Virtual Reality-Based Spatial Memory Intervention in
Patients with Mild Cognitive Impairment

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ABSTRACT

Patients with Mild Cognitive Impairment (MCI) typically show atrophy of the hippocampus, which is a major risk factor for developing Alzheimer’s disease. Prevention of hippocampal atrophy is therefore important as it may delay the onset of dementia. Previous research in our laboratory showed a specific association between the hippocampus and spatial memory (i.e., memory for locations or places). We thus developed a computerized spatial memory improvement program (SMIP) that stimulates the hippocampus. In this study, healthy older adults and participants with MCI were assigned to receive SMIP training, or not. Following training, we found that SMIP-trained healthy older adults showed significant spatial memory improvements. SMIP-trained MCI participants likewise showed individual spatial memory improvements after training. Though these results are preliminary, they are promising and suggest the effectiveness of SMIP at reducing symptoms associated with MCI.
Les patients atteints de trouble cognitif léger (TCL) présentent habituellement une atrophie de l'hippocampe, un facteur de risque majeur pour le développement de la maladie d'Alzheimer. Il est donc important de prévenir cette atrophie hippocampale car cela pourrait permettre de repousser la venue de la démence. Des études précédentes menées au sein de notre laboratoire ont démontré qu'il existe une association spécifique entre l'hippocampe et la mémoire spatiale, définie comme étant la mémoire des lieux. Nous avons donc développé un programme d'entraînement de la mémoire spatiale (PEMS) informatisé qui stimule l'hippocampe. Dans la présente étude, des patients atteints de TCL et des personnes âgées saines ont été assignées soit au groupe recevant l'entraînement PEMS soit au groupe contrôle sans entraînement. Après l'entraînement, les participants sains ayant été entrainés à l'aide du PEMS ont présenté une amélioration significative de la mémoire. Les participants TCL ayant reçu l'entraînement ont de même démontré des améliorations individuelles de la mémoire spatiale. Bien que ces résultats soient préliminaires, ils sont prometteurs et suggèrent que le PEMS pourrait effectivement aider à réduire les symptômes associés au TCL.
Chapter 1 Introduction

1.1 Alzheimer's Disease

Alzheimer’s disease (AD) is the most prevalent form of dementia. Clinically, diagnosis of this neurodegenerative disorder is confirmed through post-mortem histopathological studies of brain tissue, where probable AD is determined by an accumulation of amyloid plaques (sticky build-up of beta amyloid protein that is toxic to neurons) and the formation of neurofibrillary tau protein tangles (insoluble structures that prevent efficient nutrient transport between neurons) (Haroutunian et al., 1998; Price, Davis, Morris, & White, 1991). Neurodegeneration occurs, first in the entorhinal cortex and then in the hippocampus (HPC) of the temporal lobes gradually resulting in atrophy of these regions and in spatial memory problems, which is one of the first symptoms of AD (Apostolova et al., 2006). With time, atrophy may progress to regions of the neocortex (Henry-Feugeas, 2007; Schuff et al., 2009). As a result, patients with AD exhibit pathological memory decline and cognitive dysfunction e.g. trouble with language, decreased thinking abilities, which eventually deteriorates their quality of life. Currently, AD accounts for at least 65% of dementia cases, and is a major human, social, and economic burden. Research into
the early predictors and treatment of dementia is therefore necessary to offer potential prevention, appropriate care and support.

1.2 Mild Cognitive Impairment

One line of research that strives to investigate the early predictors of AD involves patients with mild cognitive impairment (MCI). MCI is often diagnosed in accordance with Peterson’s criteria (1999) which include subjective complaints of memory loss by the individual or family, no loss in activities of daily living, and documented objective abnormalities on a clinician’s mental status assessment that briefly covers all cognitive domains. Unlike AD, the cognitive decline of patients with MCI does not interfere with their activities of daily living.

MCI diagnostic criteria have involved subjective reports by individuals but also objective screening methods that assess cognitive functions, and brain activity and morphology. For instance, the Montreal Cognitive Assessment (MoCA), which has been shown to be sensitive to MCI, and the Mini-Mental State Examination (MMSE) have been used extensively in tandem as objective measures of global cognitive function (Folstein, Robins, & Helzer, 1983; Nasreddine et al., 2005). Further, neuropsychological work-up for detecting MCI has involved measures of delayed recall e.g. Logical Memory II Task (Weschler, 1987) and
executive function tests as poor performance on these tests have been shown to be predictors of progression to dementia (Andersson et al., 2006). Recently, objective screening methods have involved the additional use of neuroimaging and electrophysiological techniques such as Magnetic Resonance Imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET), for their sensitivity to MCI. Indeed, MRI studies have found that individuals with MCI show medial temporal lobe atrophy compared to controls (Burggren et al., 2011; Jack et al., 1999; Kantarci et al., 2009; Risacher et al., 2009; D. Zhang & Shen, 2012). FDG-PET findings have furthermore shown that MCI participants exhibit significant hypometabolism in the anterior parahippocampal gyrus and hippocampus compared to healthy controls (De Santi et al., 2001).

Currently, studies have focused on biomarkers commonly used in AD diagnosis work-up, such as total tau, phosphotau and β-amyloid taken from CSF samples, as potential predictors of progression to dementia in individuals with MCI (Blennow & Hampel, 2003; Hampel et al., 2004). Thus, MCI patients show impairment on measures that are affected in AD.

Patients with amnestic MCI (aMCI), where memory impairment is predominant, are of particular interest as they have shown AD pathology in pre- and post-mortem studies. For example, post-mortem analyses
conducted by Petersen and colleagues (2006) showed that all 15 participants with aMCI had neurofibrillary tangles in their medial temporal lobe which includes the HPC. A longitudinal study using volumetric analyses also found that patients with aMCI who developed AD after 3 years exhibited progressive hippocampal atrophy which is among the most prominent symptom of AD (Apostolova et al., 2006). Thus far, longitudinal studies investigating the proportion of MCI participants with low measures of HPC who convert to AD indicate annual conversion rates ranging from 17-44% (Amieva et al., 2004; Geroldi et al., 2006; Geslani, Tierney, Herrmann, & Szalai, 2005; Korf, Wahlund, Visser, & Scheltens, 2004; Schmidtke & Hermeneit, 2008). Hence, MCI is commonly viewed as an intermediate stage between normal aging and AD (Werner & Korczyn, 2008). Therefore, a substantial amount of research has focused on determining factors that may prevent the onset of AD among the MCI population.

1.3 The Hippocampus

A commonality that is shared between both the MCI and AD patient populations is HPC atrophy. The HPC is one of the first areas to be affected in AD (Altemus & Almli, 1997). Anatomically, this brain region is part of the medial temporal lobes, and belongs to the limbic system.
Accordingly, the HPC was historically thought to be involved in emotions (Papez, 1937); however, this idea shifted in the 1950's when research spurred by Dr. Brenda Milner’s studies of the epileptic patient H.M. (who became globally amnestic after bilateral resection of his medial temporal lobes) showed that the HPC was important in learning and memory (Scoville & Milner, 1957). Since then, the HPC has been hypothesized to be implicated in spatial memory (J. O'Keefe, & Nadel, L., 1978), episodic memory, i.e. memory for life events (Nadel & Moscovitch, 1997), explicit/declarative memory, i.e. conscious learning (N. J. Cohen, & Squire, L.R., 1980; Tulving, 1972), and relational memory, i.e. memory for associations (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996). Importantly, hippocampal place cells, which fire when an individual is in a specific place in an environment, were found in rodents (J. O'Keefe & Conway, 1978; J. O'Keefe & Dostrovsky, 1971), monkeys (Ono, Nakamura, Fukuda, & Tamura, 1991; Ono, Tamura, & Nakamura, 1991), and humans (Ekstrom et al., 2003) thereby implicating the hippocampus in spatial memory. These discoveries delineated the involvement of the HPC in the formation of cognitive maps and therefore the role of this brain region in sustaining spatial memory (J. O'Keefe, & Nadel, L., 1978).
1.4 Spatial Memory and Navigational Strategies

Spatial memory refers to an individual’s memory for locations, or how one finds their way, or navigates, from one place to another by using the relationship between landmarks in the environment. Neuroimaging studies in healthy young adults and lesion studies in non-human animals have demonstrated that navigation can be achieved by using two different strategies that depend on separate brain systems. One method, the spatial strategy, involves using knowledge of the relationship between environmental landmarks to form a cognitive map of a given environment (J. O'Keefe, & Nadel, L., 1978). For example, an individual may know that the library is East of home and that the park is North of home. Therefore, when going to the library from the park, he or she will head South-East.

Spatial learning has been shown to be critically dependent on the function of the HPC (Morris, Garrud, Rawlins, & O'Keefe, 1982). The other navigational method, the response strategy, relies on the establishment of a series of movements in response to a specific stimulus (e.g., turn left at the corner). If the person in the above example did not learn the relationships between the home, library, and park, he/she would be more likely to take a detour home, i.e. walk from the park to home to the library.

Response learning involves using well-known and automatized paths to
navigate. Unlike the spatial strategy, it does not permit the establishment of more efficient navigation through unexplored portions of the environment. Thus, if the person using response learning encounters obstructions in his/her old path, he/she would not be able to find a new route to the library as easily. Response learning is dependent on the striatum, which includes the caudate nucleus (CN) and the putamen (Packard, Hirsh, & White, 1989).

1.5 The Role of the Hippocampus in Spatial Memory

Rodent models of amnesia and lesion studies in humans have revealed the importance of the HPC for spatial memory. Indeed, rodent studies demonstrated that hippocampal-lesioned rats have long-lasting spatial memory deficits (Altemus & Almli, 1997; Morris et al., 1982; Olton & Papas, 1979). In humans, Pigott and Milner (1993) showed hippocampal involvement in spatial memory in patients with medial temporal lobe excisions that include the hippocampus. Morris and colleagues (1996) demonstrated that patients with right medial temporal lobe damage were impaired on computerized spatial tasks. Maguire and colleagues (1996) furthermore reported that patients with either right or left medial temporal resections had impaired scene recognition performance compared to controls on a spatial memory task that required subjects to
watch and learn about a real-life environment from a video. Bohbot and colleagues (1998) also found that patients with selective lesions to the right hippocampus, sparing adjacent medial temporal lobe cortices, were impaired on measures of visuo-spatial memory i.e., the object location task and Rey-Osterrieth Figure Task, providing further support for the role of the HPC in spatial memory. A PET study, where healthy participants explored a virtual environment containing either salient objects or none, further delineated the involvement of HPC surrounding regions by showing that the presence but not absence of salient objects elicited an increase in right parahippocampal activity (Maguire et al., 1998). Recently, Rauchs and colleagues (2008) strove to determine the neural correlates of memory-based virtual navigation, where participants freely explored a virtual town and were then scanned using fMRI while retrieving their way between two locations under four navigation conditions designed to probe spatial versus contextual (environment-dependent) memory components. They found that hippocampal activity was primarily associated with the spatial component. Another study has likewise indicated that good navigators make use of the HPC during consolidation of relevant landmarks (Janzen, Jansen, & van Turennout, 2008). These results show
that both the HPC and its surrounding regions are involved in processing spatial information in humans.

1.6 Dissociation of Spatial and Response Strategies

Past rodent studies have demonstrated the dissociation of hippocampal-dependent spatial and caudate nucleus and striatal-dependent response strategies. In their study that required rats to learn the location of a hidden platform in a water maze, McDonald and White (1994) found that rats with dorsal striatal damage acquired both the visible and hidden versions of the task, but preferentially swam to the old spatial location when given a choice of the spatial location they had learned and the visible platform in a new location. Conversely, rats with fornix damage (resulting in disruption of hippocampal efferents) were impaired on acquiring the hidden version of the task, but swam to the visible platform even when it was moved to a new location. Hence, these results support the independent functions of the hippocampus and striatum in spatial and response learning. Similarly, in their inactivation experiments which required rats to learn the location of a consistently baited arm in a cross maze, Packard and McGaugh (1996) found that control rats used spatial strategies on the Day 8 probe trial (where rats were placed in a different starting position), which was disrupted by lidocaine deactivation of the
hippocampi, i.e. rodents showed no preference for spatial or response learning. By Day 16, control rodents showed response leaning. Rodents with deactivated hippocampi also showed response learning on the Day 16 probe trial indicating no effect of hippocampal inactivation. Conversely, rats with lidocaine deactivated striatum displayed spatial learning during both the Day 8 and Day 16 probe trial indicating a blockade of response learning following striatum inactivation. Further, they found that while saline-treated rats showed spatial learning at Day 8, they displayed response learning at Day 16 indicating a shift in learning strategies with extended training. Thus, these results provided evidence for the dissociation of hippocampal-dependent spatial strategies and striatum-dependent response strategies.

The Bohbot laboratory further demonstrated the dissociation of spatial and response strategies when testing young adults on the 4-on-8 Virtual Maze, a task that requires remembering the locations of 4 objects in an 8-arm radial maze and can be solved using either navigational strategy. Participants who spontaneously used spatial strategies exhibited increased HPC activity (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003) in addition to increased HPC grey matter (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007). Conversely, participants who spontaneously used
response strategies exhibited corresponding increases in caudate nucleus (CN) activity and grey matter. They additionally found that with practice, some subjects who began with a spatial strategy to solve the task shifted to the response strategy (Bohbot et al., 2007; Iaria et al., 2003). This supports the temporal dynamics demonstrated in rats by Packard and McGaugh (1996) described earlier. Bohbot and colleagues’ study (2004) showed medial-temporal lobe damaged patients who tried to use spatial strategies on a virtual navigation task made more errors compared to those patients who used response strategies. Thus, these results provided additional support that response strategies involve neural circuitry independent of the HPC and spatial strategies.

1.7 Effects of Spatial Memory Use on the Hippocampus

Studies in birds, mice and humans have provided evidence of increased HPC volume as a result of extended spatial memory use. Indeed, a study in chickadees has shown that these food-storing birds, which learn the precise geographical layout of a region to locate food stores, have increased HPC volumes relative to non food-storing birds. Moreover, the HPC size varies according to demand: in seasons where the demand on spatial memory is the greatest, the HPC of these food-storing birds enlarge (Sherry & Hoshooley, 2010). Similarly, mice given
spatial memory training show increased HPC volume whereas mice given response training show increased striatum volume (Lerch et al., 2011). These results indicate that the HPC can change with spatial memory use and is relevant for accurate retrieval of stored items among these species.

In humans, London taxi drivers who have a high dependence on navigational skills exhibit a significantly larger posterior HPC bilaterally than control subjects who did not drive taxis. Moreover, there was a positive correlation between taxi-driving experience with increased volume of the posterior HPC (Maguire et al., 2000). These findings suggest that the use of spatial learning has a positive impact on HPC volume over time.

1.8 Spatial Memory and Aging

Studies in animals and humans have indicated age-related changes in spatial memory use and performance. Indeed, Barnes and colleagues (1980) found that senescent rats showed poorer performance in navigation tasks compared to middle-aged rats, suggesting that spatial memory deficits occur with age. Further, senescent rats used response strategies instead of spatial strategies when performing the tasks. Recently, studies in humans from the Bohbot laboratory have demonstrated that the use of spatial strategies decreases across the lifespan: 85% in children, 50% in young adults, and 40% in older adults.
Using voxel-based morphometry, the Bohbot laboratory has also showed that older adults who used spatial strategies while performing the Concurrent Spatial Discrimination Learning Task, a virtual task that requires remembering the locations of 6 objects in 6 pairs of a 12-arm radial maze and dissociates the two navigational strategies, had more hippocampal grey matter (submitted). Other studies in humans have demonstrated an age-related deterioration in spatial memory. For instance, Driscoll and colleagues (2003) showed that older adults had place-learning deficits compared to young adults on a computer-administered task, the Virtual Morris Water Maze Task (VMWT), in which participants were trained to navigate to a hidden platform within a circular pool located in a virtual square-shaped room based on the platform’s fixed location to distal cues. They furthermore found that these place-learning deficits were associated with decreased hippocampal volumes. A study by Iaria and colleagues (2009) additionally found that older adults made more errors than young adults when finding target landmarks in a virtual town, where participants were first given time to explore and learn the locations and spatial arrangements of six target landmarks. More specifically, older adults showed decreased efficiency in forming cognitive maps, as evidenced by the longer time it took for them to accurately point out
locations of landmarks during learning. While these memory findings could be explained by general cognitive decline in the elderly, this also suggests that there is an age-related deterioration in the hippocampus which may be associated with decreased use of hippocampal-dependent spatial strategies.

