programs to improve cognitive skills in persons with mild cognitive impairment (MCI), a population at risk of developing dementia. Our goal was to assess whether persons with MCI can improve their attentional capacities following cognitive training to the same extent as healthy older adults.

In recent years, efforts have been deployed to identify a “pre-clinical phase” of AD, particularly for intervention purposes. Although it cannot yet be said with absolute certainty that a prodromal stage of AD has been recognized, researchers agree on the existence of a cognitive syndrome which puts those affected at high-risk of progressing to AD or other types of dementia (Gauthier *et al.*, 2006). The terminology employed for this risk state for dementia is mild cognitive impairment (Petersen et al., 1999). The diagnostic criteria for MCI include a memory complaint, impaired memory function on neuropsychological tests, preserved general cognitive function, intact activities of daily living and the absence of dementia (Petersen, 2003; Petersen et al., 2001). Epidemiological studies suggest that the prevalence of MCI is around 5% of the general population. Incidence is estimated as 8 to 58 new cases per 1000 persons per year (Ritchie, 2004), with around 15% per year converting from MCI to dementia (Gauthier et al., 2006; Petersen et al., 2001). Thus, the concept of MCI is valid and useful in clinical as well as in research settings for the early identification of older adults at risk of progressing to dementia. It is also hypothesized that intervening in the MCI phase could possibly prevent or slow down future cognitive impairment associated with AD (Petersen et al., 1997).

Attentional control deficits are present quite early in AD (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Perry & Hodges, 1999) and it has been suggested that they underlie difficulties with everyday activities present in AD (Perry & Hodges, 1999). Individuals with AD perform consistently worse than controls on tasks that involve concurrent storage and processing (Belleville, Peretz, & Malenfant, 1996; Belleville, Rouleau & Van der Linden, 2003; Morris, 1986). They are also impaired on dual task paradigms in which two tasks are first executed separately (focused attention condition) and then simultaneously (divided attention condition) (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Colette, Van der Linden, & Salmon, 1999; Greene, Hodges, & Baddeley, 1995; Grober & Sliwinski, 1991; Logie, Cocchini, Delia Sala, & Baddeley, 2004; Perry, Watson, & Hodges, 2000). Very few studies have investigated attentional control in persons with MCI. In one study (Dannhauser et al., 2005), older adults with MCI were evaluated on a divided attention task involving concurrent visual and auditory detection tasks. Although they did not differ from controls on accuracy scores, they recorded longer reaction times and had attenuated prefrontal activation. Two other studies (Missonnier et al., 2005; Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006) showed normal performance on 2-back and 3-back working memory tasks in individuals with MCI. A third study (Belleville, Chertkow, & Gauthier, in revision) found that divided attention in older persons with MCI was impaired compared to controls, as measured by the capacity to retain a short series of items while carrying out a simple addition task in the Brown-Peterson paradigm. In summary, there is clear evidence that attentional control is affected in early AD, notably on dual tasks. On the other hand, findings regarding dual-tasking capacities in MCI are inconsistent. Furthermore, it is not known yet if persons with MCI can improve their attentional capacities when provided with training.

In healthy older adults, there is ample evidence to suggest that divided attention capacities can be improved, if provided with appropriate training. McDowd (1986) first demonstrated that extended practice could improve divided attention capacities for dual tasking in older adults. Moreover, a large, multi-centre, randomized controlled trial of three distinct training interventions (memory, reasoning, and speed of processing) was conducted with older adults by Ball et al. (2002). Participants were trained on speed of processing with a computerized divided attention program using visual search with distractors. The vast majority of these individuals significantly improved following training, and these cognitive effects were mostly maintained at the 2-year follow-up, especially for those who had received booster training the previous year. Kramer, Larish, & Strayer (1995) conducted a study in which they investigated the effects of variable priority training on attentional control using a dual task involving a visual monitoring task and an alphabet-arithmetic task. The variable priority training consisted in emphasizing one task more or less than the other across different blocks. The objective of this type of training is to enhance control of attentional abilities and augment dual task coordination skills. Results showed that the pre-intervention dual task decrement was significantly reduced in both aged and young participants following variable priority training. Thus, training can improve attentional control in healthy older adults when provided with appropriate conditions, such as variable priority training.

Very few cognitive intervention studies have been conducted with the MCI population, and most concern memory. One study (Rapp, Brenes, & Marsh, 2002) found that a multi-faceted memory enhancement training did not improve objective memory performance in MCI, compared to matched controls. Another study has shown that episodic memory can be significantly ameliorated following multifactorial cognitive intervention (Belleville et al., 2006). Although there have been no interventions specifically looking at divided attention in MCI, one pilot study found that a computerized cognitive training protocol focusing mainly on short- and long-term memory, but also on processing speed, showed promise in older individuals with age-associated memory impairment (analogous to MCI) (Gunther, Schafer, Holzner, & Kemmler, 2003). In a final study, a global, cognitive-motor stimulation program (including attention training) was developed by Olazarán et al. (2004) for a mixed-patient group of MCI and mild-to-moderate AD. Following the randomized single-blind intervention, trained participants conserved their general cognitive performance levels, while the control group deteriorated. However, there is no way of knowing whether the intervention produced a specific effect on attentional capacities. In summary, there is some indication that cognitive intervention can reduce objective neuropsychological deficits observed in individuals with MCI. In spite of their memory impairment, results suggest that this population might still learn and benefit from training. However, there is clearly a need for additional supportive data, given that some studies reported negative findings. Furthermore, although attentional capacities can be improved upon training in healthy older adults, no study has directly measured if this is equally attainable in MCI.

Thus, the aim of this experiment was to evaluate the efficacy of a cognitive intervention for attentional control in MCI. We propose to use variable-priority training, based on Kramer et al.'s (1995) positive findings with healthy older adults. In line with some of the most recent classification of MCI (Gauthier et al., 2006; Artero, Petersen, Touchon, & Ritchie, 2006), we selected individuals with MCI with memory deficits (single domain amnestic MCI) as well as those with memory deficits and additional impairment (multiple domain amnestic MCI). Our goal was to assess if persons with MCI would benefit from attentional training in spite of having impaired memory. Moreover, performance in MCI was compared to that of healthy older adults, who also received the same attentional training, in order to measure if they benefited to the same extent. We expected that training would bring significant improvement in performance on our divided attention outcome measure and that this improvement would be present in both MCI and healthy older adults.

Method

Participants

Twenty five older persons, sixteen individuals with MCI and nine healthy older adults participated in the study. Their characteristics are presented in Table IV. Older persons with MCI were recruited from memory clinics in Montreal and diagnosed by experienced geriatricians or neurologists. They met criteria for amnestic multiple domain or for amnestic single domain MCI (Gauthier et al, 2006). Accordingly, all participants with MCI: (a) had a memory complaint (b) performed at least 1.5 standard deviation below age normative values on the a memory test (c) scored above the cut-off for dementia on the MMSE, relative to age and educational level (d) did <u>not</u> have problems with functional independence due to their cognitive deficits (e) did <u>not</u> fulfill criteria for dementia. They underwent an extensive medical, neurological, neuroradiological and clinical assessment to identify exclusion factors, support diagnosis and characterize cognitive functioning. The clinical assessment included the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976), an abbreviated neuropsychological assessment scale; the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), a brief evaluation of cognitive status; the Geriatric Depression Scale (GDS) (Yesavage, 1988), a tool to measure depression in the elderly; and the Hachinski Scale (Hachinski, Iliff, Zilka, & et, 1975), a measure of vascular risk factors. As for the neuropsychological battery, it included tests of episodic memory: immediate and delayed story recall of the BEM (Signoret, 1991) as well as free and cued recall, French version (Van der Linden et al., 2004); a test of executive function: Stroop-Victoria (Regard, 1981); a test of visuo-constructional praxia: Rey Figure Copy (Rey, 1959) and, finally, a test of language: DO-80 naming test (Deloche & Hannequin, 1997). All individuals with MCI completed at least one of the two memory tests. Given the differences between referral sources and their routine clinical investigations, not all individuals completed all tests. In theses cases, the sample size is indicated in parenthesis in Table IV.

Normal older adults were recruited from a list of volunteers who had previously agreed to be contacted in order to participate in research projects such as the present study. They were evaluated with a subset of the clinical and neuropsychological batteries (MMSE, MDRS, BEM memory test, GDS, Hachinski scale) on which they performed within normal range. Healthy older adults were comparable to persons with MCI on age, $t\ (23) = 1.26$, $p > .05$ and educational level, $t\ (23) = -0.03$, $p > .05$. The only significant difference between individuals with MCI and controls was on the immediate, $t\ (19) = -3.06$, $p < .01$, and delayed story recall of the BEM, $t\ (19) = -3.48$, $p < .01$, which confirms memory impairment in MCI.

All participants were Francophone with normal or corrected-to-normal hearing and vision. Exclusion criteria consisted of alcoholism; general anaesthesia in the past 6 months; presence or history of severe psychiatric disorders, neurological disorders, cerebrovascular disorders or stroke. Furthermore, we excluded patients with Alzheimer's disease (NINCDS-ADRDA research criteria: (McKhann et al., 1984), as well as patients with other forms of dementia. Participants were part of a larger group enrolled in a multifactorial cognitive program offered at the Institut Universitaire de Gériatrie de Montréal that targeted memory functions in addition to attention (see Belleville et al., 2006). The data presented here pertain to the attentional training portion of the program.

Pre/post divided attention measure

The pre/post divided attention measure involved performing a visual alpha-arithmetic judgment task and a visual detection task, in either a focused attention or a divided attention condition. The task was computerized on Psyscope (Cohen, MacWhinney, Flatt, & Provost, 1993) and run on a Macintosh computer with a 14 inch screen. In the visual judgement task completed under focused attention, red and black rectangles appeared serially at the bottom of the screen for 500 milliseconds each. Participants were instructed to press the space bar upon seeing a red rectangle, as quickly and accurately as possible. Twenty rectangles were presented per block, eight of which were targets. They were allowed 750 ms to respond. In the alpha-arithmetic task completed under focused attention, equations (additions/subtractions) containing letters (A through L) and numbers (1 through 9) appeared in the middle of the screen (ex: A+2=B). Participants were asked to judge the veracity of the equation and give their response by pressing one of two keys: “x” with the left index for false equations and “/” with the right index for true equations. For example, the following equation: “A+2=B” was false, whereas the equation “G-1=F” was true. Each equation was presented individually and stayed on-screen until participants responded. No feedback was given. Twenty equations were presented per block, half of which were false and half of which were correct. Correct responses and reaction times were recorded for both tasks.

In the divided attention condition, alpha-arithmetic and visual detection tasks were completed simultaneously with the same general parameters as in focused attention conditions. Thus, equations were presented in the center of the screen and rectangles were simultaneously presented in the bottom of the screen. Participants were asked to detect the red rectangles while solving the equations, as quickly and accurately as possible. Responses to the equations were provided by pressing the same keys as in the focused condition and responses to the rectangles were provided by pressing the space bar with either thumb. Each block contained 20 equations.

Forty percent of the rectangles were targets, with a total of 20 to 100 rectangles, depending on the participant's speed.

There were two blocks per condition and task. The order of the blocks for the focused and divided attention conditions followed an ABBA design, starting with equation solving and rectangle detection in focused attention. This was done to reduce the potential impact of practice or fatigue effects. Correct responses and reaction times were recorded for both tasks. Pre-intervention testing was conducted approximately two weeks prior to the first training session. Post-intervention testing was conducted about four weeks following the last training session. These delays allowed us to reduce potential impact of practice on the equations. Experimenters administering pre/post measures were different from those conducting the intervention.

Training task

The dual-task employed in training consisted of the same visual detection task, combined with a similar version of the visual alpha-arithmetic judgment task. In order to reduce the potential impact of mere familiarity with computing items in the tested portion of the alphabet, different sets of letters were used in training and pre-post assessment. Consequently, for training, letters M through Z were employed in the alpha-arithmetic task. Dual-task training was performed under variable priority conditions across a series of blocks. Before each block, participants were informed how much attention to give each on-screen task. Three different priority proportions existed: 80-20, 50-50, 20-80. Accordingly, priority 20-80 informed participants that they had to give only 20% of their attention to the visual detection task and 80% to the alpha-arithmetic task. For priority 50-50, participants had to allocate equal amounts of attention to each task. In priority 80-20, participants were asked to give 80% of their attention to the visual detection task and 20% to the alpha-arithmetic task. These instructions were presented on-screen and read aloud to the participants. Subsequently, a rectangle-shaped box divided into two coloured parts was presented at the bottom of the screen in order to represent the requested priority proportion visually. Following each block, feedback was given on-screen in a histogram, indicating the level of performance on each task compared to baseline performance. In this manner, participants were informed as to whether they had attained the expected priority proportion or not. They could therefore adjust the attentional resources allocated to each individual task in order to better achieve the next requested priority proportion. At the beginning of the session, participants completed each task under the focused attention condition to establish a baseline level from which expected performance levels corresponding to priority proportions were computed. They subsequently completed nine blocks under divided attention, 3 for each priority proportion. The order of the three priority proportion blocks was randomized across participants and session. There were two training sessions, lasting approximately 30-45 minutes each, with a one-week interval.

Results

To assess the effects of the intervention on the pre/post divided attention measures, separate mixed ANOVAs were first used on the following dependent variables: proportion of correct responses, RT and proportion of false alarms on the visual detection task, and proportion of correct responses and RT on the alpha-arithmetic task. These ANOVAs included two within-subject factors: Attention (focused; divided) and Intervention (pre-intervention; post-intervention) as well as one between-subject factor: Group (MCI; control). Greenhouse-Geisser corrections were applied when appropriate.

Visual detection task

Accuracy data an RT on the visual detection task are displayed in Figure 4. Analysis of the accuracy data showed an effect of Attention, $F(1, 23) = 16.81$, $MSE = 1882.00$, $p < .001$, an effect of Intervention, $F(1, 23) = 23.35$, $MSE = 196.54$, $p < .001$, as well as a significant Attention by Intervention interaction $F(1, 23) = 32.91$, $MSE = 294.93$, $p < .001$. Inspection of Figure 4 and tests of mean comparisons indicated that the interaction was due to participants improving their accuracy level from pre to post intervention in divided attention, t (24) = -5.39, $p < .001$, but not in focused attention t (24) = 1.78, $p = .09$. Analysis of the RT data indicated a significant effect of Attention, $F(1, 23) = 147.62$, $MSE = 898\ 602.09$, $p < .001$, a significant effect of Intervention, $F(1, 23) = 6.80$, $MSE = 16\ 318.81$, $p < .05$, as well as a significant Attention x Intervention interaction $F(1, 23) = 7.41$, $MSE = 12\ 929.70$, $p < .05$. Inspection of Figure 4 and tests of mean comparisons indicated that the interaction was due to participants improving upon their speed from pre to post intervention in divided attention, t (24) = 2.67, $p = .01$, but not in focused attention, t (24) = 0.66, $p = .52$. None of the other effects or interactions reached significance.

