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Possible strategies and methodologies to improve spatial memory: from healthy young individuals to people with Mild Cognitive Impairment

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Chapter 1

General Introduction

From an evolutionary point of view, aging represents a physiological, irreversible, and universal process often associated with cognitive impairment and dementia. In these years, every country worldwide is experiencing growth in both the size and the proportion of elders in the population, opening new challenges for the healthcare system in promoting successful aging. Specifically, successful aging is a multidimensional concept encompassing domains of functional, social, physical, and psychological health (Annele et al., 2019). Additionally, according to the classic concept of Rowe and Kahn (1997), successful aging is defined as high physical, psychological, and social functioning in old age without major diseases (Rowe & Kahn., 1997).

This research project aims to explore the possibilities of promoting healthy aging, at the same time counteracting the typical cognitive deficits, often implying memory impairments, that characterize the aging process. Firstly, an experimental study in young healthy participants will be described. It was shown that visual stimulation flickering within the range of theta frequency band was able to enhance spatial memory, pointing out that theta oscillations may play a crucial role in spatial memory encoding even in humans. Next, a series of three experiments conducted on a population of healthy young people will be described with the aim of testing the validity of innovative virtual navigational training in promoting the ability to form allocentric spatial representations.

Evidence from behavioral and neuroimaging data will be reported. Following, results obtained in a group of elderly participant and in a group of patients affected by Mild Cognitive Impairment (from now on, *MCI*) will be presented.

1.1 Normal and Pathological Aging: a brief review

The aging of the brain represents a common characteristic in the onset of neurodegenerative diseases. The physiological aging process involves a complex set of structural and functional changes. Generally, at a structural level, the aging brain is characterized by a general progressive atrophy in the prefrontal cortical regions and related areas. Additionally, a reduction in the white substance density and a possible progressive decrease in the dopaminergic system functionality typically occurred in the normal aging process (Sachs-Ericsson et al., 2014). These neural changes are associated with specific cognitive deficits, evidenced by neuropsychological assessments and in clinical practice. It is well known that aging is characterized by a general reduction in processing speed that leads to declines in a broad range of cognitive functions, including memory performance. Although cognitive aging is a highly heterogeneous process, several researchers have highlighted a cognitive profile commonly characterized by decreased performance in tests of processing speed and memory (Hedden and Gabrieli, 2004; Sala - Llonch et al., 2014). Despite the above-mentioned structural changes, compensatory neural mechanisms often allow the adaptive maintenance of acceptable levels of functioning (Yankner et al., 2008).

It is possible to distinguish between "normal" and "pathological" aging by looking at the possible triggering factor of the decline process. Regarding normal aging, the neural areas deterioration is caused by increasing age and by longevity. For what concerns pathological aging, the neural tissue deterioration is caused by an illness and in most cases leads to more serious consequences (i.e Alzheimer Disease, AD). From a neuropsychological point of view, aging-related cognitive decline is often associated with deficits in short-term recall, spatial memory, naming and speed processing. Particularly, evidence from different studies (Petersen et al., 1992; Yankner et al., 2008) points out that working memory and the speed of processing information, gradually decline throughout the adult life span. In addition, it has been suggested that delayed recall of verbal information significantly declines in the normal aging condition as a product of a physiological process (Yanker et a., 2008). On the other hand, it is largely accepted that memory dysfunctions represent the first cognitive symptoms in Alzheimer's disease (AD) and in prodromic stage of MCI (McKhann et al., 2011; Albert et al., 2011). Generally, volume loss in the entorhinal cortex and medial temporal lobe is not observed in normal elderly people. Instead, this specific volume loss is a typical correlate of pathological memory dysfunction, which often appears in the early stages of mild cognitive disorders (Iachini et al., 2009). In this line, normal age-related memory loss differs from pathological memory loss both in the degree of impairment and in the rate of cognitive decline. As reported before, memory loss and memory impairments may represent early symptoms of cognitive decline progression. In particular, cross-species studies (Lai et al., 1995, Yankner et al., 2008) have shown that spatial memory and learning of new information are severely limited. Further, there is evidence suggesting that the allocentric component of spatial memory might be taken as a predictor of AD from MCI (Pai and Jacobs., 2004; Vannini et al., 2007). Given the frequency of visuospatial deficits in early-stage AD, the assessment of visuospatial processing is a promising approach to finding predictive markers of AD and MCI (Iachini et al., 2009). Brain networks involved in working and spatial memory are closely intertwined, outlining a potential relation between these processes, which are also affected in non-pathological aging. As a matter of fact, a decline in spatial memory and orienting is frequently reported in both healthy and pathological aging conditions, with disorders of spatial navigation ability in people with a subjective memory disorder, MCI , and AD (Amariglio et al., 2011). Furthermore, the integrity of visuospatial memory and navigation skills is crucial for the correct normal daily living activities (Ruggiero et al., 2020). Similarly, early interventions on memory-changes age-related are necessary to reduce the overall impairment impact.