1.9 Spatial Memory in AD and MCI Patients

Since HPC integrity is important for spatial memory, and HPC atrophy is a hallmark of AD pathology, numerous studies have investigated whether spatial memory is affected in AD and MCI patients. Some studies have demonstrated that AD and MCI patients have impaired spatial navigation abilities. Indeed, Hort and colleagues (2007) found that both AD and MCI patients exhibited impairment on the Hidden Goal Task (HGT), a human analog of the Morris Water Maze that requires participants to locate an invisible goal within a fully enclosed cylindrical arena. Similarly, another study found that AD and MCI patients could not identify target locations on a map or recall the order in which these locations were encountered in a route-learning task. Further, the spatial deficits observed in these AD and MCI patients were associated with atrophy of the right posterior hippocampus and right parietal lobe (Deipolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007). This
association was additionally demonstrated by Nedelska and colleagues (2012), when testing AD and MCI participants on the HGT. Clinically, these findings coincide with the Getting Lost Behaviour (GLB), the inability to find one’s way, that is prominent in the early stages of AD (Chiu et al., 2004). GLB may have drastic consequences on the safety and daily living of elderly adults because it imparts an increased risk for falling on the way home as a result of disorientation. Moreover, caregivers of individuals exhibiting GLB may experience complications i.e. the need for constant monitoring. As such, there is a need for research in intervention measures that are aimed at improving memory.

1.10 Memory Intervention Studies

Healthy Populations

Behavioural studies in healthy young and older adults have provided some evidence for the feasibility of intervention techniques. Several studies have shown training-related improvements in targeted domains e.g. dual-task training, speed of processing, auditory information processing, among healthy young and older adults (Bherer et al., 2008; Mahncke et al., 2006; G. E. Smith et al., 2009). Some studies have furthermore shown that training-related improvements can generalize to a wide variety of cognitive tasks. Participants in one study were trained in
visual and auditory selective attention that involved actively suppressing distracting background noise in four different task categories. For instance, under the visual task with auditory distractors condition, participants had to detect, classify, and/or sequence visual presentations of letters or numbers while sounds were played on speakers. They found that participants trained in visual and auditory selective attention demonstrated significant improvement in selective attention compared to controls but also showed significant improvement in untrained outcomes including speed of processing (Mozolic, Long, Morgan, Rawley-Payne, & Laurienti, 2011). Training-related improvements can likewise generalize to daily function. Indeed, in a study involving training in three different domains- verbal episodic memory, inductive reasoning or speed of processing-, healthy older adult participants who received reasoning training reported significantly less difficulty in independent activities of daily living (IADL). This was further supported by their improved performance on objective measures of IADL such as the Timed IADL Test, which assesses participants’ speed in interacting with real-life stimuli, e.g. looking up a telephone number (Willis et al., 2006). Thus, the effects of training may be transferable to untrained and daily living outcomes.

MCI Patient Populations
Numerous intervention studies have involved MCI patient populations. Since these individuals retain a large range of cognitive capacities; in particular, the ability to learn and apply new sets of strategies (Panza et al., 2009), training in these studies has involved repeated problems and exercises that are designed to work out and drill those cognitive capacities that are impaired; i.e. episodic memory (Belleville, 2008). In one study, MCI patients and healthy older adults were trained on episodic memory strategies over an eight week training period. Trained individuals improved in list-recall and face-name associations. Moreover, these individuals demonstrated increased knowledge of memory strategies (Belleville et al., 2006). A recent study that involved teaching memory strategies has likewise found that MCI participants who learned and used the techniques exhibited significant improvement in everyday memory (prospective memory) tasks, e.g. remembering to sign their own name on an envelope, compared to controls (Kinsella et al., 2009).

Several studies involving computer-based training have additionally shown positive results. For instance, in one study, intensive, computer-based cognitive training designed to improve auditory processing speed and accuracy was provided to individuals with MCI while passive
computer activities, such as reading and listening, were given to the controls. The cognitive training group showed improvement for measures of learning/memory (D. E. Barnes et al., 2009). Moreover, computer-based programs may be advantageous because they can be tailored to meet individual patient needs, and allow for objective comparisons with data (Faucounau, Wu, Boulay, De Rotrou, & Rigaud, 2010). One study further supports the role of computers in cognitive training. Here, using computer-based neuropsychological training software, cognitive exercises stimulating attention, memory, perception, visuospatial ability, language, and non-verbal intelligence were administered to individuals diagnosed with AD or MCI. Both the AD and the MCI groups showed improved performance in a separate neuropsychological battery after three months, particularly in memory and attention. Overall cognition, verbal fluency, and executive functioning scores increased in the AD group (Cipriani, Bianchetti, & Trabucchi, 2006). As such, computer-based training is feasible in participants with MCI.

These findings suggest that intervention and daily computerized training is possible in elderly individuals with memory impairments. We previously discussed the essential role of the HPC in memory. These results, along with the previously demonstrated training-induced
behavioural and cognitive improvements in both MCI and AD individuals pave the way for intervention methods that target the HPC. Such interventions that attempt to increase HPC activity and volume may help alleviate the symptoms of MCI and ensuing AD.

**Intervention Studies and Hippocampal Morphology**

Recently, studies have investigated the impact of intervention on hippocampal structure and activity. A few motor training studies, have shown modest increases in hippocampal activity or hippocampal grey matter following training suggesting that exercise has an impact on hippocampal plasticity (Boyke, Driemeyer, Gaser, Buchel, & May, 2008; Draganski et al., 2006; Erickson et al., 2011). Studies involving spatial memory training in animals and humans likewise demonstrate an effect on the hippocampus. Lerch and colleagues (2011) found that mice given spatial memory training showed an increase in hippocampal grey matter whereas mice given stimulus-response training showed an increase in striatal grey matter. In humans, Maguire and colleagues (2011) found that adults who qualified to become taxi drivers with an exam called “the Knowledge”- a three to four year process that required the learning of the complex layout of the streets of London- showed a selective increase in HPC grey matter with time. Moreover, no structural brain changes were
observed in trainees who failed to qualify. Since learning the layout of an environment is an attribute of spatial learning, these findings suggest that it is possible to stimulate the hippocampus with spatial memory training. Indeed, one study that used spatial navigation training has shown that both young and old men who underwent training had improved spatial memory performance and showed sustained hippocampal volumes after 4 months (Lovden et al., 2012). Conversely, older adult controls showed decreased hippocampal volumes. Effect sizes were not discussed in this study. The study also did not control for navigational strategies. This is especially important when administering training because of the previously demonstrated independent but parallel functioning of the HPC and caudate nucleus. In other words, participants utilizing response learning while navigating in that study would not be expected to engage their hippocampus. As discussed previously, research in the Bohbot laboratory has shown that there is a decreased tendency to use spatial strategies with age. Thus, training-induced increases in HPC activity and grey matter may be optimized by minimizing the involvement of response-based navigation and increasing reliance on spatial strategies.
1.11 Purpose of Study

The findings from intervention studies indicate that cognitive intervention, specifically computer-based intervention, is feasible in the elderly population. Moreover, these studies have shown that intervention, in particular spatial memory training, has a positive impact on hippocampal activity and grey matter. Previous research conducted in the Bohbot laboratory has shown that the use of spatial strategies is associated with greater hippocampal grey matter in young adults, older adults, and in mice. Thus, an intervention program that focuses on spatial strategies may be more effective in targeting the hippocampus. Since the hippocampus is particularly critical for spatial memory, the aim of this study was to investigate the impact of a spatial memory improvement program (SMIP) on memory in MCI patients and healthy older adults. We hypothesized that the SMIP would improve spatial navigation and possibly other hippocampal-dependent tasks and quality of life as it pertains to navigation, but would not affect control measures of executive function or general cognition.

In this study, we will first compare the performance of MCI patients and age-matched healthy older adults at baseline. Second, we will compare these measures to data of young adults in order to gain insight
on changes in spatial memory performance across the life span. We will then report the impact of our SMIP on navigational abilities in healthy participants and participants with MCI. Lastly, we will investigate factors that could help predict individual performance and success following SMIP training.
Chapter 2 Methodology

2.1 Participant Inclusion and Exclusion Criteria

All participants were required to be right-handed, between the ages of 59 and 80, and with education ≥ 8 years.

Healthy Participants

Healthy volunteers were recruited by word of mouth, or by advertisements posted in local newspapers. Interested individuals were then contacted by telephone and were given a medical screening questionnaire, developed in the Bohbot laboratory, which encompasses questions relating to medical history, vision and video game experience, and demographic data. Using this questionnaire, volunteers with a history of neurological or psychiatric disorders, or substance abuse problems were excluded from the healthy group. In addition, volunteers who reported poor vision or eye diseases, colour blindness, motion sickness, were left-handed, or were currently on thyroid or hormone medications were excluded. In addition to the criteria stated above, functional Magnetic Resonance Imaging eligible healthy volunteers had to weigh less than 250 pounds, had to have a vision prescription no more than +6/-6, were on cholesterol or blood pressure medication for less than two years, and had no cardiovascular diseases. A cognitive battery (part of the transfer tests) was additionally used to screen for depression and MCI. Specifically, participants had
to score less than 10 out of 30 on the Geriatric Depression Scale (GDS) and above 25 on the Montreal Cognitive Assessment (MoCA).

**MCI Patients**

Individuals with MCI from the memory clinics of the Douglas Mental Health University Institute, Jewish General Hospital, Montreal General Hospital, and Royal Victoria Hospital, were initially screened by their respective geriatrician and/or staff member to determine eligibility for the study. The diagnosis of MCI was done independently in each clinic in accordance with Peterson’s criteria (1999). Table 1 further summarizes the diagnostic work-up used by each clinic to determine individual patient’s cognitive status which included assessments of global cognitive function, verbal and visual memory, executive function, attention, language, subjective questionnaires, and neuroimaging e.g. CT scans. In addition, the following guidelines were implemented in the initial screening process: MCI participants who had neurological and psychiatric disorders other than MCI, significant heart disease i.e. stroke, substance abuse problems, depression, or acute decompositions such as poorly controlled diabetes, shortness of breath, or head trauma were excluded. None of the MCI participants were on cholinesterase inhibitors. Interested individuals with MCI who were deemed eligible for our study were then referred to our laboratory. Follow-up screening in our laboratory excluded potential MCI participants who
were left-handed, currently on thyroid or estrogen medication, with poor vision, colour-blindness or eye diseases, and with motion sickness. Further, participants with MCI were excluded from the fMRI component of the study if they weighed more than 250 pounds, were on cholesterol or blood pressure medications for less than 2 years, had high blood pressure, had a vision prescription greater than +6/-6, and had any metal implants that would affect scanning. Participants with MCI had to score above 21 on the MoCA and less than 10 out of 30 on the GDS.

To complement the diagnostic battery provided in the clinics, we made sure that measures of delayed recall and verbal memory, used in MCI diagnosis criteria, were included in our transfer tests: the Rey Auditory Verbal Learning Task (RAVLT), the Logical Memory I and II of the Wechsler Memory Scale, and the Rey-Osterrieth Complex Figure Task.

2.2 Participant Recruitment and Group Assignment

Healthy Older Adults

Sixty-two healthy older adults enrolled in the study and provided informed consent. Twenty-two of them were excluded during the initial transfer test sessions for the following reasons: nausea from the virtual navigation tasks (6), low compliance to tasks (4), use of blood pressure medications and/or blood thinners (3), low MoCA scores (4), high GDS scores (1), and withdrawal from the
study (4). The remaining forty healthy older adults’ data were used for the analyses of pre-transfer tests reported in this study.

The first 28/40 healthy controls were assigned to one of two groups- the experimental group (SMIP) or the no-contact control group (NCC). Three quarters through the study, a randomization schedule and an additional control group, the placebo control (PC) group were added and new healthy controls (the remaining 12/40) were then randomly assigned to one of three groups- the experimental group (SMIP), the placebo control group (PC), or the no-contact control group (NCC)- under a new randomization schedule. In summary, of the 40 healthy participants, 13/40 were in the SMIP (3 other healthy controls had not completed training at the time of the thesis), 20/40 were in the no-contact control group, and 4/40 were in the placebo control group.

**MCI Patients**

Forty participants with MCI were referred for participation in our study from May 2010-February 2012. After initial screening, 15 of them enrolled in the study and provided informed consent. Out of these, seven were excluded during baseline testing for the following reasons: low compliance to tasks (1), high GDS scores (3), and withdrawal from study (3). The remaining eight MCI participants’ data were used for the analyses in this study. Of the 8 MCI participants, 5 of 8 were in the SMIP group (2 other MCI participants in the SMIP group had not
started training at the time of the thesis) and 1/8 was in the placebo control group.

2.3 Double-blind Procedure

A double-blind procedure was also implemented three quarters through the study. As a result, the study was double-blind for 4 of the 8 current thesis' MCI participants and 10 of the 40 of healthy participants: neither the participant nor the research assistants administering the pre- and post-neuropsychological transfer tests knew which group the participant was assigned to. The experimenter in charge of training did not take part in administering the transfer tests to the participants included in the double blind procedure. The author and a research coordinator who was not involved in transfer task administration for this specific project were responsible for the randomization process, which concealed the assignment from the study team engaged in the administration of transfer tests, therefore providing an objective testing environment enabling the double blind condition (Altman et al., 2001; Hulley, 2007; Moher, 2001; Stolberg, Norman, & Trop, 2004). Therefore, the last quarter of participants obtained transfer tests that were administered by a team of approximately 8 other students and research assistants who were blind to the group assignment of participants. In addition, SMIP data presented in this thesis were acquired by an additional 3 students and research assistants over the years.
2.4 Spatial Memory Improvement Program

The virtual tasks that form the SMIP and the transfer tests that are described below were constructed using Unreal Tournament Editor 2003 (UT2003, Epic Games). This tool allows for the design of highly realistic environments varying in size from small rooms to complex cities and outdoor landscapes utilizing a rich array of textures. Previous research in healthy rodents (Packard & McGaugh, 1996) and research in healthy human individuals conducted in Bohbot’s laboratory showed that there is a shift from spatial to response strategies with practice or repetition (Iaria et al., 2003). Consequently, in order to maintain HPC stimulation, it is critical to have participants train in novel environments in order to prevent stimulus-response based habit learning, which no longer requires the HPC. As such, the Bohbot laboratory spent five years developing and validating 46 different virtual environments in which the relative positions of objects, landmarks, or rooms need to be memorized. This makes the SMIP a unique improvement program.

The training program is comprised of 16 one-hour spatial memory training sessions administered to participants twice a week during the course of eight weeks. During these sessions, instructors met with participants individually in a quiet room free of distractions. Participants were seated in front of a computer and were given instructions before starting the tasks. The program contained five
levels: Discrimination, Discrimination and Spatial Memory, Object Location, Spatio-Temporal Order, and Navigation (Figures 1-5). The level of difficulty was adjusted for each participant by starting with very easy tasks (low memory load, smaller region of exploration) and then progressing to more complex tasks (higher memory load, progressively larger and more complex regions to explore) when participants reached criteria (100% in 4 trials). Initially, trials were stopped and participants were moved to the next task even if they did not reach criteria.