The average number of false alarms in pre-intervention was 0.24 ($SD = 0.39$) and 0.56 ($SD = 0.78$), for focused and divided attention respectively. In post-intervention, average number of false alarms was 0.14 (SD = 0.23) and 0.34 (SD = 0.55), for focused and divided attention respectively. Analysis of the false alarms data indicated no significant Attention, $F(1, 23) = 3.40$, $MSE = 1.32$, Intervention, $F(1, 23) = 3.0$, $MSE = 0.60$, or Group effects, $F<1$, and no interactions, $F<1$ in all cases.

Alpha-Arithmetic task

Figure 5 shows the number of correct responses on the alpha-arithmetic task. The ANOVA on the number of correct responses indicated a significant effect of Attention, $F(1, 23) = 15.63$, $MSE = 1069.84$, $p = .001$, but no effect of Intervention $F(1, 23) = 1.16$, $MSE = 175.56$, or Group, $F(1, 23) = 1.35$, $MSE = 586.97$, and no interaction, $F<1$ in all cases. Inspection of Figure 5 indicates that participants were more accurate in focused attention than in divided attention, but they did not improve from pre to post intervention. When analyzing the effect of training on the RT variable, there was a main effect of Attention, $F(1, 23) = 25.87$, $MSE = 22\,696\,702.01$, $p < .001$, as well as a main effect of Intervention, $F(1, 23) = 27.16$, $MSE = 21\,540\,320.51$, $p < .001$. Neither the main Group effect, nor any of the interactions reached significance, F<1 in all cases. Inspection of Figure 5 indicates that participants improved upon their speed from pre to post intervention. However, it also shows that participants were faster in the divided attention condition than in the focused attention condition, most likely indicating a speed-accuracy trade-off on this task. We will address this issue in the following set of analyses.

Combined scores

In a second set of analyses, we wished to control for possible trade-off effects between speed and accuracy. Consequently, scores combining correct responses (CR) and RT were computed for each task (alpha-arithmetic and visual detection) separately. To control for scale effects, performance on pre and post-intervention were combined to obtain a dual task decrement. These dual task decrement scores represent the proportional loss (PL) of performance in the divided attention condition as compared to the focused attention condition. The following formula was used:

$$PL = [(1 - CR_{divided} / CR_{focused}) + (1 - RT_{focused} / RT_{divided})] / 2.$$

A score of 0 indicates no dual task decrement, whereas a score > 0 implies impaired performance with the decrement increasing in size as the value of PL approaches 1.

The mean PL score on the visual detection task was 0.23 ($SD = 0.02$) at pre-intervention, which is significantly different from zero (95% confidence interval: 0.20 to 0.26). At post-intervention, the PL score on the visual detection task was 0.17 ($SD = 0.02$), which is also significantly different from zero (95% confidence interval: 0.13 to 0.20). PL scores were analyzed separately for each task using mixed ANOVAs that included Intervention (pre-intervention; post-intervention) as a within-subject factor and Group (MCI; control) as a between-subject factor. Analysis of the decrement score on the visual detection task yielded a significant main effect of Intervention, $F(1, 23) = 32.07$, $MSE =$

0.05, $p < .001$, but no effect of Group, $F<1$ and no interaction, $F(1, 23) = 1.67$, $MSE = 0.002$. Thus PL is significantly diminished post intervention, indicating that the training reduced the dual task decrement on the visual detection task. The effect size (eta) was 0.58, which is considered medium in magnitude. As for the alpha-arithmetic task, the mean pre intervention PL score was -0.13 (SD = 0.03), which is significantly different from zero (95% confidence interval: -0.19 to -0.06), and the mean post intervention PL score was -0.18 (SD = 0.05), which is significantly different from zero (95% confidence interval: -0.28 to -0.07). The ANOVA indicated no effect of Intervention, $F(1, 23) = 1.25$, $MSE = 0.03$, and no Group effect, $F<1$. In other words, once accuracy and speed levels are combined into a decrement score, there is no difference in performance between the pre and post alpha-arithmetic portion of the divided attention measure.

Finally, an overall *mu* score combining dual task decrement scores from both alpha-numeric and visual detection tasks was calculated, in order to control for possible trade-off effects between the two tasks (Baddeley et al., 1997):

$$mu = [\ PL_{\text{alpha-arithmetic}} + PL_{\text{visual detection}}\ ] / 2.$$

As with the individual PL scores, a *mu* score of 0 indicates the absence of any dual task decrement. The mean pre intervention *mu* score was 0.05 (SD = 0.02), which is small but significantly different from zero (95% confidence interval: 0.01 to 0.09), whereas the mean post intervention *mu* score was -0.004 (SD = 0.03), which does not significantly differ from zero (95% confidence interval: -0.06 to 0.05). A mixed ANOVA with Intervention (pre-intervention; post-intervention) as a within-subject factor and Group (MCI; control) as a between-subject factor was used to analyze *mu* scores. Results showed a main Intervention effect, $F(1, 23) = 5.02$, $MSE = 0.04$, $p < .05$, but no effect of Group and no interaction, $F<1$ in both cases. The effect size (eta) for the overall intervention effect was 0.18 (small). Consequently, when all variables (correct responses and RT for both tasks) are combined into an overall score, there is a small but significant effect of intervention in the expected direction: training eliminated the overall dual task decrement for both groups, as measured by the pre/post divided attention task.

Discussion

The objective of this study was to assess the efficacy of a cognitive intervention, specifically, variable priority training, on attentional control in individuals with MCI. We wished to verify if attentional training was successful in improving the attentional capacities of this population. This also allowed us to address whether persons with MCI had conserved plasticity of these functions and could still learn in spite of their documented memory impairment. Overall, results show a positive effect of the intervention on one of the two tasks composing the divided attention outcome measure (the visual detection task), as well as on the overall dual task decrement score. Prior to discussing the implications of this positive training effect, we will first address the pattern of performance exhibited by persons with MCI and healthy controls on the divided attention paradigm at pre-intervention. This permits us to verify the validity of our paradigm as a divided attention task, and the pattern of performance in MCI relative to controls prior to training.

Divided attention effects

Our task consisted of an alpha-arithmetic task and a visual detection task. The tasks were completed either by themselves, in the focused attention condition; or were combined, in the divided attention condition. Participants' results at pre-test indicate the presence of a dual task decrement on the visual detection task. This is shown by a marked decrease of performance in the divided relative to focused attention condition on both RT and correct responses. Interpretation of performance on the alpha-arithmetic task is more problematic, because the data suggest a speed-accuracy trade-off. Participants were less accurate - but faster - in completing the equation in divided attention than in focused attention. It seems that having to divide their attention between two tasks motivated participants to respond more quickly to the equations, thus generally producing more errors. This may reflect the high difficulty level of the equation task in the divided attention condition. To circumvent the problem of such a speed-accuracy trade off influencing our interpretation, proportional loss (PL) scores, which represent the dual task decrement once accuracy and RT are combined, were calculated. PL scores obtained in pre intervention testing are different from zero on both the visual detection and alpha-arithmetic tasks. This suggests that, overall, the task did indeed produce a divided attention cost, even on the alpha-arithmetic component of the task, in spite of the presence of a speed-accuracy trade-off. The *mu* score, which combines dual task decrement scores from both alpha-arithmetic and visual detection tasks, though small, is also different from zero. This confirms that divided attention capacities are solicited during execution of the divided attention measure when performance of both tasks is taken into account.

Interestingly, our results are not supportive of a divided attention deficit in persons with MCI. The magnitude of the dual task decrement does not differ between groups, which suggests that divided attention capacities (as measured by our paradigm) are not impaired in older persons with MCI relative to older adults without MCI. This is consistent with one study of dual tasking in minimal AD (MMSE range: 24-30), but is inconsistent with other studies of divided attention (Dannhauser et al.,

2005) or working memory (Belleville, Chertkow, & Gauthier, 2007; Missonnier et al., 2005) in MCI. One could argue that the ceiling effect on the accuracy levels of the visual detection task was masking divided attention impairment in the MCI group. Another possible explanation is that individuals with MCI included in this study are still high functioning, since they do not differ from controls on the MMSE and MDRS. In fact, in those individuals with MCI who go on to develop AD, a continuum of neuropsychological deficits has been proposed. Episodic memory deficits would be accompanied by impairments in executive and attentional control as the disease progresses (Belleville et al., 2007). Accordingly, our MCI participants may not yet be at a stage in which divided attention deficits are present. Finally, we must acknowledge that our task may have lacked sensitivity to the presence of a very mild divided attention deficit.

Effects of intervention

The variable priority training employed in this intervention was successful in ameliorating attentional control in healthy older adults. This confirms the results reported in a previous study using a similar type of training (Kramer et al., 1995). Most importantly, a positive effect of training was found in the MCI group, and the magnitude of the effect was equivalent to that obtained in healthy controls, as evidenced by the absence of an interaction involving Group and Intervention. Analysis of individual dependent variables in the divided attention condition indicates that participants improved not only their speed of processing on the alpha-arithmetic task, but also their accuracy and speed on the visual detection task. Given the absence of a control group not receiving training, we cannot completely rule out the possibility that improvement on the pre/post divided attention measure is not caused by mere drill or practice effects due to numerous task repetitions. Indeed, participants also improved their speed of processing on the alpha-arithmetic task in the focused attention condition. However, we propose that this is unlikely. First, there was no such training effect on correct responses and RT in the focused attention condition of the visual detection task. In addition, different sets of letters were used in training and in pre-post measurement, which leads us to believe that the observed intervention effect is not simply due to practice effects. From a theoretical point of view, this result supports the idea of a specific, trainable component for dual task coordination independent of the capacities involved in the individual tasks (Logie et al., 2004).

To eliminate the possibility that improvement in divided attention is solely due to improvement in focused attention, proportional loss (PL) scores were computed. Not only do they combine accuracy and RT, they compare performance of divided to that of focused attention to give a measure of the dual task decrement. The PL score for the visual detection task is improved post intervention. However, the PL score does not show significant improvement on the alpha-arithmetic task. This reflects the fact that, through training, participants learned to vary their performance on the visual detection task, but kept accuracy levels for the alpha-arithmetic task relatively constant, which is consistent with the data reported by Kramer et al. (1995). We hypothesize that this is because the alpha-arithmetic task is most easily verbalized, more varied, and naturally occupies more attentional resources than the visual detection task. Finally, a positive effect of training was found on the overall *mu* score combining both tasks. This effect was relatively small in magnitude, perhaps due to the effect of intervention only being significant on one of the PL scores. Hence, it seems that variable-priority training influenced divided attention by permitting participants to improve upon visual detection. Another explanation for the small effect size is that the number of participants was relatively modest, which likely limited power. Greater effect sizes might have been found with more participants. Still, variable-priority training succeeded in significantly reducing the overall dual task decrement score.

There were no Group differences on the variables or analysis that targeted intervention effects. Consequently, not only did the MCI group not differ from controls in terms of divided attention capacities, but they were able to benefit just as much from the intervention, despite their memory deficits. These encouraging results suggest that older persons with MCI possess a certain level of preserved cognitive plasticity. Our study was restricted to individuals with amnestic or multiple domain plus memory MCI. It is most likely that a subgroup of MCI whose main impairments concern executive functioning and attentional capacities would benefit to an even greater degree from this type of training. This remains to be empirically verified.

Limitations

One limitation of the present study is that the effect of intervention is reported on a dual task very similar to the one used during training. Our intervention’s primary focus was to verify if individuals with MCI were able to benefit from attentional training with specific material, despite their memory impairment. We are thus unable to address the subject of generalization to tasks of daily life. Future studies could include, in pre and post test sessions, ecological tasks of divided attention (Baddeley et al., 2001), as well as measures of mood and quality of life, such as self- and spousal-assessment questionnaires, including measures of divided attention capacities in everyday activities (for example, the Divided Attention Questionnaire: DAQ, Tun & Wingfield, 1995). There are other questions left unanswered by this study. The training was limited to two sessions. While it is encouraging that such a short-term intervention produced significant results, it is unclear whether further training would have yielded even more positive benefits, for example on the alpha-arithmetic task. Indeed, Kramer et al. (1995) found slower acquisition of attentional control skills in the first two sessions of their intervention for adults receiving variable-priority training, as compared to another type of training. A related issue is whether such a relatively short intervention can produce lasting effects. Our data indicate that the effect can be durable for at least a few weeks. Attention training has been shown to have long term benefits that remain over at least two years in healthy older adults (Ball et al., 2002), but this question has not yet been addressed in persons with MCI.

Conclusion

Our results are encouraging and suggest that older persons with MCI can improve their attentional control when given relatively short variable-priority training, despite the fact that they suffer from memory deficits. This also indicates preserved plasticity of attentional capacities in persons at risk of developing dementia. Our results concur with those of other intervention studies showing positive effects of training on cognitive function in MCI (Belleville et al., 2006; Gunther et al., 2003; Olazarán et al., 2004) and extend them to divided attention. Further studies should address issues of generalization and long term effects of cognitive training in MCI. In view of the fact that a significant proportion of this population goes on to develop AD, it would be a worthy endeavour to examine whether cognitive intervention could possibly prevent or slow down future cognitive impairment associated with dementia.

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Table IV

Mean scores for age, education, and cognitive measures in controls and MCI participants (S.D. in parentheses)

	Controls (n=9)	MCI (n=16)
Age	65.89 (6.01)	62.12 (7.74)
Education	14.56 (3.47)	14.50 (5.30)
MDRS	142.11 (1.69)	139.93 (3.05)
MMSE	29.00 (0.76)	28.94 (1.24)
Hachinsky	1.50 (1.80) (n=6)	2.09 (2.50) (n=11)
GDS (/5)	0.25 (0.70) (n=8)	1.25 (1.20) (n=12)
BEM immediate recall	10.06 (1.20)	8.04 (1.17) (n=12) **
BEM delayed recall	9.67 (1.40)	7.13 (1.80) (n=12) **
Stroop color (time for plate 3)		26.22 (11.50) (n=15)
Rey Figure copy (score)		30.63 (3.20) (n=15)
RL/RI-16 free recall trial		10.75 (2.90) (n=8)
RL/RI-16 delayed free recall		12.25 (3.10) (n=8)
DO-80		78.29 (1.90) (n=14)

Note. * $p < 0.05$. ** $p < 0.01$.

Figure 4

Mean percent accuracy (left scale) and RT (right scale) for visual detection task in both groups, pre and post intervention.