To improve the training procedure and allow all participants to make progress, an easy version of the SMIP, the SMIP Light, was developed and administered to the later participants (1 healthy, 3 MCI participants) who did not reach criteria for a particular task. In the SMIP Light, environments with the lowest memory load e.g. one item to remember, were given to participants and difficulty was increased in minute increments e.g. present an additional item per trial to remember to help participants achieve criterion performance or 100% on a task for that particular level.

**Discrimination**

Participants were required to search for and locate shapes or objects (e.g., find the blue car, find the red square) across eight environments of increasing complexity (number of rooms and objects in the rooms increases) (Figure 1). With progress, attention and cognitive demands increase gradually.
Discrimination and Spatial Memory

Participants began by exploring a realistic-looking environment (Figure 2). They had to locate specific objects or rooms and remember the exact positions. Participants were then asked to reproduce a top view of the environment including either the objects therein or the layout of its rooms. Trials were given until participants placed all objects in their correct position or until they reached the maximum of 4 trials. However, after the 4 trials, 1 healthy and 3 MCI participants were given extra trials to help them reach criteria. Further, if the experimenter saw that participants were experiencing difficulty with the extra trials, participants were administered the SMIP Light. Learning was measured in terms of latencies to targets and errors made. Remembering positions of objects in a room was previously proven to require the HPC (Bohbot et al., 1998; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004).

Object Location

Participants were placed in a room and presented with an array of objects placed on a table (Figure 3). Participants were instructed to examine and learn the precise location of these objects as viewed from all four sides of the table. They were then asked to reproduce a top view of the environment including the objects in it. After this phase, they were asked to identify changes in the object positions. Trials were given until participants placed all objects in their correct
position or until they reached the maximum of 4 trials. However, after the 4 trials, the 1 healthy and 3 MCI participants were given up to 5 extra trials to help them reach criteria (100% correct). Further, if the experimenter saw that participants were experiencing difficulty with the extra trials, participants were administered the SMIP Light. Learning was measured in terms of errors. Remembering positions of objects on a table was previously proven to require the HPC (M. L. Smith & Milner, 1989; Stepankova et al., 2004). Participants were moved from Object Location to the next stage of the SMIP when they reached their 14th hour of training in order to allow 2 hours out of the 16 SMIP hours for the remaining levels.

**Spatio-Temporal Order**

Participants were walked through an environment where they saw objects or locations on either side of them (Figure 4). They were then asked to list the temporal order of previously seen objects. Trials were given until participants listed all objects or locations in their correct order or until they reached the maximum of 4 trials. However, after the 4 trials, 1 MCI participant was given extra trials to help them reach criteria. Learning was measured in terms of errors. Remembering when an event was experienced was previously proven to require the HPC (Spiers et al., 2001).

**Navigation**
Participants explored environments ranging in size from a small village to a large urban landscape that contained multiple landmarks (Figure 5). Following a minimum 20- to 60-minute first exploration period, participants were required to reach target locations (e.g., the movie theatre) by taking the shortest path possible or were required to remember and recall their position with respect to other landmarks within the environment. Some tasks additionally required participants to assess distances between their position and other locations, and identify the closest one. Learning was measured in terms of latencies, path lengths, and errors. Going to a specific landmark using the shortest way possible in a virtual town was previously proven to require the HPC (Maguire et al., 1998).

2.5 Controls

The SMIP was administered to 13 of 40 healthy participants and 5 MCI participants as described previously. The remaining 24 healthy participants and 1 MCI participant were placed in control groups. The “no contact control” (NCC) (healthy) did not receive the spatial memory training program or any type of intervention. They simply had to stay home and go about their regular activities during 8 weeks. A placebo control group (PC) was tested for both MCI and healthy participants. The purpose of this condition is to eliminate effects associated with factors that are unrelated to training. These include factors such as social interaction, change in environment, and navigation to the Douglas.
These participants still made visits to the Douglas Institute; however, they did not receive the SMIP. Instead, they engaged in an active control task.

The active control task protocol was adapted from the active control task used in the IMPACT study (G. E. Smith et al., 2009). It involves a learning-based training approach in which participants used computers to view DVD educational programs on nature, cultures and history. In each of the 16 one-hour sessions, participants watched a 45-50 minute program. Following each session, participants completed a written quiz that involved questions that related to specific factual content knowledge presented by the DVD in that session.

2.6 Transfer Tests

Transfer tests were administered one to two weeks before and after the SMIP in order to assess the effectiveness of the improvement program. With the exception of self-administered subjective questionnaires, different versions of each test, equal in difficulty, were used. They were balanced for order across groups and balanced for time of day tested. Altogether, the transfer tests were distributed over three separate sessions in order to control for fatigue effects. Each session lasted between two and three hours, including resting periods. Importantly, participants eligible for functional MRI (fMRI) underwent a Mock scan during the third testing session followed by an fMRI scan in an additional fourth testing session. During the testing of 3 of the 8 MCI participants, we found
that distributing the transfer tests over four sessions in addition to a fifth MRI scanning session was better as they tired more easily than healthy older adults.

**General Cognitive Function and Self-Administered Questionnaires**

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and Mini-Mental State Examination (MMSE) (Folstein et al., 1983) were used to assess the overall level of cognitive functioning. The Geriatric Depression Scale (GDS) was administered in order to control for depression. The Test of Nonverbal Intelligence III (TONI-III) (Brown, 1997) was administered to assess IQ. In order to evaluate participants’ overall functioning, the Quality of Life questionnaire (QOL) was administered (Bigelow, 1991). This questionnaire consists of 263 items and assesses functioning across multiple domains represented by 14 scales (i.e., psychological distress, well-being, ability to tolerate and cope with stress, basic need satisfaction, independence, interpersonal interactions, social support, work at home, work on the job, employability, meaningful use of leisure time, negative consequences of alcohol and drugs). Additionally, as memory may be affected by self-esteem and stress, a number of measures were included. We administered the Self-Esteem Questionnaire (SEQ), a ten item Likert scale with items answered on a four-point scale- from strongly agree to strongly disagree (Rosenberg, 1969). The Perceived Stress Scale (PSS), a 10 item five-point Likert scale (from never to
very often) that measures the degree to which situations in an individual’s life in the past month are perceived as stressful, was also administered to participants (S. Cohen & Williamson, 1988). Lastly, we administered the Barratt Impulsiveness Scale 11 (BIS-11), which is a 30 item self-report questionnaire that generates a total score as well as secondary factors (attention, motor, and non-planning impulsiveness) (Patton, 1995).

**Standard Neuropsychological Tests**

Standard neuropsychological tests were administered to assess generalization of the SMIP to other domains of memory such as verbal and visuo-spatial memory. Participants’ visuo-spatial memory was tested with the Rey-Osterreith Complex Figure (ROCF) (Meyers, 1995), which consists of reproducing a complex figure following a certain delay. Verbal memory was tested using the Rey Auditory Verbal Learning Task (RAVLT) (Rey, 1941) which requires learning a list of 15 words via multiple trials, with immediate recall, delayed recall, and recognition components.

In addition, several neuropsychological tests were administered to all participants in order to evaluate general neuropsychological traits non-specific to spatial memory such as executive function. For instance, we administered the Digit Symbol Test (DST) from the WAIS-R (Weschler, 1981) which consists of nine digit-symbol pairs followed by a list of digits. Participants were asked to write
down the corresponding symbol under each digit as quickly as they could. The number of correct symbols within the allowed time (120 sec) was then measured. The Logical Memory I and II Task immediate and 30-minute delay trials from the Weschler Memory Scale was administered to all participants (Weschler, 1987). In this task, the experimenter read participants two short stories that each had 25 content units. One story was read once and the other story was read twice. After each time a story was read, participants were asked to repeat the passage as close to verbatim as possible. Their recall was recorded and scored later to manual guidelines. After a 30-min delay, participants were asked to repeat each of the two passages once again for the delayed recall measure. In addition, fifteen yes/no recognition memory questions were asked about each story. Trails A and B from the Halstead-Reitan neuropsychological test battery (Reitan & Wolfson, 1985) was likewise administered. In this 2-part task, participants were told to connect a set of 25 targets as fast as possible while maintaining accuracy. In part A, all the targets were numbers and participants had to connect them in sequential order. In part B, the targets were numbers and letters, and participants had to then alternate between numbers and letters in sequential order. Errors and completion time were measured. The Stroop test was administered in order to assess focused attention and the ability to inhibit an automatic response using reaction times, errors, and interference (Card 3-1) scores. It is based on the
Stroop effect, which is a phenomenon where an individual takes longer to name the colour of the ink in which a different colour-word is printed e.g. the word red printed in green (Stroop, 1935).

In addition to these tests, the backward and forward digit span of the WAIS-III (Wechsler, 1997), which are measures of frontal cortex-dependent executive function were administered. In the forward digit span, participants were presented with a series of digits and told to immediately repeat them back in the same order. If they were successful, participants were given a longer list of digits. Similarly, in the backward digit span, participants were presented with a series of digits but were told to immediately repeat them in the reverse order.

**Assessment of Spatial Memory Function**

In order to track changes in spatial memory resulting from the training program, participants were also administered questionnaires before and after the SMIP. These included the Functional Spatial Abilities Questionnaire (FSAQ) (Liu, 1996), a 12-item assessment that uses a 3-point scale (1: yes; 2: not applicable; 3: no) to evaluate spatial orientation. Additionally, we administered the 15-item Santa Barbara Sense of Direction Scale (SBSOD) that uses a 7-point Likert scale (from strongly agree to strongly disagree) to assess participants’ sense of direction (Hegarty, 2002). Lastly, the Memory Assessment Clinics Self-Rating Scale (MAC-S), was administered to all participants. It uses a 5-point Likert scale
and consists of 21 ability-to-remember items e.g. remote, numeric, everyday, semantic and spatial memory, 24 items assessing frequency of memory failures, and 4 global rating items assessing overall comparison to others (Crook & Larrabee, 1990). Virtual navigation tasks (described below) were administered in order to track quantitative changes in participants’ spatial memory performance following the SMIP.

4-on-8 Virtual Maze

The 4-on-8 Virtual Maze is a computerized navigation task which is used to investigate spontaneous strategies used by participants (Figure 6). The task consists of an 8-arm radial maze surrounded by a rich landscape that contains landmarks. One trial is divided into two parts. In Part 1, participants are asked to visit four accessible pathways to retrieve hidden objects among the 8 arms. They are told to remember which pathways they have taken. This is because in the next part, all pathways become accessible, and participants are told to remember where they have been and avoid these pathways in order to retrieve the objects. Trials are administered until participants are able to correctly locate objects in part 2 to ensure that learning has occurred in all participants, or until they reach a maximum of 8 trials after which they are asked to stop. The 4-on-8 Virtual Maze is used to dissociate spatial and response learning strategies by way of a probe trial. In this phase, all landmarks are removed, and a wall is raised to hide the
surrounding landscape. Only the participants who learned to find the objects with a response strategy (sequence of right or left turns for a single starting position) perform well. Participants who learned the location of target objects with respect to landmarks (spatial learning strategy) make errors on the probe trial because the landmarks they used to orient are gone. Therefore, the probe trial dissociates between spatial and response strategies. Additionally, a verbal report, where participants are asked to explain exactly what they did to learn and perform the task, is obtained after task administration in order to determine which navigational strategies individual participants used in the task. Measures of learning include reference memory errors (i.e. going into the wrong path for the first time), working memory errors (i.e. entries into a previously visited path), and latencies.

**Wayfinding in the Virtual Town**

Participants explore a town containing eight landmarks (such as a pool and a movie theatre) for 20 min during which the experimenter verifies that each landmark of the virtual town has been visited at least twice (Figure 7) and that each street has been visited at least once (Etchamendy & Bohbot, 2007; Hartley, Maguire, Spiers, & Burgess, 2003). This is followed by six trials wherein participants begin at one of the eight landmarks and are asked to reach a particular target using the shortest possible route. Measures of learning include
path lengths and latencies to target locations. The ability to generate a direct route is an indication of spatial learning abilities based on a cognitive map that is formed in the 20 min exploration phase.

**Go/No-Go Task**

6 older adult participants and 3 MCI participants underwent the behavioural version of the Go/No-Go Task (Figure 8) while the 7 older adult and 3 MCI fMRI-eligible participants underwent a practice “Mock” MRI Go/No-Go scanning session that allowed participants to practice lying still, get comfortable navigating without looking directly at the keys and reduced exclusion rates due to motion artifacts. The behavioural Go/No-Go is different from the mock Go/No-Go in two ways. First, the behavioural Go/No-Go is administered to participants in a room, seated upright at a computer instead of lying in a mock scanner. Second, the behavioural Go/No-Go does not include a visuo-motor control task required during the fMRI session (described later). The Go/No-Go is a three part task. In the first part, participants are presented with six pathways in a 12-arm radial maze one at a time. Three of the six pathways contain an object and participants are asked to remember which pathways contain objects and which do not. Upon the fourth presentation, participants are given the choice between entering and not entering each of the six pathways. This step ensures that participants have learnt which pathways contain an object and which are empty. In the second
part, the pathways are presented in pairs such that each pair consists of a new pathway and an old pathway. Within each of these pairs, one pathway contains an object and the other is empty. Participants have to choose the pathway containing an object. This part tests whether or not participants have acquired the spatial relationship between the pathway containing an object and environmental landmarks. Participants who learned the spatial relationship between the pathway containing the target object and the environment will not make errors (e.g., I remember that this particular pathway did not contain the object, so I choose the other one). However, participants who did not learn the spatial relationship will make errors. Finally, in the all open phase (phase 3), all pathways are presented, and participants must now locate all objects. Learning is measured in terms of latencies as well as errors.

**Mock Scan with Go/No-Go task**

Prior to the two functional and structural scans (before and after the SMIP), fMRI-eligible participants took part in a mock scanning session at the Douglas Institute. The mock scanner is used to duplicate the actual scanning experience, including sounds heard and presentation of visual stimuli, but without any exposure to magnetic fields. These mock sessions were used to screen for claustrophobia, proper use of button manipulation, and as a practice session for the actual scan.
Visuo-motor control tasks for the Mock Scan (Go/No-Go Task)

In concurrence with the Go/No-Go experimental task, participants alternately completed visuo-motor control tasks. All tasks were set in different virtual environments. The control tasks, “Random” and “Object” are identical to the experimental task in terms of its visual and motor components. However, there is a major difference. In the “Random” task, participants were told to retrieve objects of the 12-arm radial maze, but were told that the objects are placed in random arms such that they will not be able to predict or learn its location beforehand which is unlike the experimental trial. In the “Object” task, participants were asked to go down the pathway that they could already see had an object. Panels indicating “Experiment” or “Random” or “Object” were placed in the virtual environments and were presented to the participants for about five seconds at the beginning of each trial. They were additionally asked to count backwards by 3 from 1000 during control trials in order to prevent rehearsal of object locations learned in the experimental trials (Etchamendy, Konishi, Pike, Marighetto, & Bohbot, 2012).

Concurrent Spatial Discrimination Learning Task

The Concurrent Spatial Discrimination Learning Task (Discrimination Learning Task) was likewise administered to participants as part of a behavioural pilot or presented to fMRI-eligible participants during an fMRI session. In the
learning phase, participants are presented with 6 pairs of pathways inside a 12-arm radial maze in a virtual environment different than the one used in the Go/No-Go Task (Figure 9). Within each pair, one of the two pathways always contains a target object located in a pit at the end of the pathway, while the other pathway is always empty. Participants can learn the position of the arms containing target objects by referring to the landscape that is enhanced with landmarks such as mountains, trees, a desert, or an oasis surrounding the maze. They are given multiple trials to learn the location of the six target objects, presented in six different pairs of arms. Once they have successfully learned (at least 94% accuracy or 11/12 correct within 25 trials), participants move on to the probe phase. In the probe phase, pairs are recombined such that two previously unrelated but adjacent pathways are presented together. However, the reward contingency remains the same. This part dissociates spatial learning from response learning strategies. If the participants remember the position of targets with respect to the environmental landmarks, they will perform well in the probe trials. On the other hand, if participants encoded the position of targets using a response strategy (e.g., when I see the tower, go left) they will perform poorly in the probe trials. Lastly, in the all open phase (phase 3), all pathways are presented, and participants must locate all targets. Learning is measured in terms of latencies and errors.
Visuo-motor Control Tasks for the fMRI experiment ( Discrimination Learning Task)

In concurrence with the Discrimination Learning Task experimental task, participants in the MRI group alternately completed two visuo-motor control tasks, the “Random” and “Blue” task that were set in different virtual environments. In the “Blue” task, participants were asked to retrieve objects by taking only the blue pathways of a 12-arm radial maze, whereas in the “Random” task, participants were asked to retrieve objects in the maze but were told that the objects are placed in random pathways. Panels indicating “Experiment” or “Random” or “Blue” were placed in the virtual environments and were presented to the participants for about five seconds at the beginning of each trial.

To adapt to the particular needs of our study groups, two different procedures were used for both the Go/No-Go Mock scan and Discrimination Learning Task fMRI session:

Healthy Participants

Participants were told that they will perform the control and experimental tasks while in the scanner: the “Object” task (Go/No-Go visuo-motor control task) or “Blue” task (Discrimination Learning Task visuo-motor control task), the “Random” task (visuo-motor control task), and the “Experimental” task. They
were additionally asked to count backwards by 3 from 1000 during control trials in order to prevent rehearsal of object locations learned in the experimental trials.

**MCI Participants**

After we observed that MCI patients had difficulties, we adapted the procedure in order to reduce the interval between experimental trials and increase the probability of learning the task. Specifically, the 3 fMRI-eligible participants with MCI completed only the “Random” control task in alternating order with the “Experimental” task of the Go/No-Go or Discrimination Learning Task. Participants with MCI were additionally told to count backwards by 5 from 1000 during control trials in order to prevent rehearsal of object locations learned in the experimental trials.

**2.7 Data Analysis**

**Measuring Behavioural Improvements**

Performance on every neuropsychological test and task was measured by calculating average scores, latencies, errors, or accuracy for both time points (pre- and post-training or pre- and post- 8 weeks) for both healthy and MCI experimental and control groups. In addition, we calculated average scores and percentages of all questionnaires at both time points for each group. For the virtual navigation tasks, we calculated average latencies, errors, accuracy, and trials to criteria for both time points as measures of performance. In addition, we
calculated participants’ average path lengths, distance error and time error for the Wayfinding task. Percent mean distance error represents the extra distance traveled compared to the shortest distance needed to reach individual target locations. Percent mean time error represents the extra time compared to the optimal time needed to reach individual target locations.

For comparison purposes, the 4-on-8 Virtual Maze, RAVLT, and Wayfinding data of young adults previously collected in the Bohbot laboratory were also included. We again calculated average scores, latencies, errors, or accuracy for this group.

We furthermore investigated potential predictors of individual participant improvement. For the healthy participants, we considered individual participants’ performance on the SMIP: the percent of SMIP tasks they completed, total number of SMIP tasks where criteria (100%) was reached in 4 trials, and whether SMIP Light (presentation of additional easier environments) was administered or not. Additionally, individual healthy participants’ initial strategy on the 4-on-8 Virtual Maze (spatial or response), participants’ primary method of transportation (e.g., driving, public transport) and whether they showed hippocampal growth post-training (from VBM analysis done by another member of Bohbot’s team), were considered. For the MCI participants, we likewise considered measures of individual MCI participants’ performance on the SMIP and also identified which
navigation tasks i.e. Wayfinding, Go/No-Go tasks they showed improvement in following training. Additionally, we considered individual MCI participants’ stage of impairment (early or late) based on the criteria of the Alzheimer’s Neuroimaging Initiative Protocol, which defines early/late MCI using education-adjusted scores on delayed recall of one paragraph from the Wechsler Memory Scale Logical Memory II. Lastly, we considered participants’ initial strategy on the 4-on-8 Virtual Maze (spatial or response), and their primary method of transportation.

**Behavioural Data Analysis**

We used SPSS Version 19.0 for all analyses. In the first set of analyses, independent t-tests were used to assess baseline demographic and clinical characteristics of participants. Specifically, using the performance measures mentioned above, baseline performances on virtual navigation tasks, neuropsychological tasks and tests, and baseline subjective measures of participants were compared between groups (healthy older adults versus MCI participants). We also conducted Multivariate Analyses of Variance (MANOVA) to compare healthy older adults’ and MCI participants’ baseline 4-on-8 Virtual Maze, RAVLT, and the Wayfinding performance measures to that of young adults. Lastly, we conducted several correlational analyses to determine if there was a relationship in participants’ performance on virtual navigation tasks and
scores on tests of global cognitive function and self-administered questionnaires.

In a second set of analyses, the performance measures of each neuropsychological test, virtual navigation task, and questionnaires were analyzed separately using paired-samples t-tests for each group (healthy experimental, healthy controls, MCI experimental) before and after the SMIP, or before and after 8 weeks (such as in the case of controls). The final set of behavioural results is descriptive in nature and provides tabulated summaries of factors that may contribute to participants' performance throughout the study.
Chapter 3 Results

3.1 Baseline Comparisons

The detailed results described in the proceeding sections were motivated by the exploratory nature of the study but it is important to note that all these results lack power because of the small sample size. Thus, the resulting significant results or trends that are described below are speculative in nature.

Demographic and Clinical Results

Preliminary analyses revealed a significant difference in age between the two groups, \( t(46) = 5.09, p < 0.001 \), where MCI participants were significantly older than the healthy group. As such, only the data of the oldest of the healthy older adults (Age ≥ 69, n = 11) were included for baseline comparisons. Table 2 presents the demographic characteristics of the MCI participants and the oldest old of the healthy older adults. As expected, participants with MCI showed mild cognitive deficits relative to healthy older adults as demonstrated by significantly worse performance on the MMSE and MoCA. They also reported significantly higher scores in the GDS. Participants with MCI showed similar levels of education and IQ as measured by the TONI.

At baseline, there were significant group differences for several measures of the neuropsychological battery (Table 3). Compared to healthy older adults (M = 31.70 sec, SD = 12.58), MCI participants took significantly more time to
complete part A of the Trails (M = 46.71 sec, SD = 15.24), \( t(17) = 2.35, p < 0.05 \).

MCI participants furthermore had significantly worse learning slope scores and percent retention scores (M = 4.75, SD = 1.04; M = 62.97%, SD = 27.54, respectively) on the Logical Memory I and II task than healthy older adults (M = 2.60, SD = 2.63; M = 94.86%, SD = 24.71, respectively), \( t(16) = 2.17, p < 0.05; t(17) = -2.35, p < 0.05 \), respectively. There were no significant group differences (\( p > 0.05 \)) seen in the other measures as exemplified by Stroop task interference scores (\( t(17) = -1.62 \)), Digit Span forwards and backwards scores (\( t(17) = -0.93, t(17) = -0.37 \), respectively), RAVLT delayed recall and delayed recognition list A scores (\( t(17) = -1.83, t(17) = -2.04 \), respectively), and ROCF immediate and delay scores (\( t(7) = 0.96, t(16) = -1.53 \), respectively).

**Virtual Navigation Tasks**

Baseline comparisons showed differences in performance in the virtual navigation tasks between the two groups.

**Wayfinding Task**

Figure 10 shows that MCI participants reached significantly fewer target locations (M = 47.92%, SD = 16.52) on the Wayfinding task compared to healthy older adults (M = 72.42%, SD = 13.26), \( t(17) = 2.96, p < 0.05 \). MCI participants furthermore took significantly more time per trial (M = 233.61 sec, SD = 28.25) compared to the healthy older adult participants (M = 183.16 sec, SD = 36.97), \( t \).
(17) = 2.96, p < 0.05. For preliminary observations, correlational analyses were conducted and indicate a significant negative correlation between MoCA scores and the mean time per trial on this task (Figure 11), \( r = -0.485, p < 0.05 \). Thus, higher scores on the MoCA were significantly correlated with less time per trial on the Wayfinding task. A similar analysis was performed for participant performance in the MMSE. However, no significant correlation between mean trial time and MMSE scores was found, \( r = -0.300, p > 0.05 \).

**Concurrent Spatial Discrimination Learning Task (Discrimination Learning Task)**

A behavioural version of the Discrimination Learning Task was administered to 3 of the 8 MCI participants as part of a behavioural (discussed in the methods) pilot study that served to investigate the feasibility of administering the SMIP to MCI participants. Additionally, we used results from a different set of healthy older adults for this analysis in order to obtain appropriate comparisons. That is, the data of the oldest healthy older adults who completed the behavioural CSLDT (\( n = 5 \)) and the data of the oldest healthy older adults who completed the fMRI Discrimination Learning Task (\( n = 6 \)) were included. Figure 12 shows that in both the behavioural and fMRI version of the Discrimination Learning Task, MCI participants seemingly take on average more trials to reach criteria, \( M = 12.67, SD = 10.69; M = 21.20, SD = 6.09 \), respectively, than healthy older adults, \( M = 6.00, SD = 3.93; M = 15.00, SD = 5.90 \), respectively. However, this was not
statistically significant $t(2.33) = 1.03, p > 0.05$; $t(9) = 1.71, p > 0.05$, respectively.

In addition, MCI participants appear to achieve similar percent correct performance on phase 2 in the behavioural Discrimination Learning Task ($M = 62.50\%, SD = 17.68$) to healthy older adults ($M = 62.75\%, SD = 39.42$), $t(4) = -0.01, p > 0.05$; data not shown). However, MCI participants appear to find fewer objects on average ($M = 62.50\%, SD = 17.68$), than the older adult group ($M = 80.2\%, SD = 19.05$) in the fMRI Discrimination Learning Task, $t(5) = -1.12, p > 0.05$. Again, these results were not statistically significant.

**Go/No-Go Task**

A behavioural version of the Go/No-Go task was likewise administered to the same 3 MCI participants of the behavioural pilot study. Additionally, we used a different set of healthy older adult data for this analysis in order to obtain appropriate comparisons. That is, the data of the oldest healthy older adults who completed the behavioural Go/No-Go ($n = 6$) and of the oldest healthy older adults who completed the mock Go/No-Go ($n = 7$) were included. The numbers are different here than in the pairs because one participant’s pairs data was invalid (same background was used in the Pairs and Go/NoGo) so only their Go/No-Go data was used. Another participant’s pairs data was unavailable at the time of analysis. Figure 13 shows the mean number of errors made by MCI participants and healthy older adults during the all open (phase 3) of the
behavioural and mock Go/No-Go at baseline. Though not statistically significant, MCI participants on average appeared to make more errors (M = 1.33, SD = 0.58) than the healthy older adults (M = 0.83, SD = 1.17) in the behavioural Go/No-Go, $t(7) = 0.68, p > 0.05$. Similarly, MCI participants on average allegedly made more errors (M = 1.67, SD = 1.53) than the healthy older adults (M = 0.43, SD = 0.78) in the mock Go/No-Go, $t(8) = 1.13, p > 0.05$. This was not statistically significant.

**4/8 Virtual Maze**

The MCI participants and healthy older adults showed apparent comparable performance during part 2 of the 4-on-8 Virtual Maze acquisition phase at baseline (Figure 14). That is, MCI participants made about the same number of errors as the healthy older adult participants during the first 3 trials (acquisition phase), $t(17) = 0.63$, $t(16) = -0.42$, and $t(16) = 0.35$, respectively. Moreover, MCI participants took approximately the same amount of time as the healthy group during the first three trials of the acquisition phase, $t(16) = 0.23$, $t(16) = -0.27$, and $t(16) = 1.01$, respectively. These results were not significant, $p > 0.05$. Additionally, there was no significant group difference in the number of trials needed to reach criteria, though MCI participants appeared to take on average more trials to reach criteria (M = 4.63, SD = 2.97) than healthy older adults (M = 2.82, SD = 1.47), $t(9.50) = 1.58, p > 0.05$. They additionally seemed
to make similar amount of overall errors during part 2 (M = 13.17, SD = 12.35) on the 4-on-8 Virtual Maze as the healthy older adults (M = 12.27, SD = 9.19; t(15) = 0.17, p > 0.05). On the probe trial, MCI participants appeared to make similar number of errors (M = 2.00, SD = 1.41) as healthy older adults (M = 2.88, SD = 1.17, t(15) = 0.23, p > 0.05).

**Subjective Measures**

Table 4 reports data for subjective measures taken at baseline of the MCI participants and healthy older adult participants. No significant differences were observed in the Self-Esteem Questionnaire, Functional Spatial Abilities Questionnaire, or Quality of Life Questionnaire scores between the two groups. However, MCI participants reported significantly higher Perceived Stress Scale scores (M = 20.38, SD = 5.34) compared to healthy older adult participants (M = 9.55, SD = 3.83), t(17) = 5.16, p < 0.001. Moreover, MCI participants reported significantly higher total Barratt Impulsiveness Scale scores (M = 62.25, SD = 7.76) than healthy older adults (M = 51.70, SD = 9.51), t(16) = 2.53, p < 0.05. Interestingly, MCI participants reported significantly lower scores (M = 47.00, SD = 7.48) than healthy older adults (M = 59.45, SD = 7.55) on the Santa Barbara Sense of Direction Scale (SBSDS), a subjective assessment of spatial memory t(17) = -3.56, p < 0.05. A significant difference between groups was additionally observed in percent scores on the spatial abilities component of the Memory
Assessment Clinics Self-Rating Scale (MAC-S), \( t(17) = -2.28, p < 0.05 \), where MCI participants rated their spatial abilities as significantly worse (M = 74.21%, SD = 10.28) than healthy older adults (M = 85.39%, SD = 10.69). Further, correlational analyses revealed a significant positive correlation between Wayfinding performance, and the scores on the SBSDS and MAC-S (Figure 15; \( r = 0.572, p < 0.05 \); \( r = 0.451, p < 0.05 \), respectively). Thus, better performance on the Wayfinding was significantly correlated with higher ratings on the two questionnaires.

**Comparisons with Young Adult Data**

The apparently similar performances observed in the MCI participants and healthy older adults on the 4-on-8 Virtual Maze were unexpected. Hence, the 4-on-8 Virtual Maze, RAVLT, and Wayfinding data of young adults previously collected in the Bohbot laboratory were then included in order to gain further insight of the changes in spatial memory performance across the life span and how that compares to MCI performance. For this reason, the 4-on-8 Virtual Maze, RAVLT, and Wayfinding data of the younger (Age \( \leq 68 \)) of the healthy older adult cohort were included.

**4-on-8 Virtual Maze Performance Comparisons with Young Adults**

Figures 16 and 17 show the performance of all participants on three measures of the 4-on-8 Virtual Maze. A MANOVA indicated a significant
difference between groups (Young adults, < Age 68 Older Adults, > Age 69 Older Adults, and MCI participants) in errors made on trials 1-3 of the acquisition phase $F(3, 301) = 8.810, p < 0.001$; $F(3, 301) = 26.64, p < 0.001$; and $F(3, 301) = 17.94, p < 0.001$, respectively. Post-hoc HSD Tukey tests furthermore revealed that young adults made significantly fewer errors during the first 3 trials of the 4-on-8 Virtual Maze compared to both healthy older adult groups and the MCI participants, $p < 0.05$. A MANOVA additionally indicated a significant difference in latencies between groups on trials 1-3 of the acquisition phase $F(3, 301) = 29.68, p < 0.001$; $F(3, 301) = 34.00, p < 0.001$; and $F(3, 301) = 16.74, p < 0.001$; respectively. Post-hoc HSD Tukey tests showed that young adults took significantly less time than both healthy older adult groups and MCI participants, $p < 0.05$. A third MANOVA was performed, and indicated a significant difference between groups in the number of trials needed to reach criteria, $F(3, 301) = 13.69, p < 0.001$. Post-hoc HSD Tukey tests revealed that young adults took significantly fewer trials to reach criteria compared to the two healthy older adult groups and the MCI participants, $p < 0.05$.