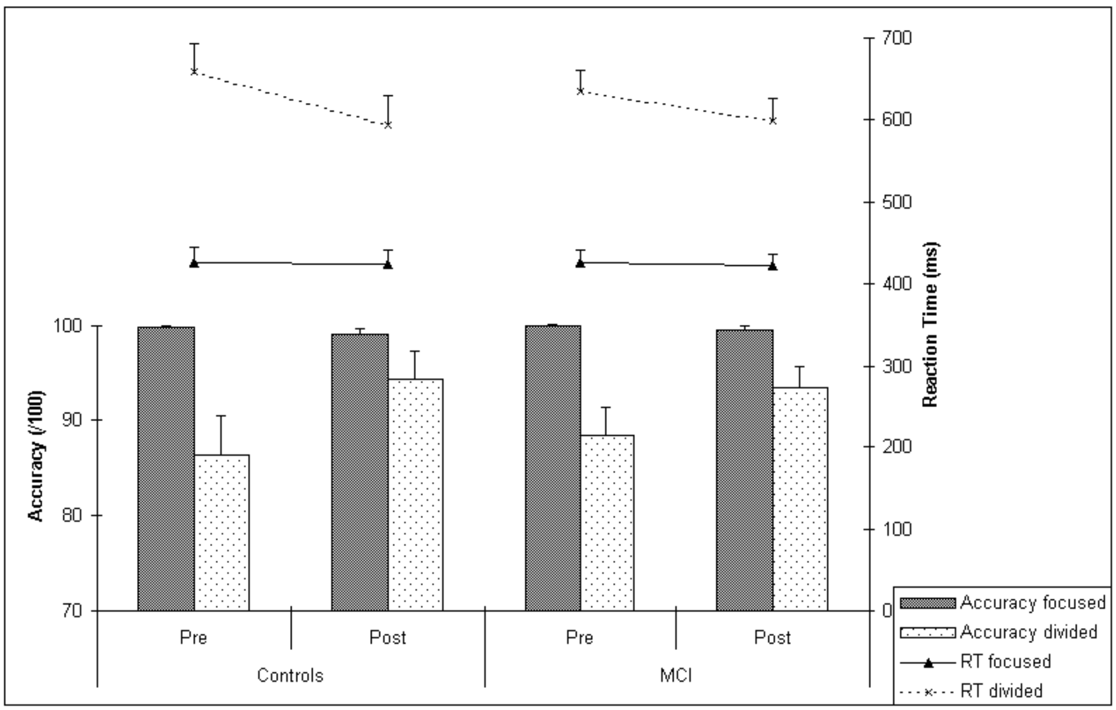
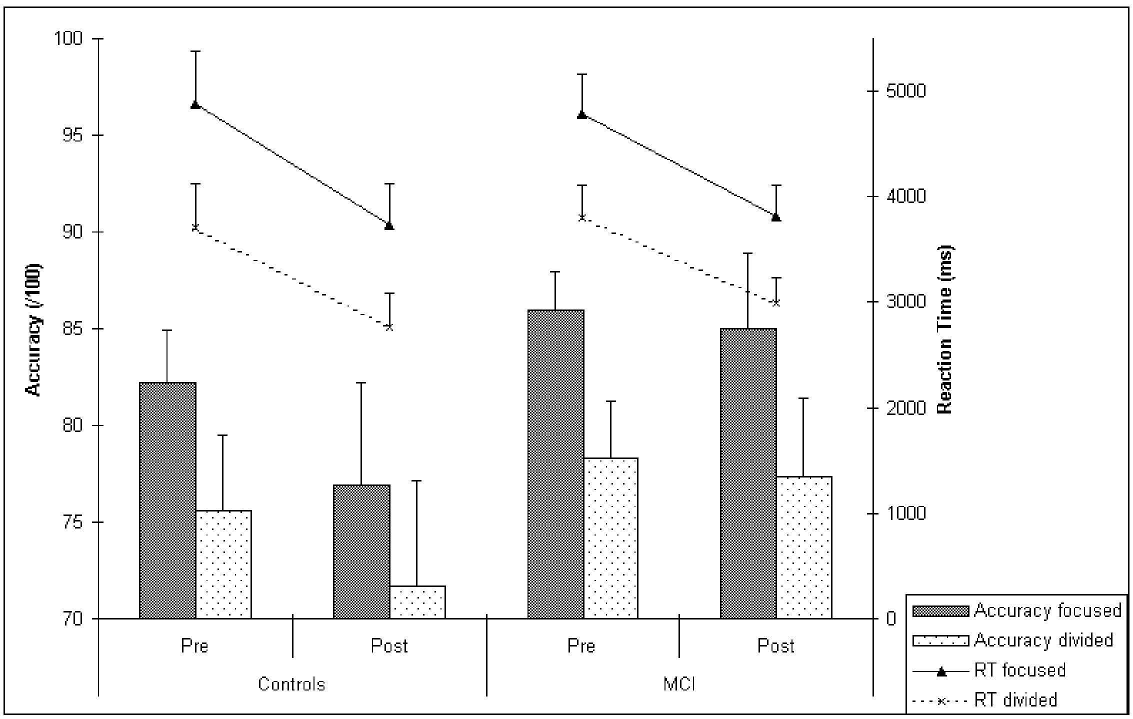


Figure 5

Mean percent accuracy (left scale) and RT (right scale) for alpha-arithmetic task in both groups, pre and post intervention.



CHAPTER 4: EXPERIMENT 3

Training of attentional control in Mild Cognitive Impairment with executive deficits: results from a double-blind randomized controlled study

Lyssa G. Gagnon 1,2, Sylvie Belleville 1,2

1 Research Centre, Institut universitaire de gériatrie de Montréal

2 Dept of Psychology, University of Montreal

Manuscript in preparation

Abstract

Objective: This study evaluated the efficacy of a cognitive intervention for attentional control in older adults meeting criteria for mild cognitive impairment (MCI) with an executive deficit. It also sought to verify if the benefits of training generalized to primary and secondary outcome measures. **Method**: Participants (n=24) were randomly assigned to a variable priority or fixed priority attentional training condition. The experimental group completed a computer-based training program involving Variably Priority (VP) coordination of both components of a dual task (Kramer, Larish, & Strayer, 1995), to which was added a self-regulatory strategy designed to augment meta-cognition. The active control group performed rote practice of the same dual task (Fixed Priority training), which involved a visual detection task combined with an alpha-arithmetic task. Six one-hour training sessions were held thrice a week for two weeks. Participants were tested pre and post training to detect improvement on attentional control capacities and transfer of benefits to new tasks. **Results**: Results show that both groups improved on the visual detection and alpha-arithmetic tasks separately, but only participants receiving VP training significantly improved their dual-task cost in accuracy for the visual detection task. As for transfer of effects, VP training produced a trend for generalisation on a secondary outcome task of divided attention, and both FP and VP training produced improvements on certain other outcome measures: focused attention, speed of processing, switching abilities. **Conclusions**: Overall, these findings indicate that cognitive intervention can improve attentional control in persons with MCI and an executive deficit.

Keywords

Mild Cognitive Impairment, cognitive training, attentional control, divided attention

Introduction

There is increasing evidence that cognitive training can be used to improve memory performance of persons with mild cognitive impairment (MCI) (Belleville, 2008; Miotto, Serrao, Guerra, Lúcia & Scaff, 2008; Teixeira et al.) This suggests that brain plasticity can be promoted in this very early phase, a notion that may have tremendous implication for the management of Alzheimer's disease (AD) (Belleville et al., 2011). The impact of MCI is not limited to memory and it is therefore critical to know whether other domains of impairment can be bolstered by training programs. There are many reasons to suggest that attentional control should be one of the domains to be targeted by cognitive training. First, attentional control deficits are present quite early in AD (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Perry, Watson & Hodges, 2000; Belleville, Peretz, & Malenfant, 1996; Belleville, Rouleau, Van der Linden & Colette, 2003; Colette, Van der Linden, & Salmon, 1999; Greene, Hodges, & Baddeley, 1995; Logie, Cocchini, Della Sala, & Baddeley, 2004) and many studies have even reported attentional control deficits in persons with MCI (Belleville, Chertkow, & Gauthier, 2007; Gagnon & Belleville, 2011; Borkowska, Drożdż, Jurkowski, & Rybakowski, 2009; Belanger, Belleville, & Gauthier, 2010). Second, it has been suggested that executive control deficits underlie difficulties with everyday activities in AD (Perry & Hodges, 1999) and that they increase memory deficit by disrupting organizational and strategic memory processes, such as information encoding and retrieval (Moscovitch, 1992). Finally, MCI is a clinically heterogeneous label (Chertkow et al., 2008) and many studies have shown that the multiple domain subtype – often including attentional deficits – carries a higher risk of developing dementia than the amnestic single domain counterpart (Busse, Angermeyer, & Riedel-Heller, 2006; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Ritchie & Tuokko, 2010). Thus, there exists clear evidence that attentional control is impaired in early AD, notably on dual tasks, that these capacities can be impaired in MCI, and that they are of a poor prognosis. This indicates that developing training programs for attentional control in MCI is highly relevant.

In healthy older adults, there is ample evidence to suggest that attentional control can be improved, if provided with appropriate training. McDowd (1986) showed that extended practice dividing attention between two perceptual-motor tasks (visual pursuit tracking and auditory choice reaction time) could ameliorate divided attention capacities for dual tasking in older adults. In the ACTIVE study (Ball et al., 2002; Willis et al., 2010), a randomized controlled trial, healthy older adults trained on a computerized divided attention task of visual search with distractors improved their searching abilities, and these cognitive effects were mostly maintained at the 2- and 5-year follow-ups. Kramer, Larish, & Strayer (1995) conducted a study in which they examined the effects of variable priority training on attentional control in a dual task comprised of a visual monitoring task and an alphabet-arithmetic task. During variable priority training, adults were instructed to emphasize one task more or less than the other across different blocks. The objective of this type of training is to promote control of attentional abilities and enhance dual task coordination. Results indicate that variable priority training significantly reduced the pre-intervention dual task decrement in both aged and young participants. Bherer et al. (2005, 2008) also showed a positive effect of dual task training in healthy older adults with no superior training benefits when using a variation on variable priority training. Thus, training can improve attentional control in healthy older adults.

A few cognitive intervention studies have been conducted with the MCI population, and most concern the effectiveness of memory training (for reviews, see Belleville, 2008; Miotto, Serrao, Guerra, Lúcia & Scaff, 2008; Teixeira et al.) Although there have been no interventions specifically looking at divided attention in MCI, Belleville et al. (2008) have reported improved spatial switching capacities following practice. Furthermore, Unverzagt et al. (2007) showed that “memory-impaired” older adults benefited as much as healthy older adults did from training on the computerized divided attention search task described previously in the ACTIVE study. Another study has focused exclusively on auditory processing speed and accuracy (Barnes et al., 2009). Their intervention group showed a non-significant trend towards better general cognitive status. Additional research has focused on training a broad range of cognitive functions, including attentional components. One pilot study found that a computer-assisted cognitive training program focusing mainly on memory, but also on processing speed, benefited older individuals with age-associated memory impairment (analogous to MCI) (Gunther, Schafer, Holzner, & Kemmler, 2003). In another study, Olazarán et al. (2004) developed a global, cognitive-motor stimulation program (including attention training) for a mixed-patient group of MCI and mild-to-moderate AD. Following the intervention, trained participants maintained their general cognitive performance levels, whereas the control group deteriorated. A third study, focusing on educational and multidimensional cognitive training, showed improved attention and everyday executive function (in finances and shopping) in individuals with MCI (Brum, Forlenza & Yassuda, 2009). Additional research has been conducted using a computer-based neuropsychological training program (TNP) which aims to stimulate not only attention, but also other cognitive domains. Persons with MCI have shown improved performance following TNP alone (Cipriani, Bianchetti & Trabucchi, 2006) as well as in combination with occupational therapy and behavioural training (Talassi et al., 2007) and with cholinesterase inhibitors (Rozzini et al., 2007). However, there is no way of knowing which ingredients in these multidimensional interventions produced a specific effect on attentional capacities, seeing as they targeted multiple cognitive domains using varied tasks.

In summary, there is an indication that individuals with MCI might still learn and benefit from cognitive training. However, the main focus has been on memory thus far, in spite of increasing evidence that attention is impaired in MCI and that this could contribute vastly to their overall cognitive deficits. Although attentional capacities can be improved upon training in healthy older adults, no study has directly measured if this is equally attainable in MCI. Positive results could have tremendous implications for the management of those individuals at risk for developing AD, as attentional control deficits appear quite early on in the disease and underlie many difficulties in every day life. Accordingly, the aim of this experiment was to evaluate the efficacy of a cognitive intervention for attentional control in MCI. Given that an intervention must centre on an observed deficit and that MCI is a clinically heterogeneous label, we selected only MCI individuals with executive deficits, with or without accompanying memory deficit (multiple domain amnestic MCI and non-amnestic single domain MCI, respectively) (Gauthier et al., 2006; Artero, Petersen, Touchon, & Ritchie, 2006). Based on Kramer et al.'s (1995) and Bherer et al.'s (2005; 2008) positive findings with healthy older adults, we employed variable-priority (VP) training, to which we added a self-regulatory strategy designed to augment meta-cognition. The active control group in this study performed only rote practice (Fixed Priority training) on the same dual task employed for VP training. We measured generalization of training effects with one proximal and five distal outcome measures. The proximal outcome measure was a dual-task comprising a visual detection task combined with a classical digit span task. We expected that training would bring significant improvement in performance on this primary outcome measure, as it taps the underlying cognitive capacity trained during the intervention. We also sought to verify if this improvement would generalize to related capacities, that is, secondary outcome measures composed of experimental and clinical tasks using different modalities (Willis & Schaie, 2009). The distal outcome measures included executive subtests of the Test of Everyday Attention (TEA) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), as well as Trails A and B. Two questionnaires (the Divided Attention Questionnaire: DAQ, Tun & Wingfield, 1995) and the Well-Being Scale (Bravo, Gaulin, & Dubois, 1996) were also included as functional outcome measures.

Method

Participants

Twenty-six individuals with MCI participated in this study. Participants were assigned semi-randomly amongst the two training conditions. Randomization was stratified for Education and

Age in order to equate groups on those dimensions. Concerning the attrition rate, two participants (one in each experimental group) abandoned during the intervention; one for family-related issues, the other for unknown personal reasons. Consequently, 24 individuals were retained for analyses. Their characteristics and clinical results are presented in Table V.

All participants were older adults with single-domain or multiple domain MCI (defined below). They were recruited from memory clinics in Montreal and diagnosed by experienced geriatricians or neurologists on the basis of an extensive clinical and neuropsychological assessment. The participants met the following criteria for MCI (Petersen et al., 1999): (a) cognitive complaint; (b) performance at least 1.5 standard deviation below age normative values on a cognitive test; (c) score above the cut-off for dementia on the MMSE, relative to age and educational level; (d) no significant limitation of functional independence due to their cognitive deficits; (e) do not fulfill criteria for dementia. In addition to these criteria, only MCI individuals with executive deficits were included in the study, as measured by impaired performance (1.5 S.D. below age-matched norms) on one or more of the following: a test of inhibition - Stroop-Victoria (Regard, 1981); a test of executive planning and visuo-constructional praxia - Rey Figure Copy (Rey, 1959); a test of attentional control - Digit-Symbol (Wechsler, 1997). Of the 26 participants, six showed only executive deficit (non-amnestic single domain MCI), whereas 18 showed executive and memory deficit (amnestic multiple domain MCI) (Gauthier et al., 2006).

All participants were assessed with a standardized clinical and neuropsychological battery in order to characterize their clinical status and cognitive functioning. The battery included the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976), an abbreviated neuropsychological assessment scale; the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), a brief evaluation of cognitive status; the Geriatric Depression Scale (GDS) (Yesavage, 1988), a tool to measure depression in the elderly; the Functional Autonomy Measurement System (SMAF; (Desrosiers, Bravo, Hébert, & Dubuc, 1995), a tool to evaluate autonomy in every day activities; the immediate and delayed recall of the Rey Figure (Rey, 1959), to measure visual memory; the free and cued word recall test (RL/RI16 free and cued recall task: Van der Linden et al. 2004), to measure verbal memory; the Boston naming test (Kaplan, Goodglass, & Weintraub, 1983), to measure naming to visual confrontation; as well as the executive tests mentioned above.

All participants were French-speaking and community-dwelling, living in the Montreal area. They possessed normal or corrected-to-normal hearing and vision. Exclusion criteria consisted of alcoholism; general anaesthesia in the past 6 months; presence or history of severe psychiatric disorders, neurological disorders, or stroke. Furthermore, we excluded patients with Alzheimer's disease (NINCDS-ADRDA research criteria: McKhann et al., 1984), as well as patients with other forms of dementia.

Intervention

Divided attention task

The two training conditions employed a dual task which consisted of a visual detection task combined with a visual alpha-arithmetic judgment task. In the former, stimuli consisted of a series of red and black rectangles appearing randomly at the bottom of the screen for a maximum of 500 milliseconds (ms) each and interspaced by 250 ms intervals. Participants pressed the space bar key upon seeing a red rectangle, as quickly and accurately as possible. As for the alpha-arithmetic task, stimuli consisted of equations (additions and subtractions) containing letters (M through Z) and numbers (1 through 9) which appeared in the middle of the screen for a maximum of 3750 ms each and were interspaced by 1500 ms intervals. Participants judged the veracity of the equation and gave their response by pressing one of two keys; left index for False and right index for True. For example, the following equation: "U-1=T" is true, because "T" comes one letter before "U" in the alphabet, whereas the equation "O+2=P" is false, because two letters down the alphabet from "O" is "Q" and not "P". All but the three keys required for the task were concealed on the computer keyboard. Twenty equations were presented per block, half of which were false and half of which were correct. During each equation, five rectangles would appear, including one to three red ones. Thus, 40% of the rectangles were targets, with a total of 20 to 100 rectangles per block, depending on the participant's speed. If a participant took less time than provided to answer the equation, the next equation was presented immediately. Accuracy and RT were recorded for both tasks.

Training conditions: Fixed Priority (FP) and Variable Priority (VP)

Divided attention training on the dual-task was performed under Variable Priority (VP) or Fixed Priority (FP) conditions. The VP training consisted of performing both tasks concurrently and varying allocation priorities across the series of blocks. Before each block, participants were informed how much attention to give each on-screen task. Three different priority proportions were practiced: 80-20, 50-50, 20-80. Accordingly, priority 20-80 informed participants to give 20% of their attention to the visual detection task and 80% to the alpha-arithmetic task. For priority 50-50, participants were instructed to allocate equal amounts of attention to each task. In priority 80-20, participants were asked to give 80% of their attention to the visual detection task and 20% to the alpha-arithmetic task. These instructions were presented on-screen and read aloud to the participants. They were supported by an illustration consisting of a rectangle-shaped box divided into two coloured parts of different proportion, in order to visually represent the requested priority proportion. Following each block, a histogram was presented to participants indicating their baseline level for the day (as measured earlier in the focused attention condition) as well as the accuracy threshold targeted according to the given priority. For example, if a participant responded correctly to 60% of alpha-arithmetic equations in focused attention, their accuracy threshold to attain in the 20-80 priority would be 48%. For the self-regulatory strategy designed to promote meta-cognition, participants were asked to draw a column on the histogram that approximated their performance on the current block of the dual-task, and to give their opinion on whether they had indeed reached the targeted threshold or not. For simplicity, the histograms only reflected accuracy for the prioritized task in the case of 80-20 (visual detection) or 20-80 (equations) priorities, and displayed columns representing accuracy for both tasks in the 50-50 priority. Once participants had drawn their own estimate on the paper histogram, actual performance for that block was displayed on-screen using the same histogram format. The experimenter then reviewed with the participant their performance, insisting on three ideas: (1) Was their performance estimate accurate? (2) Had they reached the priority threshold? and (3) If not, what would they have to do next time to attain it? An example of feedback would be ''*Very good, as we can see on-screen, you estimated your performance well. However, you did not quite attain the threshold we wanted. Next time we do the 80-20 priority, try and put even more attention on the equations, and less on the rectangles*.'' In this manner, participants were made aware as to whether they had attained the expected priority proportion or not. They could therefore adjust the attentional resources allocated to each individual task (self-regulate) in order to better achieve the next requested priority proportion. When participants started to consistently attain their targeted thresholds (usually towards the end of the training), the experimenter would praise them. In contrast, FP training consisted of dual-task practice in which participants were instructed to perform both tasks concurrently and to allocate 50% of their attentional resources on the visual detection task and 50% on the alpha-arithmetic task. There was no variation in priority allocation during FP training and no feedback was given.

Outcome Measures

Primary outcome measure

A modified version of the dual task employed for training was used as a primary outcome measure. In this version, participants were instructed to give equal amounts of attention to each task. In other words, no particular task priority was promoted. No feedback was given. The equations employed in the alphanumeric task used the letters “A” through “L which avoided potential practice effects due to familiarization with the training stimuli. Participants completed each task separately (focused attention) and simultaneously (divided attention). The divided and focused attention conditions were presented in an ABBA design: participants first completed each task in focused attention. This was followed by two blocks of divided attention. The two tasks were then completed again in focused attention. This design was used to reduce the potential impact of practice or fatigue effects.

Generalization measures

Generalization was measured with one proximal and five distal outcome measures. The proximal outcome measure was a dual-task comprising a visual detection task combined with a classical digit span task. This divided attention proximal outcome measure allowed us to verify if training effects generalized across modalities to a divided attention condition that combined tasks different from the ones used in the training (cross-modality transfer). In the visual detection task, participants fixated a green dot on the middle of the screen and pressed down on a green key until they saw a black circle (target) and a white circle (distracter). They were instructed to release the green key in order to press, as rapidly as possible, a key to the left or to the right, depending on whether the target appeared on-screen to the left or the right of the green dot. Participants generally performed at ceiling levels on this task. For the digit span task, participants' spans were first established as the largest series of digits correctly recalled in order two out of three times. Span trials were given orally by the experimenter and responses were pronounced out loud by participants. This span level was used for all subsequent blocks. Both tasks were administered separately (focused attention) and simultaneously (divided attention) following an ABBA design. Focused attention blocks contained 60 trials for visual detection and 5 trials for digit span. Under divided attention, participants did as many span trials as were needed until a full block of 60 visual detection trials was completed. Span scores were percentages of correct trials (computed by dividing the total number of individual span items correctly recalled by the total number attempted).

For distal generalization, three neuropsychological tasks were borrowed from the Test of Everyday Attention (TEA) (Robertson et al., 1994), a standardized neuropsychological battery of pencil-and-paper tests evaluating attentional capacities. We employed TEA subtests because they use familiar, everyday material, and were thus more ecological outcome measures. The Telephone Search subtest measured visual-motor selective attention (circling targets), while the Telephone Search While Counting subtest assessed divided attention. It is a dual-task involving the previously described task, combined with an auditory attention task (counting sounds). These tasks generated time-per-target and weighted time-per-target scores, respectively. In addition, the Visual Elevator subtest was used to see if training effects would generalize even further to cognitive switching capacities. This task evaluated attentional control and switching by having participants count visual stimuli out loud in one direction until a cue indicates to count in the reverse direction. A mean time-per-direction-change score was computed. Finally, the Trails A and B tasks were administered with the idea that training effects (for both groups) from the alpha-arithmetic equations might generalize to the letter-number switching component of Trails B.

We also included two questionnaires as functional outcome measures. The Divided Attention Questionnaire (DAQ) (translated from Tun & Wingfield, 1995) is a self-assessment scale designed to estimate difficulty of different combinations of everyday activities, such as driving, having a conversation, talking on the phone, cooking, etc. Internal consistency of the DAQ is high (alpha coefficient = 0.88) and test-retest reliability is good (0.63). Participants rate 16 items on a five-point scale (from very easy to very hard). Finally, the Well-Being Scale (Bravo et al., 1996) is a self-assessment instrument of subjective personal well-being. The internal consistency is high (estimated at 0.92) and its retest reliability very good (0.82). Participants respond to 14 questions on a six-point scale and 4 questions on a Likert-type scale.

Design

In addition to the clinical assessment, pre/post measurements and training were completed over 8 sessions. The first session was scheduled one week prior to training and included all outcome measures previously described. Participants were then randomized to one of the two training formats (FP or VP) by an independent research assistant. Training (FP or VP) was then provided during six one-hour sessions evenly distributed over about 2 weeks. Participants completed each task separately (focused attention condition) at the beginning of each training session. They subsequently completed nine blocks of the dual-task (divided attention condition), followed by a final block of focused attention. Participants were encouraged to take breaks one-third and two-thirds of the way into a training session. They were trained in subgroups of two, although they did not interact with each other during training and each was given their own computer. An experimenter was present during the entire training session to ensure compliance. The post-intervention outcome measures were administered one week after the end of the last training session. For TEA subtests, alternative versions were given and counter-balanced amongst participants in pre- and post-intervention sessions. This study was a double-blind design: participants were unaware of the nature of the two different training strategies, and pre- and post-training assessment was carried out by a research assistant blinded to intervention assignment and blinded to research hypotheses. To minimize variability, pre- and post-intervention sessions were conducted at the same time of day and by the same experimenter for any given participant (with two exceptions for time of day).

Results

Clinical Data

To assess whether the groups were equivalent on demographic and clinical characteristics, participants were first compared on their socio-demographic and clinical characteristics[4] using ANOVAs with Group (FP; VP) as a between-subject factor. The two groups were comparable on age, $F(1,22) = 0.25$, $p > .05$, and educational level, $F(1,22) = 0.82$, $p > .05$. In addition, groups did not differ on proportion of MCI subtypes included, for both non-amnestic single domain (three in each group) and amnestic multiple domain (nine in each group). Finally, there were no significant differences between training groups on all clinical measures as shown in Table V.

Dual-task Dependent Variables

Accuracy and RT on the visual detection task, as well as accuracy and RT on the alpha-arithmetic task were used as dependent variables in the dual-task employed for training sessions as well as primary outcome measure. RTs smaller than 150ms and RTs for commission errors were excluded. Dual task cost scores were also computed independently for each dependent variable. These dual task cost scores represented the proportional loss of performance in the divided attention condition as compared to the focused attention condition: (|focused – divided|) / focused. This decrement provides a measure of the attentional resources required to coordinate the execution of both tasks together. Because it controls for individuals' baseline performances, cost scores provide a more sensitive measure of divided attention performance.

Pre-training

Accuracy and RT data collected during the pre-training session were first analyzed to ensure that the paradigm resulted in a divided attention cost. It was also used to assess whether participants randomized in the FP and VP conditions exhibited similar performance before undergoing training. Separate mixed ANOVA's were computed on all four dependent variables with Attention (focused; divided) as a within-subject factor and Group (FP; VP) as a between-subject factor. The analysis of accuracy data on the visual detection task showed the expected main effect of Attention, $F(1, 22) = 610.49$, $p < .001$, with individuals performing the task more accurately in focused attention than in

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[4] Clinical data on a two tests (Delayed recall of Rey Figure, Boston Naming) were missing for one participant.

divided attention. Analysis of the RT data also indicated a significant effect of Attention, $F(1, 22) = 87.40$, $p < .001$, with individuals performing the task more quickly in the focused than divided attention condition. For the alpha-arithmetic task, accuracy data mirrored that of the visual detection task, in that participants were more accurate in the focused than divided attention condition, $F(1, 22) = 11.25$, $p < .01$. No significant effects were found for RT data on this same task. Thus, the divided attention task produces a dual-task decrement, or dual-task cost, as performance is generally lesser in divided attention than in focused attention. There were no Group effects or interactions for all dependant variables confirming that both groups of participants had similar baseline performances for all conditions.

Effects of training

Primary outcome measure

To assess the effects of the intervention on divided attention measures, separate mixed ANOVA's were used on the same four dependent variables mentioned above: accuracy and RT for both the visual detection and alpha-arithmetic tasks, with Attention (focused; divided) and Intervention (pre-intervention; post-intervention) as within-subject factors and Group (FP; VP) as a between-subject factor. Post-hoc tests of mean comparisons were performed with paired t tests adjusted for multiple comparisons. Data are displayed in Figure 6. Second, ANOVAs were computed on cost scores using Intervention (pre-intervention; post-intervention) as a within-subject factor and Group (FP; VP) as a between-subject factor. Data are presented in Table VI as percentage of improvement (Post – Pre) in dual-task cost scores for each dependant variable.

Visual detection task. Analysis of the accuracy data showed main effects of Attention, $F(1, 22) = 517.65$, $p < .001$, and of Intervention, $F(1, 22) = 15.51$, $p < .01$. Importantly, a significant Attention by Intervention by Group interaction, $F(1, 22) = 5.58$, $p < .05$ ($\eta^2=0.20$) indicated that participants in the VP group improved their accuracy level from pre to post intervention in the divided attention condition ($p < .01$), whereas those in the FP group did not. This increase in accuracy on the visual detection task was around 26% for the VP group, but only 3.4% for the FP group. Analysis of the RT data indicated significant main effects of Attention, $F(1, 22) = 81.58$, $p < .001$, and of Intervention, $F(1, 22) = 5.12$, $p < .05$, but no interactions with Group. All participants responded faster in focused than in divided attention. In addition, both groups were faster following training.

Alpha-arithmetic task. On the Alpha-arithmetic task, both accuracy and RT data showed significant main effects of Attention, $F(1, 22) = 14.89$, $p = .001$, and $F(1, 22) = 9.79$, $p < .01$, respectively, and of Intervention, $F(1, 22) = 72.80$, $p < .001$, and $F(1, 22) = 8.18$, $p < .01$, respectively. Participants were more accurate in the focused condition, but faster in the divided condition, indicating a speed-accuracy trade-off. Additionally, all participants improved their overall accuracy and speed following training. The Group or Intervention by group interaction effects did not reach significance.

Dual-task cost scores. Analysis of accuracy data for the visual detection task revealed a main effect of Intervention, $F(1, 22) = 10.97$, $p < .01$, as well as a significant Group by Intervention interaction, $F(1, 22) = 6.49$, $p < .05$ (η^2=0.23). Participants in the VP group significantly improved their dual-task cost scores in accuracy for the visual detection task ($p < .01$). No improvement was found in the FP condition. None of the other comparisons reached significance.

Generalization measures

Proximal generalization

For the cross-modality visual detection + verbal span dual-task, seven participants (four FP and three VP) completed only one block (instead of two blocks) in each condition (focused and divided) due to fatigue. Results are presented in Table VII. A mixed ANOVA, with Attention (focused; divided) and Intervention (pre-intervention; post-intervention) as within-subject factors, and Group (FP; VP) as the between-subject factor, revealed only a main effect of Attention, $F(1, 22) =$ 18.14, $p <= .001$ (η^2=0.45). As expected, all participants performed better in the focused attention than in divided attention, which confirms a dual-task decrement for this task. However, no Intervention effect or interaction with Intervention was found. Cost scores, computed in the same manner as above, confirmed that participants did not improve on this dual-task from pre- to post-intervention.