**Wayfinding Performance Comparisons with Young Adults**

Figure 18 shows the performance of all participants on two measures of the Wayfinding task. A MANOVA indicated a significant difference between groups on percent mean accuracy and percent mean time error $F(3,139) =$
394.14, \( p < 0.001 \) and \( F(3,139) = 50.31, \ p < 0.001 \), respectively. Post-hoc HSD Tukey tests showed that young adults reached significantly more target locations, and took significantly less time to reach target locations than both older adult groups and MCI participants, \( p < 0.001 \). However, results additionally indicated that both older adult groups (age \( \leq 68 \) and \( \geq 69 \)) reached significantly more target locations than MCI participants, \( p < 0.001 \).

**RAVLT Performance Comparisons with Young Adults**

Figure 19 shows the performance of all participants on two measures of the RAVLT. A MANOVA indicated a significant difference between groups on the delayed list A recognition and delayed list A recall, \( F(3, 109) = 5.86, \ p < 0.05 \); and \( F(3, 109) = 8.63, \ p < 0.05 \), respectively. Post-hoc HSD Tukey tests were then performed. MCI participants showed significantly poorer performance on the delayed list A recall compared to healthy young adults and the 2 healthy older adult groups, \( p < 0.05 \). Further, MCI participants were found to perform significantly worse on the delayed list A recognition than young adults and healthy older (\( \leq 68 \)) adults, \( p < 0.05 \). The healthy older adults (\( \geq 69 \)) were additionally found to perform significantly worse on the delayed list A recognition compared to young adults, \( p < 0.05 \).
3.3 Pre versus Post

All healthy participants were randomly assigned to either the experimental or control groups. Preliminary analyses in healthy older adults showed that there were no significant differences in pre/post performance between the NCC and PC groups. For this reason, the two control groups’ data were pooled for analyses in this study.

Table 5 shows the pre- and post-demographic and clinical characteristics of the healthy older adults and MCI participants. In this set of analyses, we initially sought to match the data of the oldest healthy older adult participants who completed the study with our MCI participants using the youngest MCI participant (age=68) as threshold. However, we found that using this criterion resulted in the inclusion of only three SMIP-trained oldest healthy. Since there were no healthy older adults age= 68, we therefore included the data of healthy older adults age ≥ 69 from both the SMIP-trained (Experimental group) and the controls. The resulting mean age of the six Experimental group participants was 70.00 years (SD = 3.40), and their mean education was 16.00 years (SD = 2.82). The mean age of the eight healthy older adult controls was 70.88 (SD = 2.99), and their mean education was 15.25 (SD = 3.45). One of the eight MCI participants enrolled in the study withdrew after baseline testing. The remaining seven MCI participants completed the study. The mean age of the six SMIP-trained MCI
participants was 73.00 years (SD = 3.40), and their mean education was 13.83 years (SD = 2.99). There was additionally one MCI placebo control participant, who is 78 years old and has 11 years of education. A MANOVA indicated no significant group differences in age, education, or IQ. Additionally, paired-samples t-tests showed no significant differences in pre/post values observed on the MMSE, MoCA, or GDS within each subgroup (i.e. healthy experimental, healthy controls, MCI experimental, MCI controls). Given this reduced sample size, it is important to note that the results described below were conducted due to the exploratory nature of the study despite lacking power.

**Healthy Older Adult Behavioural Results**

The data on neuropsychological tests of verbal memory, spatial memory, or executive function were inconclusive (see Table 6). However, there were significant SMIP-related improvements observed in the Experimental group for three out of the four virtual navigation transfer tests. Paired-samples t-tests were conducted to compare individual group performance before and after training or before and after 8 weeks (for the controls). The most important findings are described in the following section.

Figure 20 shows the pre- and post-training part 2 errors made in the first two trials during the acquisition phase of the 4-on-8 Virtual Maze for the healthy Experimental and Control groups. Errors in the first two trials were chosen
because asymptotic performance is often reached by the third trial and is error free. Therefore, trials during which errors are made are more sensitive to detect differences in errors made between groups. Paired t-tests showed a significant difference in the pre-training ($M = 6.00$, $SD = 2.00$) and post-training ($M = 2.67$, $SD = 2.07$) scores of the Experimental group; $t(5) = 2.65$, $p < 0.05$. That is, SMIP-trained participants made significantly fewer total part 2 errors during the acquisition phase on the 4-on-8 Virtual Maze following training. This was not seen in the Control group.

The healthy Experimental group likewise showed significant improvement in the fMRI version of the Discrimination Learning Task following training ($n=5$ since one participant was included in the behavioural group of the Discrimination Learning Task, Figure 21). A significant difference was observed in the pre-training ($M = 12.00$, $SD = 4.12$) and post-training ($M = 6.60$, $SD = 0.89$) trials taken to reach criteria; $t(4) = 2.83$, $p < 0.05$. Thus, the healthy Experimental group took significantly fewer trials to learn the Discrimination Learning Task following training. This was not seen in the healthy Control group.

Paired-samples t-tests were additionally conducted to compare individual group performance on the Wayfinding task before and after training or 8 weeks. Figure 22 shows the pre- and post-percent mean distance error (A) and percent mean time error (B) achieved on the Wayfinding task for the healthy
Experimental and healthy Control group. There was a significant difference in pre-training (M = 51.46, SD = 13.68) and post-training (M = 30.35, SD = 15.69) percent mean distance error of the healthy Experimental group; t(5) = 2.89; p < 0.05. There was furthermore a significant difference in pre-training (M = 62.71, SD = 12.24) and post-training (M = 44.85, SD = 20.41) percent mean time error of the healthy Experimental group; t(5) = 2.97, p < 0.05. Thus, following training, the healthy Experimental group took significantly shorter routes and took significantly less time to reach target locations. This improvement was not seen in the healthy Control group.

**MCI Participant Behavioural Results**

Within group analyses showed no significant improvements on neuropsychological tests of verbal memory, spatial memory, or executive function for MCI participants after SMIP. There were additionally no global significant SMIP-related improvements observed in this group. However, inspection of individual MCI participants’ pre- and post- SMI performance indicated that each MCI patient showed improvement in at least one out of the four virtual navigation transfer tests. This is described below.

Figure 23 shows the pre- and post-training percent correct scores in the all open (phase 3) achieved by individual MCI participants on the behavioural and mock Go/No-Go task. Notable improvements were observed in the majority of
MCI participants who received SMIP training: participants MCI-02, 03, 04, 05 and 06 made more correct identifications of pathways containing objects following training. This improvement was not seen in MCI-01. MCI-07, who was in the placebo control group, likewise did not show improvement.

Figure 24 shows the pre- and post-training performance of MCI participants on the Discrimination Learning Task. Participants who were unable to reach criteria were given a ceiling value of 25 trials for comparison purposes. Two of the six MCI participants who received training, MCI-02 and MCI-05, showed improvement following training, where they took substantially fewer trials to reach criteria. Further, it was found that these participants, along with MCI-03, showed improvement in the probe trial, or part 2, of the task, where the use of spatial strategies is required to perform well. In fact patient MCI-02 went from a 0% use of spatial relationships during the probe to a 75% score, showing a marked improvement at using spatial memory strategies. The remaining MCI participants did not show improvements on this task.

Pre- and post-results on the Wayfinding task of MCI participants indicated improvement in two of the six SMIP-trained participants (Figure 25). Specifically, MCI-01 and MCI-02 reached all target locations and took less time per trial after training. Additionally, MCI-01 took shorter routes to target locations following training.
Altogether, individual MCI participants who received training apparently showed improvements on at least one of the spatial memory tasks as opposed to the MCI patient in the placebo group who did not show improvements before and after the placebo control task. However, note that the control MCI patient was 1.5 SD’s older, had an IQ 1 SD lower, and a GDS score 2 SD’s worse than the SMIP-trained MCI participants which could have influenced the results.

3.4 SMIP Performance Results

Given the above results, we sought to identify factors that could perhaps explain the observed pre- and post-performances in the MCI participants. For comparison and completeness purposes, we additionally looked at factors in all the SMIP-trained healthy older adults.

Healthy Older Adults

For the healthy Experimental group, we found that all 3 spatial learners showed increases in hippocampal grey matter following training. This is compared to 5 of the 10 response learners who showed hippocampal growth following training. Also, comparisons of these results with performance on virtual navigation tasks revealed that the majority of healthy older adults showed improvement in all virtual navigation tasks- 4-on-8 Virtual Maze, Wayfinding Task, Go/No-Go, and Discrimination Learning Task- following training regardless of differences in other factors (Table 6).
MCI Participants

Table 7 summarizes factors we considered for the SMIP-trained MCI participants (n = 6). Inspection of these factors along with individual MCI pre-training and post-training performance on navigational tasks provided some interesting results. As shown, MCI-01, a late-stage MCI, reached criteria in most SMIP tasks, completed most SMIP environments, but showed improvement only on the Wayfinding Task. MCI-05, an early-stage MCI, likewise reached criteria and completed the majority of SMIP environments, and similarly showed improvement on only one task, the Go/No-Go. On the contrary, MCI-02, an early-stage MCI, showed improvement across all virtual navigation tasks, reached criteria and completed a substantial amount of the SMIP, and is a spatial learner. Though MCI-03, 04, and 06 reached criteria in 50% of SMIP environments, they still demonstrated improvement on the Go/No-Go Task. Moreover, MCI-04 and MCI-06 required the SMIP Light, which involves the presentation of additional virtual environments for extra spatial memory practice. At this time, MCI participants’ primary means of transportation appears to be unrelated to their performance on the virtual navigation tasks.
Chapter 4 Discussion

In this study, we first compared the performance of MCI participants and age-matched healthy older adults at baseline. For a few measures, we extended the baseline comparisons to include data of young adults. We then investigated the impact of our SMIP on navigational abilities in the oldest healthy participants and participants with MCI. Lastly, we looked at whether there are factors that could help predict individual performance and success following SMIP training.

4.1 Baseline differences

Demographic and neuropsychological characteristics

As mentioned previously, the diagnosis of MCI is often made in accordance with Peterson’s criteria (1999) which defines MCI as those individuals who demonstrate objective memory impairments and subjective complaints of memory loss, but show no loss in activities of daily living. This criteria has previously been used by multiple studies involving MCI patients (Belleville et al., 2011; Belleville et al., 2006; Kurz, Leucht, & Lautenschlager, 2011; Petersen, 2003). Thus, to obtain a cognitive profile of our subgroup of MCI participants, we compared their performance in a battery of neuropsychological tasks and tests to that of our healthy older adults. Importantly, the effect of sample size must be considered in all analyses as this study included the data of only 8 participants with MCI.
Baseline comparisons revealed that MCI participants had significantly lower scores than healthy older adults for both tests of global cognitive function, the MoCA and MMSE.

MCI participants had significantly higher scores on the GDS compared to the healthy group. They also showed comparable scores to healthy older adults on the Self-Esteem Questionnaire. Therefore, the memory problems associated with MCI do not appear to influence self-esteem. While it may appear that MCI patients have symptoms of depression, this is falsely represented by the GDS because it includes questions that would present a favourable bias by definition i.e. “Do you feel you have more problems with memory than most?”. Hence, the cognitive deficits seen in participants with MCI may have artificially boosted the GDS symptoms (Feher, Larrabee, & Crook, 1992).

The MCI group furthermore demonstrated significant impairment relative to the healthy group on the Trails test, but showed comparable performance in the interference measure of the Stroop test. Both these tests are measures of attention control, and deficits in attention control have been found to occur in MCI (Saunders & Summers, 2010). Thus, poor performance on the Trails was expected, but the observed comparable performance on the Stroop test was not. Still, the findings of past studies investigating MCI participants’ attention control using the Stroop test have been mixed. One study found that MCI participants
showed impaired performance on the Stroop test (Kramer et al., 2006). However, other studies found that MCI participants exhibited normal performance (Duong, Whitehead, Hanratty, & Chertkow, 2006; Y. Zhang, Han, Verhaeghen, & Nilsson, 2007). Interestingly, Belanger and colleagues (2010) reported that performance on the Stroop test is affected by whether trials are administered in congruent (e.g. word green written in green) or incongruent (e.g. word green written in red) blocks. They found that while MCI and AD participants showed impaired interference relative to healthy controls in the incongruent trial blocks, only the AD participants showed impaired performance relative to healthy controls on the congruent trial blocks. Still, the Stroop test used in this study consisted of incongruent trial blocks and thus the version of the test is not a valid reason for the observed comparable performance. However, it is possible that the current study’s method of administering the Stroop test, i.e. presenting the words on a computer screen, may have played a role as older adults may not be accustomed to reading words or identifying colours from a computer screen.

Typical MCI diagnosis criteria has included poor performance on delayed recall components in visual and verbal memory i.e. Logical Memory in order to distinguish people with MCI from healthy controls (Gauthier et al., 2006). Indeed, our MCI participants showed impairment on the Logical Memory Task I and II
relative to healthy controls. However, MCI participants did not show significant deficits in delayed recall in the ROCF task or the RAVLT.

Our findings are contrary to past studies that have shown that the delayed recall of the RAVLT is one of the best predictors of dementia (Andersson et al., 2006). To help us better understand this, we compared the RAVLT performance of young adults to our cohort’s data. Interestingly, the delayed recall component of the RAVLT showed sensitivity to MCI, where MCI participants performed significantly worse than both young and older adults. The healthy participants, however, demonstrated performance similar to young adults. Age has been demonstrated to affect RAVLT performance in a Greek population study that involved 205 healthy participants, aged 18-78 years old (Messinis, Tsakona, Malefaki, & Papathanasopoulos, 2007). Thus, a possible reason for the lack of difference in the older adult and young adult performance may be the small sample size (≤ 68: n=29, ≥ 69: n=11). Still, another point to consider is that our group of healthy older adults were high-functioning given that they were recruited from newspaper ads. Additionally, we found that healthy older adults (age ≥ 69) performed significantly worse on the delayed recognition compared to young adults. Further, MCI participants showed comparable performance to age-controlled older adults (age ≥ 69), but performed significantly worse than young and older adults (age ≤ 68). The lack of difference in the ≤ 68 group and young
adult performance is unexpected as the recognition measure in the RAVLT is analogous to cued recall. Cued recall was previously proposed by Dubois and colleagues (2007) to be a better indicator of prodromal AD than free recall, which can be impaired in normal aging making it less sensitive in detecting pre-dementia symptoms. Indeed, in their study that used a controlled learning task where healthy and demented older adults had to search for and identify 16 items and then complete three trials of free and cued recall, Grober and Buschke (1987) found that cued recall was the best way to identify people with memory problems possibly linked to dementia. Thus, while it is possible that the delayed recognition measure of the RAVLT is less sensitive to MCI-related impairment in this age-controlled pilot study because the older adults experienced comparable difficulty on the task as the MCI participants, it is also likely that the lack of effect was due to our small sample size.

The ROCF performance data indicated low sensitivity of this visual task to MCI impairment as MCI participants showed comparable performance to healthy older adults. Vogel and colleagues’ study in healthy older adults (2012) suggest that delayed-recall performance on the ROCF is highly dependent on the initial copy strategy i.e., whether the individual copies the figure accurately and whether he/she uses a systematic or abstract approach in copying the figure. Hence, it is possible that our participants used similar strategies in copying the
figure leading to comparable performance; however, this was not measured in the current study.

**Virtual Navigation Performance**

There have been a number of studies investigating the use of virtual environments in assessing MCI and AD. As mentioned previously, these studies have demonstrated that MCI and AD patients have poor spatial navigational ability (Cushman, Stein, & Duffy, 2008; Deipolyi et al., 2007; Tippett et al., 2009). In our study, we tested MCI participants and healthy controls on four different navigation tasks previously developed in the Bohbot laboratory as measures of spatial abilities.