Distal generalization

For the remaining generalization measures, separate mixed ANOVA's were used on the various dependent variables measured. The within-subject factor was Intervention (pre-intervention; post-intervention), whereas the between-subject factor was Group (FP; VP).

Concerning subtests from the TEA battery, for visual selective attention, the ANOVA on the time-per-target measure revealed no significant effects of Intervention or of Group, and no interaction. For divided attention, the ANOVA on the weighted time-per-target measure revealed a significant effect of Intervention (p=.04) and an Intervention by Group interaction that was marginally significant (p=.08, η^2=0.14), in favour of the VP group. For switching, the ANOVA on the time-per-switch measure revealed only a significant effect of Intervention, $F(1, 21) = 12.24$, $p < .01$, η^2=.37).

All participants reduced their switch cost from pre- to post-sessions. For the Trails tests, the ANOVA on completion time for Trails A revealed a main effect of Intervention only $F(1, 22) = 15.91$, $p = .001$, $\eta^2=.42$), with all participants showing faster completion times post-intervention. For Trails B, the ANOVA's on completion time and on number of errors revealed no significant effects of Intervention or of Group, and no interaction.

Questionnaires

On the Divided Attention Questionnaire, the ANOVA on total scores revealed a main effect of Intervention only $F(1, 22) = 5.55$, $p < .05$, $\eta^2=.20$) but no interaction with Group. Unexpectedly, all participants showed higher scores post-intervention. On the Well-Being Scale, the ANOVA on total scores revealed no significant effects of Session or of Intervention format, and no interaction.

Performance During VP Training Sessions

Figure 7 presents mean accuracy and RT performance for the visual detection and alpha-arithmetic tasks during the VP training sessions. Figure 8 illustrates performance operating characteristic (POC) curves, which represent the cross-plotted standardized accuracy scores for the visual detection and alpha-arithmetic tasks across training sessions 1, 3 and 6. Scale values at the bottom left-hand portion of the figure correspond to poor performance whilst scale values that converge towards the top right-hand portion of the figure indicate good performance. As illustrated, participants trained in the VP group gradually improved their efficacy in matching their allocation of attentional resources to the requested priority, thus increasing their dual-tasking coordination.

Correlates of Improvement

To better appraise the influence of various biopsychosocial factors (education, age, depression, severity of global cognitive deficit) on intervention outcome, correlations between these variables and the main finding from VP training (improvement on the accuracy cost score for visual detection) were computed. The main result was a significant positive correlation between age and improvement: older individuals with MCI benefited more from VP training, $r(10) = .56$, $p < .05$. In addition, a trend towards a significant negative correlation was revealed between improvement and the MMSE, a global measure of severity of cognitive deficit: individuals with slightly greater impairment seemed to benefit more, $r(10) = -.50$, $p = .051$. We did not find any correlation between education or depression and training effects.

Discussion

The goal of this study was to evaluate the efficacy of a cognitive intervention for attentional control in persons with mild cognitive impairment (MCI) suffering from executive deficit. We employed computer-based Variable Priority (VP) training to which we added a self-regulatory strategy and feedback. This condition was compared to an active control condition (Fixed Priority) in which participants simply practiced on a divided attention task without any given priorities or feedback. On our main outcome measure, participants in both FP and VP training groups improved upon their performance (accuracy and RT) on the alpha-arithmetic task and this was found when tested in both focused and divided attention conditions. As for the visual detection task, both groups ameliorated their speed of response. However, only the VP training produced better accuracy levels under divided attention following the intervention. This finding was confirmed by analysis of the cost scores, which demonstrated a reduced dual-task decrement on accuracy in the visual detection task for VP training only. This suggests improved capacities of attention control and executive coordination. The fact that the improvement is present only in the VP group leads us to conclude that VP training involves unique characteristics that are conducive to ameliorating efficacy in dual-task coordination and that are not present in rote divided attention practice (FP training). Potential candidates will be discussed further on.

One strength of the study design was to include multiple proximal and distal generalization measures. On the proximal, cross-modality generalization measure of divided attention, participants were required to complete a visuo-motor detection task, combined with a verbal span task. No effect of Intervention was found, signifying that neither training strategy generalized to this dual task. This is different from the results of Kramer et al. (1995) and Bherer et al. (2005) which revealed transfer effects to cross-modality dual tasks, but similar to data from Bherer et al. (2008) who did not find reduced dual-task cost on two cross-modality transfer tasks. There are many possible explanations for our lack of a generalization effect. One possibility is that the strong memory component of the transfer task, which was not trained during intervention, is responsible for the lack of improvement. Perhaps a divided attention task not relying so heavily on the storage component of working memory would have been more suitable to detect generalization of newly learned coordination skills. An alternative possibility is that participants did not modulate their attentional control on this transfer task because the two tasks were poorly balanced - in that it was composed of one very simple, repetitive task and one very difficult, captivating task. Indeed, it is probable that the verbal digit span required a great deal of attention resources. Participants may not have seen the need to modulate their attention back to the simple task on which they were already performing at ceiling levels. Lastly, it is highly likely that the self-paced nature of the tasks also played a role in masking any potential improvement (Bherer et al., 2008). Indeed, participants may have improved on the speed of response or the speed of verbal output, but this variable was not measured.

In contrast, we found a number of intervention effects on distal generalization measures. First, there was a trend (η^2=0.14) towards significant improvement for the VP training group on the TEA divided attention measure (visual selective attention in combination with an auditory counting task). This suggests that the ability to efficiently allocate ones attentional resources - trained during VP intervention - gave this group an advantage on a different dual task. Both groups showed improved performance on the switching task of the TEA task, and on Trails A. It is possible that these observed gains are solely due to practice effects; however, to counter this argument, we note that not all cognitive abilities showed an effect of Intervention. Indeed, in addition to the proximal generalization dual-task, no improvement was detected for visual selective attention (TEA) as well as for Trails B. Consequently, it would appear that FP training is conducive to certain gains in attentional control, although not to the same extent as VP training.
Regarding functional outcome measures, participants did not report any change in well-being, as measured by a self-report questionnaire. This is at odds with certain studies (e.g. Belleville et al., 2006; Brum et al., 2009) that did show an effect of cognitive training on subjective well-being. However, unlike other studies, we did not include any behavioural, psychosocial or psychoeducation component which could have affected participants' impressions of themselves. In terms of transfer to real-world outcomes, the absence of an effect is not particularly surprising, given that individuals with functional impact were carefully screened out and thus, our participants were not yet impaired in everyday functional abilities. Interestingly, participants reported having more difficulty with various dual-tasks in everyday life (e.g. talking on the phone while another person in the same room is talking) following the intervention. This result could easily be explained by the expertise participants gained through practicing dual-tasking. Following intervention, their heightened awareness of the difficulty of executing two tasks at once might have led them to reappraise the perceived difficulty of the everyday dual tasks proposed in this questionnaire of a more ecological nature.

A novel feature of the training was to include a self-regulatory strategy designed to promote meta-cognition in participants. Indeed, the development of awareness and meta-cognition during cognitive training has been highlighted as an important factor in a successful intervention (Clare, Wilson, Carter, Roth & Hodges, 2004). Indeed, control beliefs and goal setting have been shown to enhance performance, even in older adults (West & Yassuda, 2004). Thus, awareness concerning cognitive potential and performance can bring participants to realize that they can exert a certain level of control over their own cognition. The feedback module following every block in the VP training group can be interpreted to have had several effects on the participants' attentional control. Firstly, having to estimate their own performance obliged them to reflect upon their execution of the dual task under the proposed priority. Second, confronting their self-perception to the actual performance permitted them to evaluate the accuracy of their judgement. Third, they learned to adjust their allocation of attentional resources for the next block. Fourth, the strategy encouraged goal setting and confirmed progress. As was illustrated in Figure 8, VP participants did indeed improve in terms of controlling the amount of attention allocated to each part of the task. We can infer that they developed their meta-cognition as well as a sense of control over their ability to dual-task and, consequently, their level of efficacy in dual task coordination improved. Had the pre- and post-intervention sessions included variable priority conditions, we assume the difference between training groups would have been even larger than that observed in the primary outcome measure, which contained only 50/50 trials. In terms of correlates of training benefits, it appears that older individuals with MCI benefited more from VP training. In addition, a trend was observed in which individuals with slightly greater global cognitive impairment seemed to benefit more from VP training. These findings could be explained by the fact that these individuals found the dual-task more challenging at first and thus, had more room for improvement.

It is important to address some limitations in this study. First, the sample size is small, mainly due to very strict selection criteria and limited availability of participants for multiple consecutive sessions. Although it proved sufficient to detect some statistical differences, larger groups would have allowed us to confirm or refute the trend observed on the divided attention subtest of the TEA. In addition, it is to be noted that participants were mostly high-functioning, motivated individuals. Second, although our study design purposely did not include a waiting list control group, this does make it impossible for us to determine if some of the gains observed following VP training might be masked by gains obtained due to FP training, seeing as this group carried out hours of practice on the 50/50 condition, making it more of an active intervention relative to a passive control group. Although risky, this design certainly represents a strong test of our hypothesis. Furthermore, our design did not include booster sessions or long term follow-up, making it unclear whether the effects lasted longer than a week. An additional limitation concerns the validity of the generalisation measures, both in terms of ecological value and transfer distance. It is obvious that our tasks, although carefully selected, do not represent actual activities of daily living, nor did they show strong generalizability. This is a caveat that plagues many intervention studies and necessitates further study and consensus (Dahlin, Bäckman, Neely, & Nyberg, 2009;

Noack, Lovden, Schmiedek & Lindenberger, 2009). Future research on cognitive training in MCI could also greatly benefit from the inclusion of pre- and post-training brain imaging, to investigate the brain structures involved in the improvement. A recent study in our laboratory indicated that memory training was associated with enhanced recruitment of alternative regions that were not affected by MCI prior to training (Belleville et al, 2011). It is unclear whether a similar pattern would be associated with different training formats or training of non-memory domains, such as attentional control. Measuring whether training in combination with pharmacological treatment has potential additive effects is another important question to address (Yesavage et al., 2007)

In summary, our findings confirm for the first time the feasibility and importance of intervention for attentional control in persons with MCI and an executive deficit. The VP strategy showed a significant advantage over the FP training on the main outcome measure as well as a trend for generalisation on another divided attention task. Both FP and VP training produced improvements on certain outcome measures (focused attention, speed of processing, switching abilities). This suggests that persons with MCI, despite their cognitive impairment, maintain a certain amount of cognitive plasticity which makes them amenable to training. Our results indicate that individuals with MCI are capable of improving their attentional control, as has been found in healthy older adults.

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Table V

Mean scores for age, education, and clinical measures in MCI participants (S.D. in parentheses)

	Fixed priority (n=12)	Variable priority (n=12)	*t* value	*p* value
Age	67.00 (7.80)	68.42 (6.04)	-0.48	0.62
Education	15.00 (4.63)	13.08 (5.66)	0.91	0.37
MDRS	137.08 (4.93)	135.83 (4.15)	0.67	0.51
MMSE	28.08 (1.16)	27.83 (1.47)	0.46	0.65
GDS (/15)	3.25 (2.30)	3.42 (2.11)	-0.19	0.86
Coding	50.42 (13.30)	46.17 (13.63)	0.77	0.45
Boston Naming	13.36 (1.36)	12.92 (1.68)	0.70	0.49
Stroop color (time for plate 3)	31.88 (8.14)	33.29 (9.04)	-0.40	0.69
Rey Figure copy (score)	30.21 (3.37)	30.13 (3.11)	0.06	0.95
Rey Figure Copy (time)	224.33 (147.89)	254.67 (77.93)	-0.63	0.54
Rey Figure recall (immediate)	17.50 (6.09)	14.67 (7.03)	1.06	0.30
Rey Figure recall (delayed)	16.14 (5.10)	14.46 (7.67)	0.59	0.56
RL/RI-16 free recall trial	17.10 (1.52)	6.58 (1.38)	0.38	0.71
RL/RI-16 delayed free recall	10.70 (1.77)	8.92 (2.97)	1.30	0.21
SMAF	-1.17(0.91)	-0.79 (0.54)	-1.22	0.24

Figure 6

Visual detection task: accuracy and RT data (error bars represent standard error)

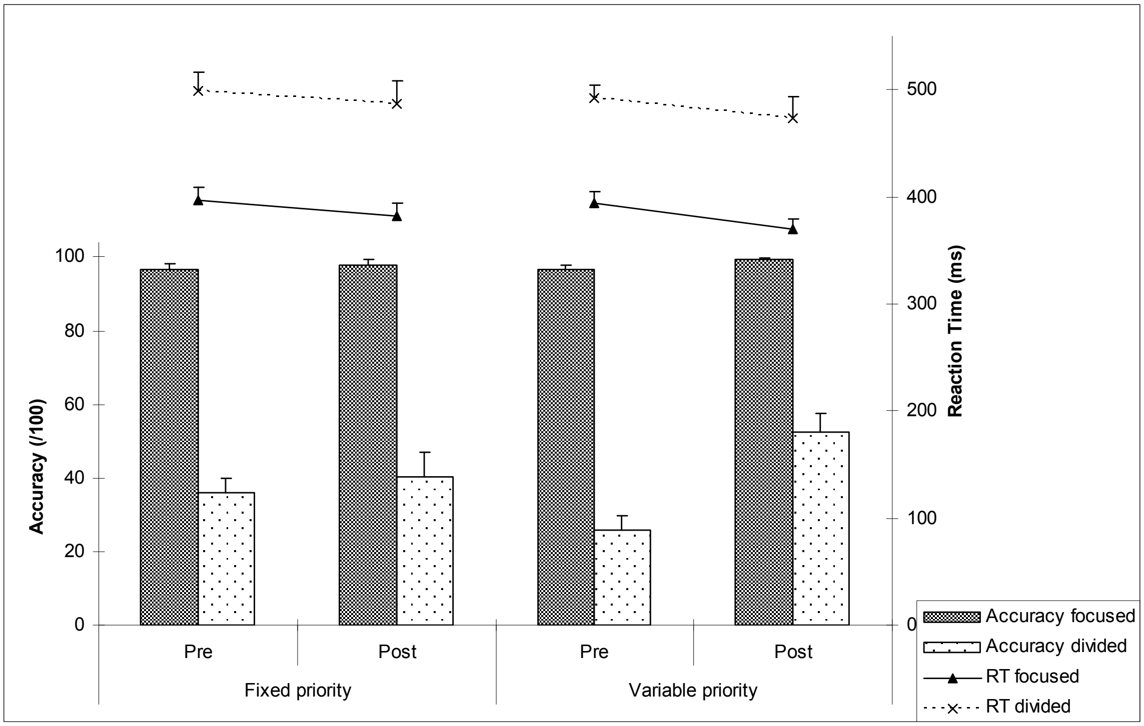


Figure 6 (continued)

Alpha-arithmetic task: accuracy and RT data (error bars represent standard error)

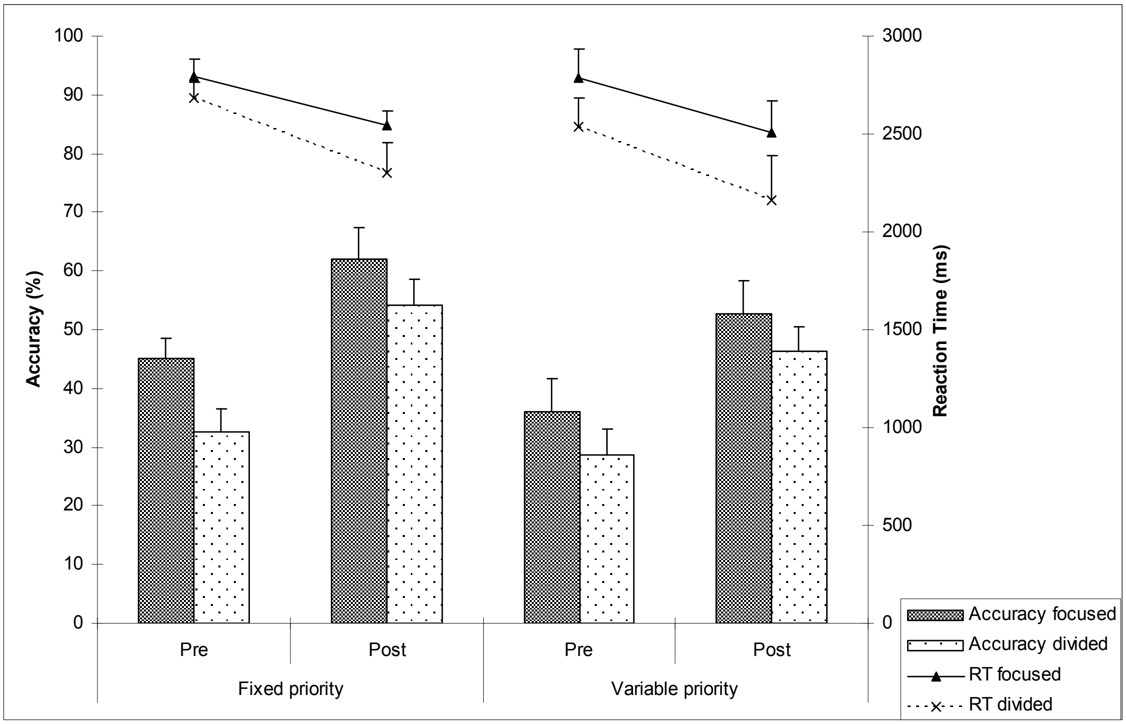


Table VI

Improvement (Post – Pre) in cost scores (%) on accuracy and RT data for alpha-arithmetic and visual detection tasks (S.E. in parentheses)

	Visual detection	
	Accuracy	Reaction time
Fixed priority	3,39 (5,31)	-2,09 (5,40)
Variable priority	25,98 (7,10)*	-3,29 (7,21)

	Alpha-arithmetic	
	Accuracy	Reaction time
Fixed priority	4,38 (4,03)	6,53 (6,49)
Variable priority	0,83 (4,41)	11,76 (10,82)

* $p < .05$

Table VII

Generalization measures pre and post training (S.D. in parenthesis)

a) Cross-modality dual-task (span items recalled correctly in %)

	Pre		Post	
	Focused	Divided	Focused	Divided
FP	85.74 (11.25)	78.76 (9.01)	85.80 (11.88)	79.49 (16.47)
VP	88.38 (11.92)	82.09 (14.07)	91.02 (7.61)	81.15 (17.40)

b) Visual selective attention (time-per-target in seconds)

	Pre	Post
FP	3.87 (0.78)	3.74 (0.56)
VP	4.50 (1.09)	4.36 (1.19)

c) Divided attention (weighted time-per-target in seconds)

	Pre	Post
FP	6.37 (3.26)	6.17 (2.69)
VP	8.39 (4.11)	6.14 (2.18)

d) Switching (time-per-switch in seconds)

	Pre	Post
FP	4.72 (0.47)	4.17 (0.48)
VP	4.94 (0.84)	4.71 (0.89)

e) Trail Making Tests (completion time in seconds)

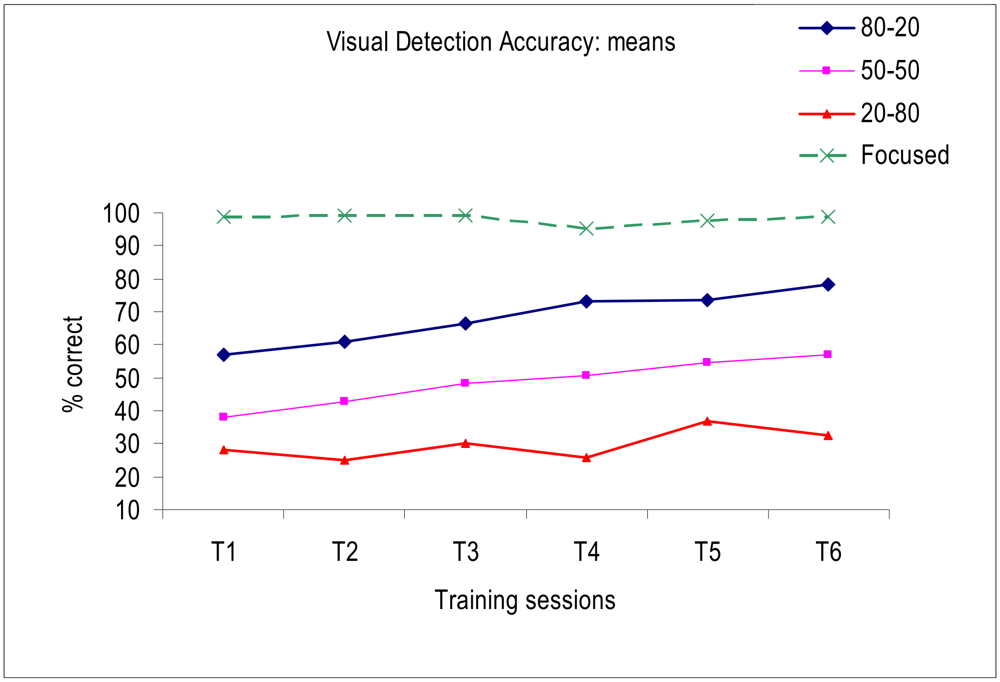
		Pre	Post
FP	Trails A	56.08 (22.87)	43.85 (13.59)
	Trails B	109.93 (43.28)	110.90 (25.38)
VP	Trails A	44.78 (13.46)	36.34 (34)
	Trails B	130.38 (70.10)	137.82 (73.81)

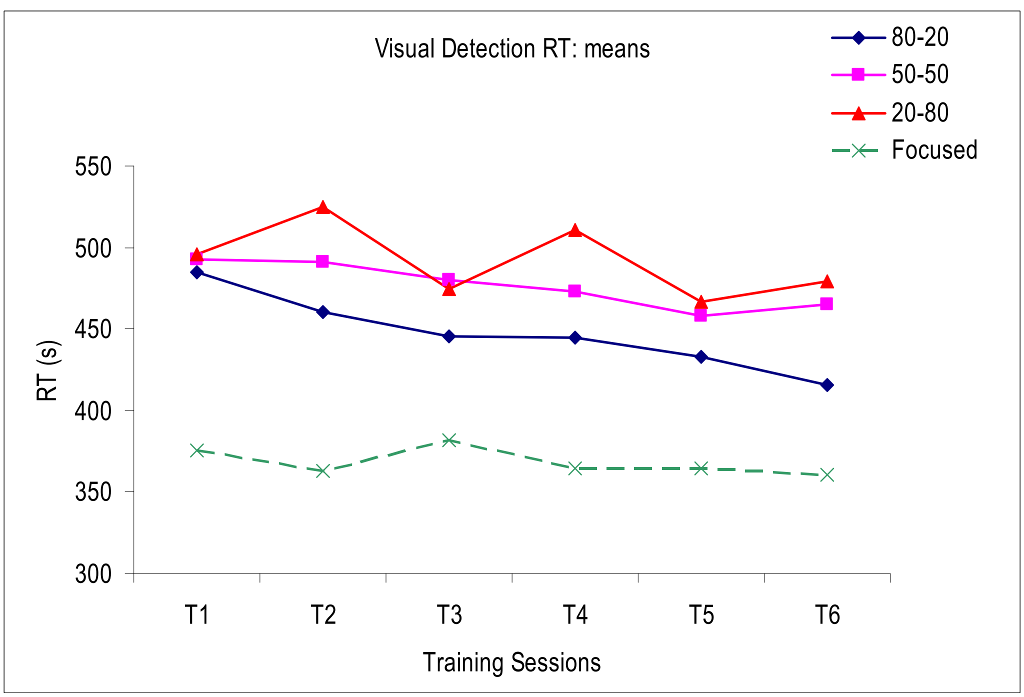
f) Questionnaires (totals)

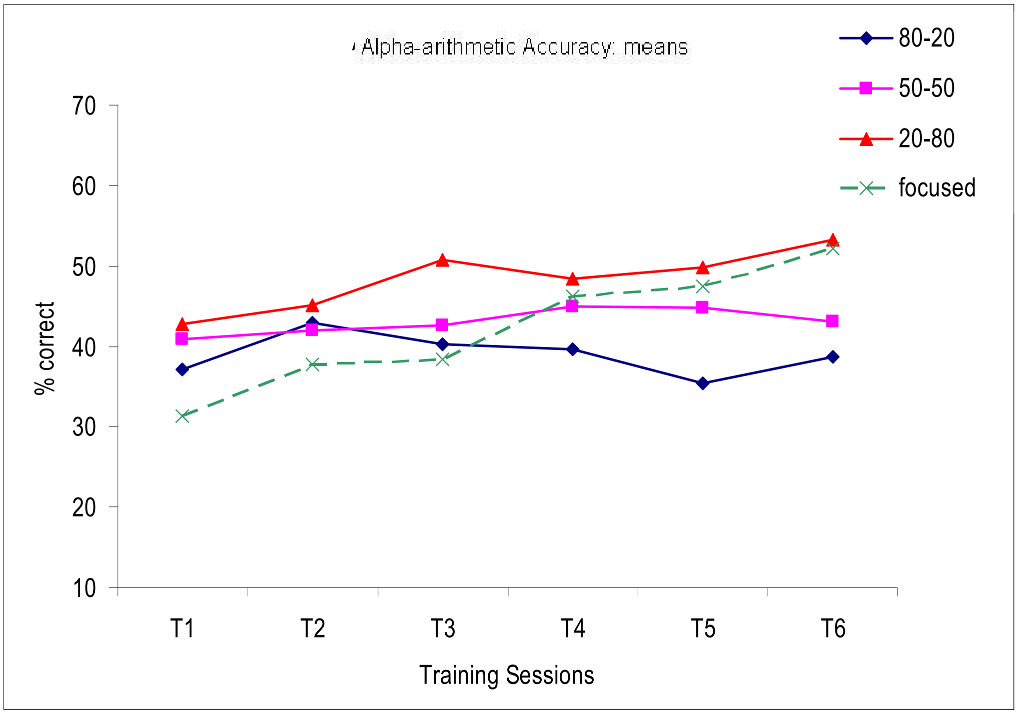
		Pre	Post
FP	Well-being	73.75 (16.10)	74.17 (16.62)
	Divided Attention	43.58 (11.56)	45.17 (11.44)
VP	Well-being	69.33 (14.52)	72.17 (13.90)
	Divided Attention	42.42 (10.71)	46.92 (7.95)

Figure 7

Mean accuracy and RT performance for the visual detection and alpha-arithmetic tasks across VP training sessions






Alpha-arithmetic Accuracy: means
80-20
50-50
20-80
focused
70
60
50
40
30
20
10
% correct
T1
T2
T3
T4
T5
T6
Training Sessions

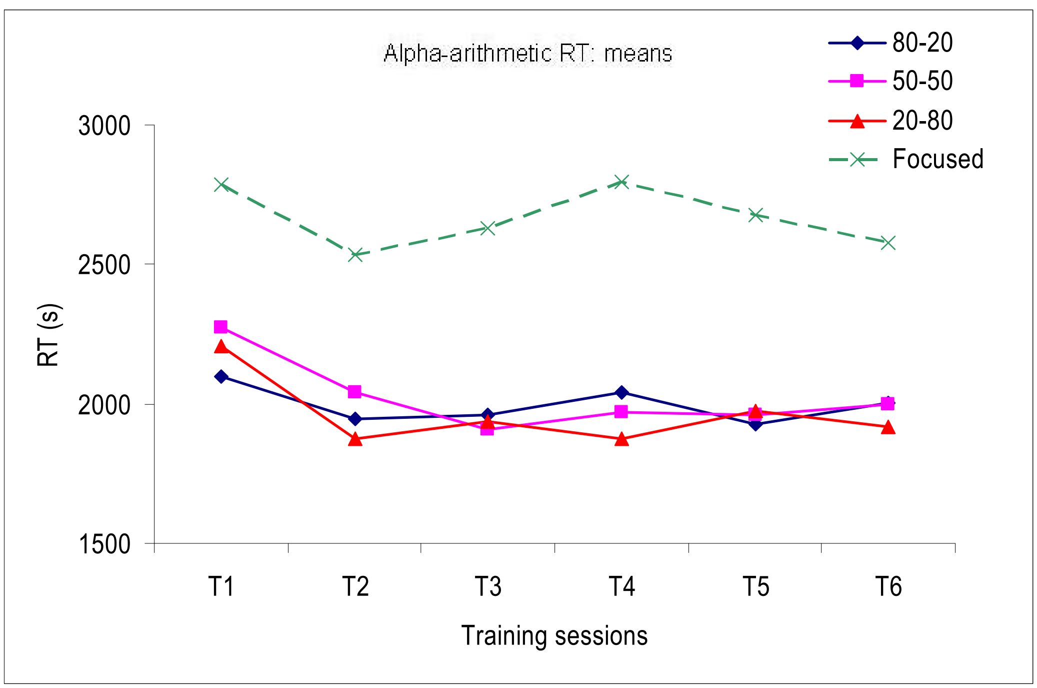
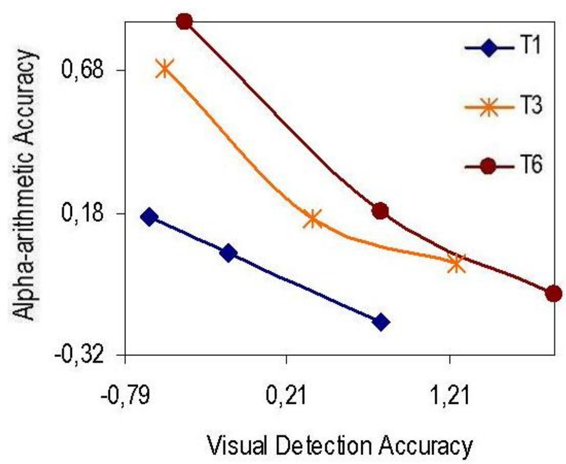

Alpha-arithmetic RT: means
80-20
50-50
20-80
Focused
3000
2500
2000
1500
RT (s)
T1
T2
T3
T4
T5
T6
Training sessions

Figure 8

Cross-plotted Z scores representing accuracy performance for the visual detection and alpha-arithmetic tasks across first, third and last VP training session



CHAPTER 5: GENERAL DISCUSSION

The main goal of this thesis was to examine and intervene upon working memory deficits in persons with MCI, in order to better characterize their profile and attempt to minimize their impairment. In this discussion, the main results of the three empirical articles will be summarized and compared to the existing literature. Finally, strengths and limitations of our experiments will be discussed and future directions proposed.