When tested on the Wayfinding task, MCI participants demonstrated significantly poorer performance compared to healthy older adults at baseline. The Wayfinding task is a specific measure of participants' ability to build cognitive maps as it requires participants to learn the locations of targets in a virtual town and then take the shortest path from one target to another. As such, our results suggest that our MCI participants have significant spatial deficits compared to healthy older adults. Interestingly, when we included the data of young adults into the group comparisons, we found a significant difference in performance between the three groups; where young adults performed significantly better than the older adults and MCI participants, and the older adults performed significantly
better than the MCI participants. These findings indicate that the Wayfinding task is sensitive to spatial memory changes associated with healthy aging, and also is sensitive to spatial memory deficits associated with MCI. Indeed, age-related decline in wayfinding abilities has been reported by Head and Isom (2010), where healthy older adults showed difficulty in recalling landmarks and recognizing scenes compared to young adults after navigating in a virtual environment.

Correlational analyses further revealed a significant negative correlation between performance on the Wayfinding and the MoCA, where higher MoCA scores were correlated with less time per trial on the Wayfinding task. This significant correlation was not seen in correlational analyses involving Wayfinding performance and the MMSE. While both the MMSE and MoCA have been used as standard measures of global cognitive function, the MoCA has been shown to be particular sensitive to MCI (Nasreddine et al., 2005). Thus, they are important as previous research from the Bohbot laboratory has likewise shown that MoCA scores are negatively correlated with older adult performance on another virtual navigation task, the Discrimination Learning Task, indicating that older adults who use spatial strategies have better overall cognition (Dossa, 2010). Hence, the significant negative correlation seen in our Wayfinding results and older adult
performance suggest that this virtual navigation task may also be a potential tool for detecting MCI-related changes in global cognitive function.

There were no significant group differences seen on the 4-on-8 Virtual Maze at baseline. Thus, we included the 4-on-8 Virtual Maze data previously collected from young adults to better understand these results. Comparisons with young adult data indicate that our 4-on-8 Virtual Maze has varying sensitivity to spatial memory deficits that is age-dependent. Specifically, significant group differences were seen in 4-on-8 Virtual Maze performance, where young adults performed significantly better than older adults and MCI participants during the acquisition phase. They also took significantly fewer trials to learn the task. This suggests that older adults experience the same difficulty with the task as MCI participants during the acquisition phase resulting in the observed floor effect. Thus, the 4-on-8 Virtual Maze is sensitive to spatial memory associated with aging, perhaps leading to floor effects thereby making this task insensitive to spatial memory changes associated with MCI.

Baseline comparisons showed no significant group differences on the Go/No-Go Task, and Discrimination Learning Task. However, previous research conducted in the Bohbot laboratory showed that healthy older adults performed significantly worse than young adults on the Discrimination Learning Task on the probe trial where accuracy is best achieved by using a spatial strategy.
(Etchamendy et al., 2012). As such, it is possible that older adults already exhibit similar impairment on the Discrimination Learning Task as MCI participants resulting in the observed floor effect. Similarly, the probe trial of the Go/No-Go task determines if participants have successfully learned to make spatial relationships. Previous research in the laboratory demonstrated that there is a decreased use of spatial strategies across the lifespan (Bohbot, Schachar, Boivin, & Robaey, 2010). All these findings suggest that our virtual navigation tasks are sensitive to spatial memory deficits in various ways. For instance, the 4-on-8 Virtual Maze is sensitive to spatial memory changes associated with aging, but is not sensitive to spatial memory changes associated with MCI. On the other hand, the Wayfinding task, with its larger scale for error, is sensitive to spatial memory changes associated with aging and with MCI. Additionally, we found a significant correlation between Wayfinding performance and the MoCA, a test of global cognitive function to support this notion. These findings suggest that our virtual navigation tasks can quantify age-related decline in spatial memory and also quantify cognitive decline. Indeed, age-related decline in virtual spatial memory tasks have been shown in a previous study conducted in the Bohbot laboratory where healthy older adults displayed a deficit compared to young adults in performance on the Discrimination Learning Task (Etchamendy et al., 2012). Moreover, these findings support previous arguments that state how
the use of virtual environments is advantageous because it allows for the quantification of age-related deficits in human spatial navigation and detailed objective records of behaviour (Moffat, Zonderman, & Resnick, 2001).

**Subjective Measures**

There were significant differences observed for several self-report measures between the two groups. First, MCI participants had significantly worse scores than healthy older adults on the Perceived Stress Scale (PSS). These results are consistent with the findings of past studies investigating the relationship between affective status including stress, and risk for developing dementia and MCI. They found that everyday stress may accelerate cognitive decline, and that high levels of chronic stress is associated with increased incidence of MCI (VonDras, Powless, Olson, Wheeler, & Snudden, 2005; Wilson et al., 2007). As such, the stress reported by our MCI participants is typical. MCI participants’ significantly lower scores on the Memory Assessment Clinics Self-Rating Scale (MAC-S) and the Santa Barbara Sense of Direction Scale (SBSDS) are likewise expected. Indeed, the MAC-S has been used by studies as a measure of subjective memory complaints, which are predominant in individuals with amnestic MCI (Karantzoulis, Rich, & Mangels, 2006). Further, the results of the SBSDS provide support for studies that have shown individuals with MCI as having spatial difficulties (Deipolyi et al., 2007). Lastly, MCI participants showed
significantly higher scores than healthy participants on the Barratt Impulsiveness Scale (BIS). These findings are consistent with the current literature. Indeed, a few studies involving disorders such as schizophrenia and Borderline Personality Disorder have demonstrated a positive association between behavioural inhibition and hippocampal volumes. That is, they found that low hippocampal volumes are associated with increased impulsive behaviour (Cherbuin et al., 2008; Kumari et al., 2009; Sala et al., 2011). Thus, the increased impulsivity in our MCI participants may be related to hippocampal atrophy, which occurs at higher rates in MCI. In fact, Apostolova and colleagues (2006) found that MCI participants with smaller hippocampi had greater risk of conversion to AD, a disorder which includes marked impulsive behaviour.

There were no significant group differences seen in the Functional Spatial Assessment Questionnaire (FSAQ), or Quality of Life (QoL). Since our MCI participants are high-functioning, alert and independent individuals albeit abnormal memory impairment, it was expected that they would show comparable self-report assessments to the healthy group on these measures.

4.2 Pre versus Post Performance

Healthy Older Adults

Healthy older adults who were trained in the SMIP showed significant spatial memory improvements following training. It is unlikely that the SMIP-
trained healthy participants’ improvements are a result of a test-retest effect because alternative versions of the spatial memory transfer tasks were used before and after training. Moreover, our healthy Control group (NCC and PCC) who did not receive training but was administered the same battery of pre- and post-transfer tests did not exhibit any significant spatial memory improvements. These preliminary results are encouraging as the SMIP was designed to promote the use of hippocampal-dependent spatial learning strategies. Further, differences in outcome performances observed in the healthy Experimental and healthy Control group may be in part due to the individualized and adaptive nature of the SMIP. Indeed, Peretz and colleagues (2011) found that older adults who were given individually tailored and self-adjusting computer-based training showed significant improvements compared to older adult controls that were given general content training.

The transfer effects of the SMIP were additionally considered. Though inconclusive, we found that in general, neither the SMIP-trained healthy Experimental nor Control group showed significant improvements in non-targeted outcome measures including executive function, verbal memory, and quality of life following training. These preliminary findings hinted at the selectivity of SMIP at improving spatial memory, i.e. perhaps affecting specific components of the brain, as opposed to other studies in the literature which describe that extended
practice were generalized to non-trained areas of cognition (Mahncke et al., 2006; Zelinski, 2009). For instance, a cognitive training study involving training in three different domains—verbal episodic memory, inductive reasoning or speed of processing—found that healthy older adult participants who received reasoning training reported significantly less difficulty in independent activities of daily living (IADL). These training effects extended to trained participants’ improved performance on objective measures of IADL such as the Timed IADL Test, which assesses participants’ speed in interacting with real-life stimuli, e.g. looking up a telephone number (Willis et al., 2006). While sample size and time allotted to training may be factors, another explanation for the null transfer effect observed in this pilot study is whether SMIP training is capable of eliciting transfer effects. According to Barnett and Ceci’s taxonomy of transfer (2002), improvements in secondary outcomes are dependent on the similarity of the trained skills to untrained areas. Indeed, the treatment group of an auditory and visual attention training study showed significant improvement in untrained domains such as processing speed. Upon closer inspection, it was found that the indirect neuropsychological tests that measured processing speed involved skills that were accounted for in the training regime; for example, the attention training tasks required speeded manipulations of letters, words, and numbers in addition to purposeful control of attention (Mozolic et al., 2011). In sum, our results offer
preliminary evidence for the specificity of the SMIP to spatial memory improvements.

On another note, inspection of factors that could help predict individual healthy adult pre-training and post-training performance on spatial memory transfer tests provided inconclusive results. All SMIP-trained healthy participants showed improvement following training on the virtual spatial memory transfer tasks regardless of differences in SMIP performance factors, driving experience, and initial strategy on the 4-on-8 Virtual Maze. Interestingly, we did find evidence of a possible relationship between healthy participants’ initial strategy on the 4-on-8 Virtual Maze and HPC grey matter (from previous VBM analyses) among the SMIP-trained individuals. That is, 7 of the 11 SMIP-trained healthy older adults showed increases in hippocampal grey matter following training while no changes were observed in the healthy Control group. Further, out of the SMIP-trained, 100% of spatial learners (5 of 10) showed growth compared to 50% of response learners (submitted). Thus, these preliminary results suggest that the SMIP has an impact on grey matter, and specifically hippocampal growth. They furthermore suggest that the SMIP is particularly effective in spatial learners.

**MCI Participants**

MCI participants showed notable SMIP-associated spatial memory improvements following training. However, these improvements differed
individually. No spatial memory improvements were observed in the placebo control MCI participant. Thus, we sought to identify factors - individual SMIP performance, stage of impairment, initial strategy on the 4-on-8 Virtual Maze, and primary method of transportation - that could perhaps explain the observed pre- and post- performances in our current sample of SMIP-trained MCI participants.

Among our MCI SMIP-trained participants, the one spatial learner improved across all tasks, compared to the other patients, who were response learners and only improved in 1 or 2. That is, the MCI participant who is a spatial learner showed improvement across all virtual navigation tasks following training, and furthermore reached criteria and completed a substantial amount of the SMIP despite being classified as late-stage MCI. Conversely, an early-stage MCI participant, who is a response learner, reached criteria and completed the majority of SMIP environments, and showed improvement on 2 of the 4 virtual navigation tasks. The rest of the SMIP-trained MCI participants are response learners and showed post-training improvement in only 1 of the 4 virtual navigation tasks. Thus, these findings suggest that early SMIP intervention may optimize SMIP-related improvements and possibly delay spatial memory decline.

These preliminary findings are promising as they are consistent with our VBM results from SMIP-trained healthy older adults, where we demonstrated that 100% of spatial learners exhibited increases in hippocampal grey matter.
compared to 50% of response learners following SMIP training (Konishi et al., 2011). Hence, we speculate that spatial strategy may influence sensitivity of the SMIP.

We also found that SMIP-related improvements varied depending on the type of virtual navigation task. Most participants showed improvement on the Go/No-Go Task. In fact, even participants who reached criteria in fewer SMIP environments or received extra practice in the form of SMIP Light showed improvement on this task. This is possibly because the Go/No-Go task is simpler and easier to learn than the other virtual navigation tasks. For instance, the Go/No-Go task requires participants to learn spatial relationships of pathways containing an object or not, one at a time. While the probe trial of this task is more complex e.g. choose the pathway containing an object within a pair, it depends on participants’ successful acquisition during the learning phase. Conversely, the Discrimination Learning Task and Wayfinding task are more difficult as they require participants to remember multiple spatial relationships at once, or remember the layout of a stimuli-rich environment, respectively, in order to perform successfully. Hence, only participants who reached criteria (100% in 4 trials) in more SMIP environments showed improvement in the difficult virtual navigation tasks such as the Wayfinding and Discrimination Learning Task. Similarly, SMIP-trained MCI participants showed no improvement in the 4-on-8
Virtual Maze task. It is possible that MCI participants, who already show impaired cognition, have great difficulty in performing this task. The 4-on-8 Virtual Maze may be cognitively demanding for MCI participants because it requires them to remember all four previously visited pathways and to avoid them regardless of the navigational strategy they employ. Further, landmarks in the 4-on-8 Virtual Maze may be difficult to identify because of their ambiguous and distal locations relative to the radial maze. Hence, the 4-on-8 Virtual Maze may elicit a floor effect in MCI participants in which training offers little or no improvement in performance.

The remaining factors- primary method of transportation and hippocampal volume - did not appear to have an influence on performance based on the current results.

Neuropsychological results furthermore indicated no overall improvement in measures of spatial memory and episodic memory among our SMIP-trained MCI participants. There was likewise no improvement seen in our placebo control MCI participant. Closer inspection of the SMIP-trained MCI participant results revealed that while there was no overall improvement, there was also no significant overall change in neuropsychological results. On the other hand, the post-session episodic memory data for the placebo control MCI participant is missing as the participant did not want to complete the tasks. Although
speculative, this behaviour suggests that the participant may have had reduced motivation due to the difficulty in the task.

On another note, the results of a study conducted by Rapp and colleagues (2002) suggest that participants’ subjective positive outlook as a result of training may predict later improvement. In their study, they administered memory skills training over 6 weeks (12 hours) in MCI patients and demonstrated no improvements in memory performance immediately following training but reported that trained MCI patients had significantly better memory appraisals than the control group. During the six month follow-up sessions, MCI participants who received training furthermore showed a trend towards better memory i.e. better word recall. As such, it is possible that the SMIP effects in our MCI participants may be more apparent at the six month follow-up sessions. Indeed, our SMIP-trained MCI participants reported positive effects following training; however, we are still in the process of obtaining their 6 month follow-up data.

The transfer effects of the SMIP were additionally considered. We found that the SMIP-trained MCI participants did not show significant overall improvements in non-targeted outcome measures such as executive function and attention. However, baseline results revealed that MCI participants were already impaired relative to healthy controls on these tasks. Since the SMIP targets hippocampal-dependent functions; specifically spatial memory, we would
not expect an increase in non-trained areas. However, closer inspection of SMIP-trained MCI participants’ post-training data showed no overall change in these measures. A possible reason for this may be the carry-over effect due to the study protocol. For instance, some of the executive function and attention tests, e.g. digit span, Stroop, had only one version. Thus, MCI participants may have showed similar pre- and post-performance on these tests as they were given the same versions of these tests at both time points.

4.3 Advantages and Limitations of SMIP

The SMIP design uses a repetitive and an extended practice approach (gradual increases of spatial memory difficulty) that may be advantageous compared to other memory intervention methods. For instance, direct strategy training, where there is no graduated learning, may be effortful as it requires high demands on memory function. In this way, the SMIP design is ideal for healthy older adults who may demonstrate age-related slowing of abilities. Further, the computerized delivery of the SMIP allows for the SMIP to be adapted to each individual. In this way, the SMIP design may benefit MCI participants as it can be adapted to meet the needs of MCI participants who may have trouble regulating their conscious strategic activities in memory retrieval.

The SMIP is also unique from other memory intervention methods in that it has been designed to specifically target hippocampal-dependent functions. Still,
our preliminary results suggest that the SMIP’s effects may be selective. In fact, our above-mentioned observations of individual MCI participant improvement and previous VBM results in SMIP-trained healthy older adults suggest that the SMIP may be most effective for participants who use spatial strategies. In healthy older adults who use response strategies, SMIP-related improvement may be enhanced by additional SMIP training. However, for MCI participants who use response strategies, it may be more difficult to exert a SMIP effect because these individuals may already be impaired at using spatial strategies. In order to cater to the specific needs of these MCI participants, SMIP training may be adapted to include other factors i.e. social interaction, shortened training that could enhance training effects. Indeed, a meta-analysis study of 31 mnemonic training studies of healthy older adults revealed that factors such as social interaction (group sessions) and shorter session length were associated with training-related improvements (Verhaeghen, Marcoen, & Goossens, 1992).