5.1 Summary and discussion of findings

5.1.1 Assessment of working memory: Experiment 1

5.1.1.1 Main findings

Experiment 1 highlights impaired working memory (WM) on complex span tasks in AD. This finding is coherent with previous studies showing WM deficits in AD (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Belleville, Chertkow, & Gauthier, 2007; Huntley & Howard, 2010). It also confirms previous reports of reduced sentence span (Maylor et al., 2002; Waters and Caplan, 2002) and dot span (Rochon et al., 2000) in AD. Thus, it appears so far that WM spans are systematically impaired in AD, no matter the type of material (visual, verbal, arithmetic), the mode of presentation (auditory, visual), or the nature of the processing task (sentence completion, arithmetic operation, validity judgement, simple listening) involved.

For the first time, our results show impaired performance of persons with MCI on both operation and sentence span tasks as compared to healthy older adults. This is consistent with reports of impaired WM on other tasks requiring attentional control, updating, switching, or inhibition (Belleville et al., 2007; Borkowska, Drożdż, Jurkowski, & Rybakowski, 2009; Belleville, Bherer, Lepage, Chertkow & Gauthier, 2008; Belanger, Belleville, & Gauthier, 2010; Bélanger et al. 2009; Alescio-Lautier et al., 2007). Our results contrast with a minority of other studies showing normal WM on n-back tasks (Missonnier et al., 2005, and Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006). This is perhaps due to ceiling effects on those particular tasks, which would suggest that the level of difficulty of WM tasks must be relatively high to capture impairment in MCI. In our study, we found that the deficit in MCI was less than that of AD, which is consistent with current literature showing that the level of cognitive impairment across domains is habitually less severe in MCI than in AD (Bäckman & Small, 1998; Collie & Maruff, 2000). Hence, our findings extend the known gradient in cognitive impairment between MCI and AD to the domain of WM and thus, further confirm the prodromal status of MCI.

In our experiment, the effect of forgetting was assessed by manipulating the length of the retention interval to reproduce the classic stimulus order effect. When examining retention cost scores that take into account baseline performance, we found that AD individuals and MCI progressors/converters were more affected by an increase in retention duration than were normal controls. In other words, their performance was disproportionately impacted by keeping items in storage for a longer duration. Our data thus support a role for forgetting within WM on both sentence and operation span. Indeed, the classical stimulus order effect (Hitch et al. 2001) was confirmed in normal aging, MCI and AD. Since increasing the retention interval impacted storage and subsequent recall, it would appear that forgetting over time plays a role in WM, at least in complex span tasks. One point which was brought to our attention is the apparent lack of retention effect on sentence span for normal older adults. Although it may appear, looking at the results, that older adults have very little sensitivity to the retention interval manipulation, this result was not significant in the statistical analysis, as we did not find a significant Group x Retention interaction, nor a triple interaction with Material.

Another point concerning forgetting is that some studies suggest that ensuring appropriate encoding before recall eliminates the importance of delay length, especially in AD (Degenszajn, Caramelli, Caixeta, & Nitrini, 2001; Kopelman, 1991; White & Ruske, 2002). As the nature of our task did not afford us the liberty to apply any particular strategies to the encoding phase, we cannot rule out the impact of this variable. That being said, if weakness of encoding was the main culprit, we might not have observed the AD group being most sensitive to the manipulation of the duration of storage. The resulting interpretation, that forgetting plays a greater role in WM for AD than for normal aging, is further confirmed by the finding of reduced primacy in the face of preserved recency. This is coherent with the literature in AD suggesting that information encoded at an earlier time is subject to greater forgetting than that presented more recently in time (Buschke et al., 2006; Morris & Baddeley, 1988; Simon, Leach, Winocur, & Moscovitch, 1994). Although our findings involving the stimulus order effect can be attributed to forgetting over time, the exact nature of that forgetting is subject to great debate. As mentioned in the introduction to this dissertation, there exist many possible theoretical accounts of this effect. These accounts shall be discussed in relation to the current findings in a later section addressing theoretical implications.

5.1.1.2 Clinical implications

One goal of Experiment 1 was to identify and characterize the WM impairment in MCI in order to contribute to clinical knowledge. In this line of thought, perhaps the most remarkable finding in Experiment 1 was the prognostic value of the stimulus order effect found in both sentence and operation span tasks. Among individuals with MCI, those who later showed significant clinical deterioration or progression to AD were more impacted by retention interval than those who remained stable. This could not have been predicted from baseline assessments, as MCI who progressed did not statistically differ from MCI who remained stable in terms of age, educational level and performance on clinical measures. Hence, the stimulus order effect employed in this study was more sensitive in detecting future progression of disease than traditional clinical neuropsychological tasks.

This finding is coherent with previous studies showing that executive-type impairments, such as WM capacity as measured by the alphabetical serial recall task (Belleville et al., 2007) and semantic inhibition on the Hayling task (Belanger & Belleville, 2009), can predict future progression of MCI towards AD. These tasks all rely heavily on executive functions, in particular, attentional control. Consequently, the attentional control deficit typical of AD may also be present in MCI who significantly decline or progress to AD, making this impairment a marker for progression. Another contributing factor may be a more pronounced retention deficit in these groups, as performance on both alpha-span and stimulus order manipulation within complex span tasks is sensitive to forgetting. Hence, it may be that the two impairments appearing first in AD, information retention and attentional control, contribute jointly in making those tasks sensitive markers for future decline in MCI.

Also of interest is the fact that, as is reported in the literature (Ritchie & Tuokko, 2010), more multiple-domain MCI (around 58%) than single-domain MCI (around 23%) showed clinical deterioration or progression to AD in our study. It is known that as the disease progresses more cognitive deficits appear, which suggests that the multiple-domain MCI may have been subtly more advanced on the continuum of cognitive decline at baseline and thus, closer to conversion to AD.

In sum, our study lends support to the idea that multiple cognitive deficits, particularly information retention and executive attention, may represent sensitive markers for progression in MCI. This could have important implications for neuropsychological assessments aiming to better identify MCI at highest risk of developing AD. To our knowledge, clinical evaluations of MCI often include few measures of WM or attentional control beyond simple digit span tasks.

5.1.1.3 Alternative accounts of WM deficit

Other factors could play a role in the WM deficit found here on sentence and operation span tasks in MCI and, to a greater extent, in AD.

5.1.1.3.1 Lexical access

The fact that we found impaired WM in a verbal task requiring generation of to-be remembered items could be explained by impairment of lexical access (Belleville, Rouleau, & Van der Linden, 2006), as word finding difficulties have been well documented in AD (Astell & Harley, 1996; Balota & Ferraro, 1996). This concern is validated by the finding that the AD group performed significantly worse on a clinical measure of naming to visual confrontation (Boston Naming Test). In a preliminary analysis (not included in the article), we assessed the performance of participants on the processing component of the task: sentence completion. The proportion of correctly completed sentences across all attempted trials was 95.15%, 93.11% and 88.51% for controls, MCI and AD, respectively. Although individuals with AD did produce slightly more errors in generating a sentence-final word, their alternate responses most often consisted of words fitting the context. In addition, participants were scored on the correct recall of their generated word, even if this word was not the intended target. Thus, their recall performance was not dependant on whether they generated the correct word or not. Finally, perhaps the most convincing argument against a lexical access case is that performance on sentence span did not differ significantly from that of operation span, suggesting that the impact of word finding difficulties in the AD group was minimal at best.

5.1.1.3.2 Order recall

In a typical WM span, participants must recall sentence- or operation-final items in the correct temporal order. Maintaining the serial order of to-be remembered items solicits frontally-mediated executive processes (Marshuetz & Smith, 2006), such as organizational and strategic memory processes involved in information retrieval (Moscovitch, 1992). This serial requirement adds a layer of difficulty for healthy older adults (Rowe, 2010). If this is the case for normal aging, one may safely assume that the order requirement also makes WM span tasks more difficult for individuals with MCI or AD. In our study, errors were classified as omissions, order errors or intrusions. Omissions were the most frequent type of recall error, followed by order errors. Although this suggests that items were more often forgotten than misplaced, it is still possible that re-scoring participants' answers without the order requirement might lead to different results. However, our design makes this comparison impossible because not all participants completed the same number of trials, given our discontinue rule.

5.1.1.3.3 Proactive interference

Proactive interference (PI) is known to play a role in disrupting information retention within working memory (Jonides & Nee, 2006). In complex span tasks, PI may build up throughout ascending trials, as participants are exposed to an increasing amount of stimuli (Lustig, May, &

Hasher, 2001). In our study, order of presentation of conditions was counter-balanced to ensure that PI was relatively evenly distributed. However, the existence of a discontinue rule results in participants being exposed to differing levels of PI; for example, individuals attaining a span level of seven (usually healthy older adults) are exposed to more stimuli than persons ending at a span level of three (usually adults with AD). On the other hand, possibly off-setting the previous effect is the finding that individuals with AD and MCI, especially those who progress to dementia appear more vulnerable to proactive semantic interference in the first place (Ebert & Anderson, 2009; Loewenstein, Acevedo, Agron, & Duara, 2007; Loewenstein et al., 2004). Thus, AD and MCI groups may obtain shorter spans and be subjected to less PI, but be more affected by it. Support for impact of PI could be found in our finding of increased intrusions errors on complex span in AD. However, PI build-up does not appear likely as these errors were most often words of the current – not previous – trial, suggesting that items from previous trials were forgotten, not ''built up'' to create interference.

A second issue potentially involved in PI within WM span tasks is material similarity (Nairne, 2002). Some designs, as ours, include stimuli of the same nature (e.g. words, or numbers) for both processing and retention within the same task. Others increase the distinctiveness of the to-be-recalled items by making them a different material type; for example, an arithmetic operation followed by a word to be remembered. This has been shown to dramatically enhance performance by releasing much of the PI (Bunting, 2006). As mentioned above, the fact that AD and MCI are particularly susceptible to PI, coupled with our use of material-similar stimuli, may possibly have enhanced the group differences we obtained.

5.1.1.4 Theoretical implications for models of the stimulus order effect

As described in the introduction to this dissertation, WM span tasks are believed to involve two concurrent processes: manipulation and storage. The stimulus order effect strives to keep cognitive load constant while manipulating temporal duration of information retention in order to isolate the passage of time (Hitch, Towse, & Hutton, 2001). Task-switching views of WM propose that time-related decay impacts recall performance (Towse & Hitch, 1995) which, in a way, resembles Salthouse's (1996) principle of simultaneity in aging whereby the products of early processing may no longer be available at a later time because of slowed speed of processing. On the other hand, accounts focusing on limited attentional resources stipulate a trade-off between processing and storage demands (Case, 1985; Saito & Miyake, 2004).

Our results could be interpreted as lending support to both views. The fact that retention duration showed a unique contribution to the magnitude of deficit in AD and in MCI who deteriorated suggests that temporal factors do indeed play a role within WM. This interpretation is especially appealing since AD is a disease known for its devastating impact on information retention over time. The time-based view is further supported by our finding of reduced primacy in AD, suggesting that items learned earlier in time are subject to greater forgetting than more recent items. On the other hand, there is a potential confound in the paradigm, as the stimulus order effect, as it was constructed in our experiment, can also be re-interpreted to measure interference between processing and storage (Saito & Miyake, 2004). Indeed, the long-final condition exposes the participant to more words during the retention interval than does the short-final condition. In the context of limited attentional resources, this trade-off is what appears to elicit the executive control component involved in WM spans (Jarrold & Towse, 2006). Accordingly, our results could be explained by the known executive deficits documented in AD. Two findings support this executive, or attentional control, view. First, the AD group performed significantly worse on a clinical measure of attentional inhibition capacities (Stroop task). Second, individuals with AD produced significantly more intrusions errors (non-target words from the current trial). Taken together, these findings could suggest that the stimulus order effect in WM spans is not only measuring forgetting over time, but also the executive, inhibitory control ability to "delete" irrelevant items so that they are not mistakenly retrieved during recall (Hasher et al., 2007).

5.1.2 Cognitive intervention

The goals of last two experiments were to examine the efficacy of a computerized protocol of attentional control training. In Experiment 2, the feasibility of design as well as the direction of VP training effects were measured in healthy older adults and persons with MCI. The third study carried out a double-blind randomized controlled study of the training protocol. Four main innovations were added to the first design: (a) the study focused solely on individuals with MCI <u>and</u> an executive deficit; (b) an active control condition (FP training) was added; (c) training frequency was augmented; (d) a meta-cognition enhancement (self-regulatory) step was added, based on research showing the importance of awareness in cognitive interventions (Clare et al., 2004).

5.1.2.1 Training effects

In both our experiments, VP strategy showed significant benefits in reducing the dual-task accuracy cost on the main outcome measure. This shows that modulating attentional priorities throughout different blocks and receiving feedback allowed participants to develop enhanced executive coordination skills. Thus, they became more adept at managing competing priorities through self-regulation of their own attentional control. Rote practice (FP training) with the same dual task did not produce similar effects in Experiment 3, indicating that simple exposition and repetition drills were not the source of the newly learned skill. This finding is coherent with previous reports of a VP training advantage in healthy older adults. Indeed, Kramer showed superior benefits of VP over FP training in normal aging (Kramer, Larish, & Straye, 1995; Kramer, Larish, Weber, & Bardell, 1999). However, our results contrast with other studies showing similar training effects for both VP and FP strategies (Bherer et al., 2005, 2008).

Differences in methodology may partly account for these discrepancies. Whereas our study and that of Kramer et al. (1995) employed numerical proportions (e.g. 20-80, 50-50) in the variable-priority instructions given to participants, Bherer et al.'s studies included verbal statements, such as ''Respond to this task first''. This could be construed as more of a direct rule to follow rather than a prioritization goal to attain in a strategic manner. In terms of data analyses, Bherer et al.'s analyses employed ANCOVAs to control for age-related slowing in speed of processing difference. As our study did not include distinct age groups, we chose not to use speed as a covariate with the assumption that all MCI participants exhibited similar slowing, though it is possible that this may not have been the case.

The most salient difference across these studies of VP training is the nature of the tasks used in training. This is perhaps the most likely explanation for the contrasting findings. While our protocol included a self-paced working memory task (alphabet-arithmetic) in combination with a forced-paced detection task with variable-appearing stimuli, Bherer et al.'s design consisted of concurrent two-choice, forced-pace discrimination tasks which involved fixed timing and discrete presentation of stimuli. Clearly, the nature of these tasks differs greatly. It is possible that the inclusion of one self-paced task afforded more room for individuals to try out different strategies and switch between tasks, as they controlled the response speed (up to around 5 seconds). Also, the fact that the stimuli appeared at fluctuating – not fixed – intervals for the second task may have contributed to making the dual-task more difficult and unpredictable. These two factors appear to have enhanced the development of dual-task coordination skills in our protocol. Of the two designs, Kramer et al's study most resembles our experiments. Moreover, we both included the same alpha-arithmetic task of working memory as part of the paradigm. Interestingly, Kramer found VP training to be superior to FP training, just as we did. In consequence, the nature of the tasks used may explain why VP strategy showed significant superiority over FP training in these studies. In sum, it appears that VP training consistently leads to superior benefits as compared to a non-active control condition, but only when using certain experimental tasks does VP training produce greater effects than FP training.

5.1.2.2 Control training conditions

The aforementioned data underlines the importance of selecting an appropriate control training condition in the design of intervention studies. One wants an active control condition to make sure that training effects are observed only in the experimental protocol – not in a group stimulated otherwise– and thus are attributable to the specific ingredients in the training regimen. However, using a condition that trains the actual target component may be a problem if the control is too active, in the sense that it closely resembles the training protocol.

Comparing an intervention to a control condition that is particularly active (such as FP) may mask obtained gains, though it certainly represents a strong test of the studied hypothesis. For example, in experiment 3, both FP and VP training produced improvements on certain distal outcome measures: focused attention, speed of processing, switching abilities. This could be interpreted as test-retest practice effects, but only comparison with a waiting-list-type control group would have clarified this point. As it stands, we cannot posit with certainty that gains demonstrated by both FP and VP groups represent equal training effects from both priority conditions or, alternatively, practice effects.

On the other hand, relying solely on a waiting-list-type or passive control group for comparison purposes may lead to overestimation of training-specific effects, since benefits could always be attributable to general cognitive stimulation, or to some non-specific effect related to receiving a treatment. In fact, a very recent Cochrane Review by Martin, Clare, Altgassen, Cameron, & Zehnder (2011) stresses caution in interpreting improvements following cognitive intervention in healthy aging and MCI (these studies focused on memory training). The authors concluded that although most changes observed were positive gains, they did not exceed the improvement in active control conditions. Therefore, it appears that the ideal study design would include both active and passive control groups against which to compare obtained trainings effects.

5.1.2.3 Generalization effects

One of our objectives in Experiment 3 was to determine generalization of training effects to proximal and distal outcome measures. Our analyses did not detect any transfer effect on the proximal outcome measure: a dual-task comprised of a two-choice visual detection task combined with a classical digit span task. This finding is consistent with Bherer et al. (2008)'s null results on their cross-modality transfer tasks following a VP training regimen. Transfer effects have proven elusive in most studies (Noack et al., 2009) and improvements are often domain-specific (Li et al., 2011). Our proximal outcome measure was a cross-modality dual-task and, thus, probably too dissimilar to the trained dual-task to demonstrate generalization. Had we included a within-modality transfer task, for example, a dual-task consisting of two visuo-motor tasks similar to the ones used in training, we hypothesize that transfer might have been found. Worthy of note is the fact that we did observe a trend towards significant improvement for the VP training group on one distal outcome measure: a dual-task involving visual selective attention in combination with an auditory counting task. Looking back, this transfer task could be considered slightly closer in nature than our proximal transfer task, even though it was not computerized and output modes were different. As for the other distal outcome measures, both FP and VP training produced improvements on certain tasks: focused attention, speed of processing, switching abilities. This could indicate transfer effects from both types of training, as was found by Bherer et al. (2005, 2008). To summarize, we uncovered some evidence for transfer effects of VP training in our experiment, but it is not particularly strong. This particular limitation has been repeatedly reported in studies of cognitive intervention with older adults (Noack, Lovden, Schmiedek, & Lindenberger, 2009; Owen et al., 2010) and unquestionably necessitates further study.

5.1.3 Contribution of assessment to intervention design

Intervention should be based on a model of impaired and intact capacities. Therefore, in-depth comprehension of impaired WM components in MCI is important to devise appropriate training programs. One may propose that the training tasks employed in Experiments 2 and 3 are quite remote from the tasks used in Experiment 1. However, we will argue that this is not the case. Working memory, seen as an executive system of attentional control, is related to retention by the maintenance of information in an active and quickly retrievable state. Consequently, training the executive control component should benefit WM by enhancing maintenance of information in an active state in the face of interference.

More concretely, our study of complex span led us to conclude that not only does forgetting play a role in WM performance, but that attentional control deficits also impact storage. Indeed, the executive capacity to manage interference resulting from the coordination of concurrent storage and processing demands is impaired in AD and MCI. This result highlights the importance of distinguishing different components within executive functioning and also led us to the hypothesis that training this specific coordination skill would result in improved WM capacities. We could have chosen to have participants simply practice one WM task, such as the alpha-arithmetic task embedded in our dual-task paradigm. However, the components within that type of task (processing and retention) are quite intertwined and it may have been difficult for individuals to distinguish them and modulate their attention between the two. Instead, we chose to train it concurrently with another task (visual detection) while varying the proportion of attention allocated to each task. This proved to be superior to active attentional control practice, thus confirming our initial hypothesis that the executive capacity to coordinate and manage interference is a central key in WM training.

The findings from the assessment and intervention studies in this thesis confirm the importance of undertaking a detailed evaluation of the components involved in a cognitive deficit before elaborating a training protocol. We show that the designated skills targeted during training need not be the exact ones used in assessment, as the most important factor for soundness of design is the theoretical underpinnings. Ideally, we would have enrolled our participants from the first study in the second and third studies, but this was not possible in logistic terms. Nevertheless, we did focus our second intervention on MCI with executive deficits, only their assessment was based on clinical – not experimental – tasks.

5.2. Strengths

One of the strengths of the studies included in the present thesis is the depth of the neuropsychological assessment of MCI participants. Indeed, individuals were evaluated with a vast number of clinical measures in order to accurately characterize their profile and confirm their classification. This also permitted us to identify and focus on MCI with executive deficits in our third study. This is a powerful methodological detail, given the vast variability in MCI subtypes. To our knowledge, no intervention study as yet controlled for the type(s) of cognitive deficit(s) of MCI participants.

Furthermore, the experimental WM tasks employed within our studies are highly-controlled and precise in nature. This allowed us to perform fine-grain analyses of cognitive components involved; for example, isolating the temporal contribution in WM span, or quantifying dual-task decrements for both accuracy levels and RTs within attentional control. Our studies were also solidly theory-based, in that they aimed to verify specific hypotheses based on cognitive models. This included models of WM and the stimulus order effect in complex spans for the first experiment, and executive control models for the second and third experiments. In addition, our randomized-controlled training study incorporated a novel self-regulation strategy promoting meta-cognition, based on the theory that increasing control beliefs and goal setting abilities can enhance performance. Additional strengths of this experiment include comparison of training group with an active control group (FP training), numerous generalization measures to evaluate transfer effects and, finally, controlling for a variable known to affect cognitive performance in aging: circadian arousal patterns (May, 1999; Rowe, Hasher, & Turcotte, 2009). In experiment 3, which involved intra-individual comparisons of pre- and post-training measures, we tested participants at their preferred time of day (peak time) for both pre- and post-training sessions, to ensure observed effects were not due to time-of-day-dependant differences in arousal.

5.3. Limitations

5.3.1 Sample composition

Though the studies included in this dissertation boast many strong points from both methodological and innovative viewpoints, it is equally important to address some of their limitations. In terms of sample composition for the first experiment, our participants with Alzheimer's disease were carefully diagnosed by experienced geriatricians or neurologists on the basis of an extensive clinical and neuropsychological assessment and they met NINCDS-ADRDA research criteria for probable AD (McKhann et al. 1984). However, their pathology was not confirmed by autopsy, a criteria which would have made their diagnosis definite. Concerning our participants with mild cognitive impairment, they formed a rather heterogeneous group, with some meeting criteria for amnestic single domain MCI, amnestic multiple domain MCI, etc. (Gauthier et al., 2006; Petersen et al., 1999). As studies have shown that the multiple domain subtype carries a higher risk of developing dementia than the amnestic single domain counterpart (Ritchie & Tuokko, 2010), it is possible that these participants were situated at different points on the continum between normal aging and AD. A second important point is the unknown aetiology of these participants with MCI. Indeed, there is mounting evidence for the existence of a vascular MCI subtype, the prodromal phase of vascular dementia (Frisoni, Galluzzi, Bresciani, Zanetti, & Geroldi, 2002), as well as MCI of mixed aetiology combining both AD pathology and vascular factors such as hypertension, hypercholesterolemia, obesity and diabetes (Knopman & Roberts, 2010). Accordingly, we do not know if all our participants with MCI truly represented incipient AD or another form of dementia (Jicha et al., 2006). Although these uncertainties in sample composition are of importance for characterizing the cognitive profile of these populations in the first experiment, they are of less importance for the intervention studies, given that the main goal of these was intra-individual improvement and not inter-group comparisons.

5.3.2 Design and methodology

In terms of methodology and design, some caveats already mentioned in the articles included, for the first experiment: lack of reaction time data, added requirement of order recall, and level of task difficulty too high for individuals with more advanced AD. For the cognitive intervention studies, limits mentioned were lack of passive control group, absence of within-modality transfer task, and no long-term follow-up to assess lasting effects. Moreover, conducting these experiments with clinical populations carries the often-mentioned drawback of dealing with small sample sizes, especially for the cognitive training studies. Fortunately, our numbers proved sensitive enough to answer most of our research questions. Furthermore, all our computerized training protocols involved training more than one participant at a time, with the intention of saving time and resources, as in many intervention studies. However, this may create a potential psychosocial confound, as participants interacting amongst themselves may be considered a form of social stimulation or networking, which has been shown to moderate the impact of brain pathology on cognitive function (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). Hence it is possible that part of the shared benefits observed for both VP and FP training could have been induced by social stimulation and mood enhancement, although this seems unlikely given the fact that VP training did show an advantage over FP training on the main outcome measure.

5.4. Future directions

The data reported in the present thesis offer original contributions to the scientific literature on working memory (WM) in mild cognitive impairment (MCI) and Alzheimer's disease (AD) and open new doors to further research possibilities. With regard to complex span tasks, additional investigations should be made into the neural correlates of the interaction between processing and storage constructs. From a clinical perspective, future studies should focus on the conception of neuropsychological tasks sensitive to retention interval, as this tool may hold promise as a predictive marker in distinguishing persons with MCI who will progress to AD from those who remain stable in the short-term. This could lead to better detection rates and prospects of earlier interventions, both pharmacological and cognitive in nature.

As for cognitive interventions, improving transfer effects remains a top priority, perhaps by developing a more individualized, adaptive and multidimensional regimen. Inclusion of pre-training teaching (for example, education about memory or stress reduction) might enhance likelihood of success (Floyd & Scogin, 1997). Pharmacological treatment might potentiate training (Yesavage et al., 2007), as could physical exercise (Larson, 2008; Thiel et al., 2011). For complex activities involved in daily functioning (for example, using a phone), it may be necessary to train the targeted task directly, especially for more advanced stages of cognitive impairment (Lekeu, Wojtasik, Van der Linden, & Salmon, 2002).

In terms of sample identification, apolipoprotein E (ApoE) genotyping could be useful in increasing the probability that participants selected for future studies are indeed situated on the disease continuum (Elias-Sonnenschein, Viechtbauer, Ramakers, Verhey, & Visser, 2011).. Indeed, ApoE ε4 is a well-known genetic risk factor for development of AD (Poirier et al., 1993). Even non-demented older adults with an APOE ε4 allele show greater cognitive (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002) and neural (Bondi, Houston, Eyler, & Brown, 2005) changes than ε4 non-carriers, especially ApoE 4 homozygotes (Caselli et al., 2007). Moreover, there exist other specific factors known to potentially moderate cognitive function, response to training and progression of disease (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). For example, lifestyle and environmental variables such as participants' baseline level of physical exercise (Lautenschlager et al., 2008), social networking (Bennett et al., 2006), bilingualism (Craik, Bialystok, & Freedman, 2010), chronic stress (Marin et al.) and medications (Ancelin et al., 2006; Knegtering, Eijck, & Huijsman, 1994). These could be useful to measure in future studies, as they may influence cognitive performance.

Finally, the upcoming years will reveal very interesting insights into the neural correlates of brain plasticity in MCI, as brain imaging studies focus on which brain structures are involved in post-training improvements (Belleville et al., 2011). From a theoretical viewpoint, studying breadth of transfer may provide insight into the neural mechanisms underlying brain plasticity. As mentioned previously, in healthy adults, WM is thought to involve parietal as well as prefrontal cortices (Wager & Smith, 2003) and WM training has been showed to increase cortical activity in these same regions (Olesen, Westerberg, & Klingberg, 2004). This multi-modal frontoparietal network does not appear to be stimulus-specific and thus, could represent the basis of training-induced plasticity. As long as the tasks used in training solicit this neural network which appears to be commonly activated in WM, transfer effects should be obtained, irrespective of sensory modality (Klingberg, 2010). Alternatively, others have proposed that although fronto-parietal activity can be modified by training, it is subcortical regions which mediate transfer effects to novel tasks. Indeed, in a review focusing on updating training, Dahlin, Bäckman, Neely, & Nyberg (2009) conclude that increases in subcortical areas activity following training are linked to the newly acquired skill. Finally, a different principle of transfer has been suggested to involve not brain regions, but neurotransmitter systems recruited during training. As recent evidence has found dopamine to be involved in WM plasticity (Brehmer et al., 2009), it has been proposed that transfer effects could be at least partly mediated by underlying neurotransmitter activity common to both trained and non-trained tasks (Klingberg, 2010). These studies have all been conducted in healthy populations and thus, it remains to be seen if similar mechanisms are responsible for WM training and transfer effects seen in MCI.

CONCLUSION

The present thesis focused on two clinical aspects of working memory (WM): assessment and intervention. Overall, our results fit with the idea of a progressive WM deficit from healthy aging to degenerative disease, with a gradient between MCI and AD. They are the first to show impairment on complex span tasks, the most widely used measures of WM capacity. Moreover, using the stimulus order effect, our experiment underlined the contribution of forgetting within the WM deficit in AD. We also highlighted the impact of this variable as a marker for deterioration in MCI, which has important clinical implications in terms of characterizing the profile of individuals at highest risk of developing AD. Once identified, these individuals can profit from early intervention studies. Indeed, the experiments included in this thesis emphasized the feasibility and importance of intervention for the attentional control component of WM in persons with MCI and an executive deficit, suggesting preserved plasticity of attentional capacities. Computerized training protocols, notably variable-priority training, hold promise as an intervention tool. However, further research is required into the optimisation of transfer effects to novel tasks and everyday activities. Future studies may also focus on identifying the neural correlates of training-induced plasticity

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