Limitations of our pilot study include the sample size. The previously described analyses and results therefore were conducted to fulfill the exploratory nature of this pilot study with this limitation in mind. Our small sample size may have contributed to the lack of significant global spatial memory improvements in our MCI participants. Indeed, past studies involving the training of MCI participants have used relatively small (< 100) sample sizes leading to mixed
results. While some studies showed significant improvements in trained measures for small sample sizes, e.g. 10 patients, others with larger sample sizes showed positive but not significant training effects (D. E. Barnes et al., 2009; Belleville et al., 2006; Cipriani et al., 2006). Recent studies also denote methodological limitations that may contribute to null effects. For instance, some training studies involving MCI patient populations lack control group comparisons (Olazaran et al., 2004; Rozzini et al., 2007). Similarly, it was difficult to make appropriate comparisons for our small sample as there was data of only one control MCI participant in this pilot study. With a greater sample size, the behavioural results could be further validated. Moreover, a larger sample size would enable fMRI and structural MRI comparisons which would help determine the impact of SMIP on MCI participants' hippocampal activity and grey matter.
Chapter 5 Summary and Conclusions

In this study, we demonstrated that there are differences between healthy older adults and patients with Mild Cognitive Impairment in standard neuropsychological tests but also in virtual navigation tasks. Comparisons with young adult data further delineated the varying sensitivity of our virtual navigation tasks to spatial memory changes associated with aging and MCI. Preliminary SMIP results from our healthy older adult participants are promising and suggest that the SMIP is successful in promoting better navigational skills, and in improving hippocampal-dependent spatial memory. Previous analyses conducted in our healthy participants furthermore indicate that the SMIP has a positive impact on hippocampal activity and grey matter. Results in our MCI participants are promising because they show SMIP-related improvements in each individual. Future research should therefore include the additional testing of this patient population in order to better determine the impact of SMIP on navigational skills, hippocampal-dependent memory, and hippocampal grey matter and volume.
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Appendices

I. Tables

Table 1: Comparison of MCI diagnostic work-up across recruiting sites

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>MGH/RVH¹</th>
<th>Aging Centre²</th>
<th>Memory Clinic²</th>
<th>Jewish</th>
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<tbody>
<tr>
<td>MoCA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GDS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WMS-III</td>
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<td></td>
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<tr>
<td>WAIS III</td>
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<tr>
<td>Block design</td>
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<tr>
<td>Digit symbol coding</td>
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<td>Similarities</td>
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<td>X</td>
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<tr>
<td>WAIS IV</td>
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<tr>
<td>Vocabulary</td>
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<tr>
<td>Stroop</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Controlled Oral word fluency (FAS and animals)</td>
<td></td>
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</tr>
<tr>
<td>Rey-Osterrieth Figure</td>
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<tr>
<td>CVLT</td>
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<td></td>
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</tr>
<tr>
<td>BDI</td>
<td></td>
<td></td>
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<tr>
<td>Praxies</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td>Subjective reports</td>
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<td>X</td>
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<td>X</td>
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<td>CT scan</td>
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<td>X</td>
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<td>CERAD battery</td>
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<td></td>
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</tr>
<tr>
<td>CDR</td>
<td>X</td>
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<tr>
<td>BNA</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

¹Montreal General Hospital/Royal Victoria Hospital; ²Douglas Mental Health University Institute; MoCA= Montreal Cognitive Assessment; MMSE= Mini-Mental State Examination; GDS= Geriatric Depression Scale; WMS-III= Wechsler Memory Scale III; WAIS III, IV= Wechsler Adult Intelligence Scale III, IV; CVLT= California Verbal Learning Test; BDI= Beck Depression Inventory; CERAD= battery developed under the Consortium to Establish a Registry for Alzheimer's Disease; CDR= Clinical Dementia Rating
Table 2 Demographics of oldest healthy older adults and MCI participants at baseline; Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Older Adults (N=11)</th>
<th>MCI Participants (N=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.73 (2.28)</td>
<td>74.50 (4.03)</td>
<td>0.073</td>
</tr>
<tr>
<td>Education, years</td>
<td>15.22 (3.73)</td>
<td>13.38 (2.72)</td>
<td>0.267</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>28.90 (1.13)</td>
<td>27.75 (1.16)</td>
<td>0.044</td>
</tr>
<tr>
<td>MoCA (/30)</td>
<td>26.73 (1.61)</td>
<td>24.38 (2.67)</td>
<td>0.029</td>
</tr>
<tr>
<td>GDS (/30)</td>
<td>1.81 (1.53)</td>
<td>4.13 (2.70)</td>
<td>0.030</td>
</tr>
<tr>
<td>IQ (TONI-3)</td>
<td>104.56 (11.97)</td>
<td>99.75 (6.94)</td>
<td>0.336</td>
</tr>
</tbody>
</table>

MMSE= Mini-Mental State Examination; MoCA= Montreal Cognitive Assessment; GDS= Geriatric Depression Scale; TONI-3= Test of Nonverbal Intelligence 3
Table 3 Clinical characteristics of healthy older adults and MCI participants at baseline; Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Older Adults (N=11)</th>
<th>MCI Participants (N=8)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Trails (H-RNB)</td>
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<tr>
<td>A Time, seconds</td>
<td>31.70 (12.58)</td>
<td>46.71 (15.24)</td>
<td>0.031</td>
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<tr>
<td>B Time, seconds</td>
<td>73.47 (20.26)</td>
<td>118.60</td>
<td>0.100</td>
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<tr>
<td>Logical Memory I &amp; II (WMS)</td>
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<tr>
<td>Learning Slope</td>
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<td></td>
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<tr>
<td>% Retention</td>
<td>2.60 (2.63)</td>
<td>4.75 (1.04)</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>94.86 (24.71)</td>
<td>62.97 (27.54)</td>
<td>0.020</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>17.97 (10.39)</td>
<td>11.02 (7.17)</td>
<td>0.123</td>
</tr>
<tr>
<td>Digit Span (WAIS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forwards</td>
<td>9.81 (2.27)</td>
<td>8.88 (2.03)</td>
<td>0.364</td>
</tr>
<tr>
<td>Backwards</td>
<td>6.91 (2.58)</td>
<td>6.50 (2.13)</td>
<td>0.720</td>
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<tr>
<td>Digit Symbol Completed (WAIS)</td>
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<tr>
<td></td>
<td>54.95 (14.08)</td>
<td>50.00 (8.38)</td>
<td>0.110</td>
</tr>
<tr>
<td>RAVLT</td>
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<tr>
<td>Delayed Recall</td>
<td>8.73 (2.90)</td>
<td>6.38 (2.56)</td>
<td>0.085</td>
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<tr>
<td>Delayed Recognition</td>
<td>12.91 (2.70)</td>
<td>10.38 (2.62)</td>
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<td>Rey-Osterrieth Complex Figure</td>
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<tr>
<td>Immediate</td>
<td>17.90 (3.71)</td>
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<tr>
<td>Delay</td>
<td>21.09 (5.06)</td>
<td>15.79 (9.74)</td>
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</tbody>
</table>

H-NRB = Halstead-Reitan Neuropsychological Battery; WMS = Wechsler Memory Scale; Stroop Interference = Card 3 – Card 1 score; WAIS = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test
Table 4: Subjective measures in healthy older adults and MCI participants at baseline; Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Older Adults (N=11)</th>
<th>MCI Participants (N=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived Stress Scale</td>
<td>9.55 (3.83)</td>
<td>20.38 (5.34)</td>
<td>0.000</td>
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<tr>
<td>Barratt Impulsiveness Scale (/120)</td>
<td>51.70 (9.51)</td>
<td>62.25 (7.76)</td>
<td>0.022</td>
</tr>
<tr>
<td>Self-Report Memory Scale</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spatial abilities, %</td>
<td>85.39 (10.69)</td>
<td>74.21 (10.28)</td>
<td>0.035</td>
</tr>
<tr>
<td>Santa Barbara Sense of Direction Scale (/75)</td>
<td>59.45 (7.55)</td>
<td>47.00 (7.48)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table 5: Pre-/Post-demographic and clinical characteristics of healthy older adult participants and MCI participants; Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Older Adults Experimental (N=6)</th>
<th>Healthy Older Adults No-Contact/Placebo Controls (N=8)</th>
<th>Amnestic MCI Experimental (N=6)</th>
<th>Amnestic MCI Placebo Controls (N=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>70.00 (3.40)</td>
<td>70.88 (2.99)</td>
<td>73.00 (3.40)</td>
<td>78</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>2 M, 4 F</td>
<td>3 M, 5 F</td>
<td>3 M, 3 F</td>
<td>1 M</td>
</tr>
<tr>
<td><strong>Education, years</strong></td>
<td>16.00 (2.82)</td>
<td>15.25 (3.45)</td>
<td>13.83 (2.99)</td>
<td>11</td>
</tr>
<tr>
<td><strong>IQ (TONI-3)</strong></td>
<td>107.00 (11.26)</td>
<td>102.50 (9.32)</td>
<td>101.33 (7.42)</td>
<td>94</td>
</tr>
<tr>
<td><strong>MMSE Pre</strong></td>
<td>29.50 (1.22)</td>
<td>28.75 (0.88)</td>
<td>28.50 (1.38)</td>
<td>28</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td>29.17 (1.17)</td>
<td>29.00 (0.76)</td>
<td>28.17 (1.47)</td>
<td>27</td>
</tr>
<tr>
<td><strong>MoCA Pre</strong></td>
<td>27.16 (1.17)</td>
<td>26.63 (1.69)</td>
<td>25.33 (2.73)</td>
<td>22</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td>28.50 (1.87)</td>
<td>26.63 (1.92)</td>
<td>23.83 (2.04)</td>
<td>23</td>
</tr>
<tr>
<td><strong>GDS Pre</strong></td>
<td>1.50 (1.04)</td>
<td>1.75 (1.75)</td>
<td>3.83 (2.48)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td>1.66 (1.21)</td>
<td>2.83 (3.54)</td>
<td>4.33 (2.80)</td>
<td>2</td>
</tr>
</tbody>
</table>

TONI-3 = Test of Nonverbal Intelligence 3; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; GDS = Geriatric Depression Scale
Table 6: Pre-/post- results summary chart of neuropsychological battery in healthy older adult A) SMIP participants (N=6) and B) Control participants (N=8)

<table>
<thead>
<tr>
<th>A) SMIP Participants Test Variable</th>
<th>Pre</th>
<th>Post</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT Total Recall</td>
<td>50.75</td>
<td>4.99</td>
<td>49.25</td>
<td>5.70</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>9.50</td>
<td>1.25</td>
<td>10.50</td>
<td>1.55</td>
</tr>
<tr>
<td>Delayed Recognition*</td>
<td>14.25</td>
<td>0.25</td>
<td>12.00</td>
<td>0.40</td>
</tr>
<tr>
<td>Trails</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference</td>
<td>39.61</td>
<td>16.34</td>
<td>39.77</td>
<td>18.90</td>
</tr>
<tr>
<td>Rey-Osterrieth Delayed Recall</td>
<td>20.08</td>
<td>5.54</td>
<td>20.08</td>
<td>2.50</td>
</tr>
<tr>
<td>Digit Symbol Complete (%)</td>
<td>68.17</td>
<td>17.80</td>
<td>70.33</td>
<td>19.12</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>11.68</td>
<td>5.66</td>
<td>9.09</td>
<td>8.30</td>
</tr>
<tr>
<td>Digit Span Total</td>
<td>17.60</td>
<td>6.99</td>
<td>19.40</td>
<td>6.91</td>
</tr>
<tr>
<td>Story Recall Retention (%)</td>
<td>92.75</td>
<td>7.80</td>
<td>93.45</td>
<td>9.77</td>
</tr>
<tr>
<td>Perceive Stress Scale</td>
<td>10.17</td>
<td>5.42</td>
<td>12.83</td>
<td>8.13</td>
</tr>
<tr>
<td>Self-Esteem Questionnaire</td>
<td>30.00</td>
<td>6.23</td>
<td>30.17</td>
<td>7.39</td>
</tr>
<tr>
<td>Sense of Direction Scale- Tukey*</td>
<td>55.20</td>
<td>6.18</td>
<td>52.40</td>
<td>5.32</td>
</tr>
<tr>
<td>MAC-S Total</td>
<td>169.80</td>
<td>18.24</td>
<td>170.60</td>
<td>18.61</td>
</tr>
<tr>
<td>Remote Personal Memory (%)</td>
<td>81.00</td>
<td>13.87</td>
<td>76.00</td>
<td>18.84</td>
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<tr>
<td>Spatial Memory (%)</td>
<td>85.20</td>
<td>8.73</td>
<td>87.87</td>
<td>7.34</td>
</tr>
<tr>
<td>General Forgetfulness (%)</td>
<td>97.33</td>
<td>3.65</td>
<td>93.33</td>
<td>11.55</td>
</tr>
<tr>
<td>QoL Total (%)</td>
<td>78.13</td>
<td>2.02</td>
<td>80.65</td>
<td>4.80</td>
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<table>
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<tr>
<th>B) Control Participants Test Variable</th>
<th>Pre</th>
<th>Post</th>
<th>t-value</th>
<th>p-value</th>
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<tr>
<td>RAVLT Mean</td>
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<td>8.91</td>
<td>46.00</td>
<td>5.90</td>
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<td>1.83</td>
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<td>Delayed Recognition</td>
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<td>3.55</td>
<td>12.14</td>
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</tr>
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<td>Trails</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference</td>
<td>40.38</td>
<td>23.11</td>
<td>42.49</td>
<td>25.32</td>
</tr>
<tr>
<td>Rey-Osterrieth Delayed Recall</td>
<td>20.88</td>
<td>5.22</td>
<td>19.13</td>
<td>6.35</td>
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<tr>
<td>Digit Symbol Complete (%)</td>
<td>55.25</td>
<td>18.91</td>
<td>61.75</td>
<td>14.95</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>16.27</td>
<td>11.65</td>
<td>15.99</td>
<td>7.61</td>
</tr>
<tr>
<td>Digit Span Total</td>
<td>18.33</td>
<td>2.66</td>
<td>18.50</td>
<td>2.81</td>
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<td>Story Recall Retention (%)</td>
<td>98.67</td>
<td>30.23</td>
<td>94.24</td>
<td>11.64</td>
</tr>
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<td>Perceive Stress Scale</td>
<td>14.75</td>
<td>7.21</td>
<td>17.13</td>
<td>7.79</td>
</tr>
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<td>Self-Esteem Questionnaire</td>
<td>25.75</td>
<td>6.67</td>
<td>27.13</td>
<td>8.61</td>
</tr>
<tr>
<td>Sense of Direction Scale- Tukey*</td>
<td>55.38</td>
<td>12.52</td>
<td>56.25</td>
<td>8.80</td>
</tr>
<tr>
<td>FSAQ (/36)</td>
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<td>2.14</td>
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<td>2.62</td>
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<tr>
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<td>55.86</td>
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<td>12.80</td>
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<td>MAC-S Total</td>
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<td>23.06</td>
<td>162.33</td>
<td>22.50</td>
</tr>
<tr>
<td>Spatial Memory (%)</td>
<td>77.00</td>
<td>17.10</td>
<td>86.00</td>
<td>6.38</td>
</tr>
<tr>
<td>General Forgetfulness (%)</td>
<td>85.00</td>
<td>12.62</td>
<td>86.66</td>
<td>14.40</td>
</tr>
<tr>
<td>QoL Total (%)</td>
<td>91.67</td>
<td>6.38</td>
<td>85.00</td>
<td>10.00</td>
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</tbody>
</table>

QoL Total (%)
Table 6: Summary of healthy SMIP-trained older adults

<table>
<thead>
<tr>
<th>ID</th>
<th>Initial Strategy (determined from 4/8 VM)</th>
<th>Percent of SMIP Tasks Completed</th>
<th>Total # of Completed Tasks that Reached Criteria (46)</th>
<th>SMIP Light used (y/n)</th>
<th>HPC Grey Matter Increase (y/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMIP-4</td>
<td>Response</td>
<td>80.43</td>
<td>37</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SMIP-12</td>
<td>Response</td>
<td>65.21</td>
<td>28</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SMIP-13</td>
<td>Response</td>
<td>60.87</td>
<td>27</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SMIP-19</td>
<td>Response</td>
<td>93.48</td>
<td>43</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SMIP-25</td>
<td>Spatial</td>
<td>78.26</td>
<td>27</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-27</td>
<td>Response</td>
<td>76.09</td>
<td>34</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-28</td>
<td>Response</td>
<td>97.82</td>
<td>44</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-30</td>
<td>Response</td>
<td>86.96</td>
<td>40</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SMIP-32</td>
<td>Spatial</td>
<td>100</td>
<td>41</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-33</td>
<td>Response</td>
<td>84.78</td>
<td>38</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-46</td>
<td>Spatial</td>
<td>100</td>
<td>42</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMIP-62</td>
<td>Response</td>
<td>100</td>
<td>44</td>
<td>No</td>
<td>Yes (middle hpc)</td>
</tr>
<tr>
<td>SMIP-69</td>
<td>Response</td>
<td>95.65</td>
<td>41</td>
<td>Yes</td>
<td>Yes (middle hpc)</td>
</tr>
</tbody>
</table>

1 Determined from pre-training performance on the 4/8 VM 2 Criteria= 100% in 4 trials 3 SMIP light= presentation of additional virtual environments
Table 7: Summary of MCI SMIP-trained participant characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>MCI Stage¹ (early/late)</th>
<th>Initial Navigational Strategy²</th>
<th>Virtual Tasks where Improvement was Seen</th>
<th>Percent of SMIP Tasks Completed</th>
<th>Total # of Completed Tasks that Reached Criteria³ (/46)</th>
<th>SMIP Light Administered⁴ (yes/no)</th>
<th>Primary means of transportation</th>
<th>HPC Volume (number of voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI -01</td>
<td>Late</td>
<td>Response</td>
<td>Wayfinding</td>
<td>82.61</td>
<td>44</td>
<td>N/A</td>
<td>Car</td>
<td>N/A</td>
</tr>
<tr>
<td>MCI -02</td>
<td>Late</td>
<td>Spatial</td>
<td>Wayfinding, Go/No-Go, CSDLT</td>
<td>76.08</td>
<td>36</td>
<td>N/A</td>
<td>Public transport</td>
<td>N/A</td>
</tr>
<tr>
<td>MCI -03</td>
<td>Early</td>
<td>Response</td>
<td>Go/No-Go</td>
<td>52.17</td>
<td>24</td>
<td>N/A</td>
<td>Public transport</td>
<td>N/A</td>
</tr>
<tr>
<td>MCI -04</td>
<td>Late</td>
<td>Response</td>
<td>Go/No-Go</td>
<td>80.43</td>
<td>26</td>
<td>Yes</td>
<td>Public transport</td>
<td>149</td>
</tr>
<tr>
<td>MCI -05</td>
<td>Early</td>
<td>Response</td>
<td>Go/No-Go, CSDLT</td>
<td>89.13</td>
<td>40</td>
<td>Yes</td>
<td>Public transport</td>
<td>126</td>
</tr>
<tr>
<td>MCI -06</td>
<td>Late</td>
<td>N/A</td>
<td>Go/No-Go</td>
<td>60.87</td>
<td>24</td>
<td>Yes</td>
<td>Public transport</td>
<td>127</td>
</tr>
</tbody>
</table>

¹ Determined using the Alzheimer’s Disease Neuroimaging Initiative Protocol ² Determined from pre-training performance on the 4/8 VM ³ Criteria= 100% in 4 trials ⁴ SMIP light= presentation of additional virtual environments; n/a= not available at time of testing
II. Figures

Figure 1: Discrimination Level 1 of the Spatial Memory Improvement Program. Participants must search for and locate shapes or objects across increasingly more complex environments. With progress, attention and cognitive demands increase gradually (Figure borrowed from Nicholas Andersen’s thesis (2009) with permission).
Figure 2: Discrimination Level 2 of the Spatial Memory Improvement Program.

Participants engage in an exploration phase of a realistic looking environment. They must locate the position of objects or rooms and remember their exact position. Participants are asked to reproduce a top view of the environment including the objects in it or the relative position of rooms. Trials are given until participants place all objects in their correct position or until a maximum of 4 trials. Learning is measured in terms of latencies to targets and errors made (Figure borrowed from Nicholas Andersen’s thesis (2009) with permission).
Figure 3: Object Location of the Spatial Memory Improvement Program.

Participants must learn the location of objects on a table. They are shown the objects from four different perspectives. Participants are then asked to identify changes in the positions of objects placed on arrays. Participants are asked to reproduce a top view of the environment including the objects in it. Trials are given until participants place all objects in their correction position or until they reach a maximum of 4 trials. Learning is measured in terms of errors (Figure borrowed from Nicholas Andersen’s thesis (2009) with permission).
Figure 4: Spatio-Temporal Order of the Spatial Memory Improvement Program.

Participants are walked through an environment where they see objects or locations appear on either side of them. Participants are asked to list the temporal order of previously seen objects. Trials are given until participants list all objects or locations in their correct order with a maximum of 4 trials. Learning is measured in terms of errors (Figure borrowed from Nicholas Andersen's thesis (2009) with permission).
Figure 5: Navigation of the Spatial Memory Improvement Program. Participants explore large environments containing multiple landmarks. Following exploration, participants must reach target locations. Some tasks require participants to assess distances between their position and other locations, and identify the closest one. Learning is measured in terms of latencies, path lengths, and errors (Figure borrowed from Nicholas Andersen’s thesis (2009) with permission).
Figure 6: 4-on-8 Virtual Maze. Part 1: Participants are asked to visit the 4 accessible pathways to retrieve the objects. They are told to remember which pathways they have taken. Part 2: Participants are told avoid the paths that were previously closed to retrieve the objects. That is, they had to retrieve the objects in the previously blocked pathways. Landmarks surrounding the maze apparatus provide orientation cues. This task is used to dissociate spatial and response strategies with the use of a probe trial during which all landmarks are removed and a wall is raised in order to hide the landscape. A verbal report is additionally administered to determine specific strategies. Measures of learning include reference memory errors (i.e. going into the wrong path for the first time), working memory errors (i.e. entries into a previously visited path), and latencies.
Figure 7: Wayfinding Task. Part 1: participants are placed in a virtual town and are asked to visit and identify the different locations that make up the town, e.g. shops, pool, etc. They are given approximately 20 minutes of this initial exploration. Part 2: participants are placed in front of one target location, and are asked to travel to another target location using the shortest way possible. Measures of learning include path lengths and latencies to target locations.
Figure 8: Go/No-Go Task. Part 1: Participants visit 6 pathways, one by one, 3 of which contain an object. Upon the 4th presentation of the 6 pathways, participants have to choose whether to enter into a pathway if they believe it contains an object. Part 2: Pairs of pathways are presented. Participants have to choose the pathway containing an object. This part dissociates the ability to use hippocampal-dependent spatial learning from response learning. Part 3: All pathways are presented in an “all open” phase. Participants must now locate all objects (lower figure showing the maze from a bird’s eye view is not seen by the participant). Learning is measured in terms of latencies, reference and working memory errors.
Figure 9: Concurrent Spatial Discrimination Learning Task (Discrimination Learning Task). Part 1: Participants visit 6 pairs of pathways. In each pair of pathways, one path contains an object while the other path is empty. Participants have to learn which path contains an object. Part 2: Pairs consisting of 2 previously unrelated pathways are presented. This part dissociates spatial versus response strategies. Part 3: All pathways are presented, participants must locate all objects. This experimental condition is presented with control and randomized conditions in alternation, to healthy older adult participants. MCI participants, however, are administered the experimental condition on alternation with only the randomized condition. Learning is measured in terms of latencies, reference and working memory errors.
Figure 10: The percent mean accuracy on the Wayfinding task for MCI participants and healthy older adult participants at baseline. Percent mean accuracy represents the average number of target locations reached during the task. Significant differences were observed between the two groups, where MCI participants (n = 8) reached significantly fewer target locations than healthy older adult participants (n = 11) on the Wayfinding Task. The asterisk indicates p < 0.05. Bars indicate the standard error of the mean (SEM).
Figure 11: A scatterplot with fit line showing the significant negative correlation in all participants between their MoCA scores and their mean trial time on the Wayfinding task at baseline ($r = -0.485$, $p < 0.05$).
Figure 12: The mean trials to criteria/maximum trials taken by participants during the acquisition phase of the behavioural and fMRI Concurrent Spatial Discrimination Learning Task at baseline. A ceiling value of 25 trials was given to participants who could not reach criteria within the time allotted in order to allow for comparisons to be made. There was no significant group difference observed in the behavioural Discrimination Learning Task. This performance was additionally seen in the fMRI Discrimination Learning Task. N indicates the number of participants per group. Bars indicate the standard error of the mean (SEM).
Figure 13: The mean errors made by participants during the all open phase (phase 3) of the behavioural and mock Go/No-Go task at baseline. No significant differences were observed between the MCI participants and healthy older adult participants on the behavioural and mock Go/No-Go. N indicates the number of participants per group. Bars indicate the standard error of the mean (SEM).
Figure 14: A) The mean errors and B) mean latencies made by participants during part 2 of the 4-on-8 Virtual Maze acquisition phase (trials 1-3) at baseline. No significant differences were observed between the 2 groups, where MCI participants (n = 8) and healthy older adult participants (n = 11) showed similar performance for all three trials. Bars indicate the standard error of the mean (SEM).
Figure 15: A scatterplot with fit line shows the significant positive correlation in all participants between their self-reported sense of direction on the Santa Barbara Sense of Direction Scale and their percent mean accuracy on the Wayfinding task at baseline ($r = 0.572$, $p < 0.05$). A scatterplot with fit line shows the significant positive correlation in all participants between their self-reported spatial abilities on the MAC-S and their percent mean accuracy on the Wayfinding task at baseline ($r = 0.451$, $p < 0.05$).
Figure 16: A) The mean errors made by participants (MCI: n = 8; ≥ 69: n = 11; ≤ 68: n = 29; Young Adults: n = 258) during part 2 of the acquisition phase (trials 1-3) at baseline on the 4-on-8 Virtual Maze. A MANOVA indicated a significant difference between groups in each trial, all p < 0.001. Post-hoc HSD Tukey tests revealed that young adults made significantly fewer errors during the first 3 trials compared to both older adult groups and MCI participants, p < 0.05. B) The mean latencies of participants (MCI: n = 8; ≥ 69: n = 11; ≤ 68: n = 29; Young
Adults: n = 258) during part 2 of the acquisition phase (trials 1-3) at baseline on the 4-on-8 Virtual Maze. A MANOVA indicated a significant difference between groups for each trial, all p < 0.001. Post-hoc HSD Tukey tests showed that young adults took significantly less time per trial compared to the other 3 groups, p < 0.05. Bars indicate the standard error of the mean (SEM).

Figure 17: The mean trials to criteria/maximum trials given of all participants on the 4-on-8 Virtual Maze at baseline. A MANOVA indicated a significant difference between groups, p < 0.001. Post-hoc HSD Tukey tests revealed that young adults (n = 258) took significantly fewer trials to reach criteria compared to healthy older adult groups (>69: n = 11; ≤68: n = 29) and the MCI participants (n=8) as indicated by the asterisk p < 0.05. Bars indicate the standard error of the mean (SEM).
Figure 18: A) The percent mean accuracy and B) percent mean time error of all participants (Young Adults: n= 95, ≤68: n=29, ≥69: n=11, MCI: n=8) on the Wayfinding task. MANOVAs indicated significant differences between groups in both measures, p < 0.001. Post-hoc HSD Tukey tests showed that young adults reached significantly more target locations, and took significantly less time to reach target locations than both older adult groups and MCI participants, p <
0.001. However, results additionally indicated that both older adult groups (age ≤ 68 and ≥ 69) reached significantly more target locations than MCI participants, p < 0.001. All asterisks indicate p < 0.001. Bars indicate the standard error of the mean (SEM).

Figure19: A) The mean delayed recall and B) mean delayed recognition of List A on the Rey Auditory Verbal Learning Test in all participants (Young Adults: n=66; ≤ 68: n=29; ≥ 69: n=11; MCI: n=8). MANOVA’s indicated a significant difference
between groups in both measures, \( p < 0.05 \). Post-hoc HSD Tukey tests revealed that MCI participants have significantly poorer performance on the delayed recall compared to healthy young adults and the 2 healthy older adult groups \( p < 0.05 \). Further, MCI participants performed significantly worse on the delayed recognition than young adults and healthy older (\( \leq 68 \)) adults, \( p < 0.05 \). The healthy older adults (\( \geq 69 \)) performed significantly worse on the delayed recognition than young adults, \( p < 0.05 \). The asterisks all indicate \( p < 0.05 \). Bars indicate the standard error of the mean (SEM).

![Bar chart](image)

Figure 20: The pre- and post-training total part 2 errors made in the first 2 trials during the acquisition phase of the 4-on-8 Virtual Maze for Experimental (\( n = 6 \)) and Control (\( n = 8 \)) groups. Following training, the Experimental group made significantly fewer errors, \( p < 0.05 \). This was not seen in the Control group. Bars indicate the standard error of the mean (SEM).
Figure 21: The pre- and post-training number of trials to criteria achieved in the fMRI version of the Concurrent Spatial Discrimination Learning Task for the healthy Experimental (n = 6) and healthy Control (n = 8) groups. Following training, the Experimental group took significantly fewer trials to reach criteria. This was not seen in the Control group. The asterisk indicates p < 0.05. Bars indicate the standard error of the mean (SEM).
Figure 22: A) The pre- and post-training percent mean distance error achieved in the Wayfinding task for the healthy Experimental (n = 6) and healthy Control (n = 8) groups. Following training, the Experimental group took significantly shorter routes to target locations. No significant improvement was seen in the Control group. B) The pre- and post-training percent mean time error achieved in the Wayfinding task for the healthy Experimental and healthy Control groups. Following training, the Experimental group took significantly less time to reach
target locations. No significant improvement was seen in the Control group. The asterisk indicates $p < 0.05$. Bars indicate the standard error of the mean (SEM).
Figure 23: The pre- and post-training percent correct in the all open phase achieved by individual MCI participants on the behavioural and mock Go/No-Go task. MCI-02 to MCI-06 made more correct identifications of pathways containing objects following training. This improvement was not seen in MCI-01 or MCI-07, who was in the placebo control group.
Figure 24: A) The pre- and post-number of trials needed to reach criteria in individual MCI participants on the Concurrent Spatial Discrimination Learning Task. Please note that participants who were not able to reach criteria were given a maximum value of 25 trials for comparison purposes. As shown, two of the six MCI participants who received training, MCI-02 and MCI-05, took
substantially fewer trials to reach criteria following training. B) The pre- and post-training percent correct achieved by individual MCI participants on the probe trial (part 2) of the Discrimination Learning Task. Following training, MCI-02, -03, and -05 made more correct identifications of pathways containing rewards.
Figure 25: A) The pre- and post-training percent mean accuracy of individual MCI participants on the Wayfinding task. Following training, MCI-01 and -02 reached
all target locations. B) The pre- and post-training mean distance travelled per trial of individual MCI participants on the Wayfinding task. Improvement is seen in MCI-01. C) The pre- and post-training mean time per trial of individual MCI participants on the Wayfinding task. Following training, MCI-01 and -02 took substantially less time per trial when finding target locations.