In the next paragraph, the pre-clinical condition of MCI and the role of associative spatial memory in cognitive deterioration mechanisms will be described.

1.2 The Mild Cognitive Impairment: treatments models

MCI refers to a marked decrease in cognitive functioning beyond the typical age-related changes. The National Institute on Aging-Alzheimer's Association (NIA/AA) defines

MCI (Albert et al., 2011) includes a change in cognition reported by the patient, client, or clinician, objective evidence of impairment in one or more cognitive domains, functional ability preservation, and the absence of dementia (Sachs-Ericsson et al., 2014). So far, MCI has evolved over the past 2 decades to represent a state of cognitive function between that seen in normal aging and dementia (Petersen., 2016) and it can be considered an intermediate stage along a continuum from physiological pathological aging. In addition, MCI is a disorder that can evolve into AD (Sachs-Ericsson e Blazer, 2015). As such, it is important to implement new clinical protocols in order to counteract the evolution to severe stages of cognitive decline. In this perspective, the American Psychological Association (APA, 2013) has included some taxonomic changes within the new edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Specifically, the diagnostic criteria and the nomenclature for dementia and other cognitive disorders have been revised. In particular, the section previously entitled "Delirium, dementia, and amnestic and other cognitive disorders" (DSM-IV and DSM-IV-RT) has been replaced by the new label "Neurocognitive Disorders" including MCI as minor neurocognitive disorder. As mentioned before, although people with MCI are at high risk of getting AD, they do not fit the criteria for diagnosis. One of the main characteristics of MCI is the existence of persistent and progressive memory impairments, at different levels (Belleville et al., 2008). Memory is the primary issue in amnestic MCI (aMCI). Further, non-amnestic types of MCI exist as well (Asada et al., 1996). Importantly, memory and other cognitive domains are impaired in multiple-domain MCI. Interestingly, people with multiple-domain MCI may be more likely to develop dementia (Crocco & Loewenstein, 2005). Petersen and Morris (2005) have suggested that when MCI is likely a prodromal syndrome of AD, clinical trials with disease-modifying drugs that target underlying pathological mechanisms such as amyloid-beta accumulation and neurofibrillary tangle formation may help develop effective treatment options in the future (Karakaya, Fußer, Schroder, & Pantel, 2013). There are also non-pharmacological treatments for MCI. For example, evidence from animal paradigms suggested that exercise may reduce the progression of neurodegenerative disorders (Hosseini, Alaei, Reisi, & Radahmadi, 2013). Particularly, physical exercise can positively impact cognitive functioning in individuals with MCI (Nagamatsu et al., 2013). Other studies showed better cognitive performance after a period of exercise when compared with no-exercise controls among patients with dementia or MCI (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Interestingly, physical exercise was associated with significantly larger hippocampal volumes and better spatial memory (Ahlskog et al., 2011). A recent systematic review (Song, Stern & Gu, 2021) highlighted the role of seven main factors which are diet, smoking, alcohol consumption, physical activity, recreational cognitive activity, sleep, and meditation that can be modified in lifestyle to stimulate the cognitive reserve and, consequently, mitigate the relation between typical brain changes associated with physiological and/or pathological aging and cognition (Stern, 2009; 2012; 2021). So far, it is well known that neuropsychological interventions on cognitive-behavioral symptoms can reduce disability and improve patients' quality of life (Clare and Woods, 2004). Over the past decades, three main types of non-pharmacological interventions aimed at cognitive enhancement of patients with cognitive impairment have been developed: *Cognitive stimulation; Cognitive training; Cognitive rehabilitation*.

First, cognitive stimulation programs showed a positive effect on global cognition in patients with MCI (Streater et al., 2016). Second, cognitive training protocols have been proven to be effective in improving general cognitive functioning in patients with minor neurocognitive disorder. (Tsantali, Economidis & Rigopoulou, 2017). Finally, cognitive rehabilitation represents an individualized intervention focused on maintaining and improving skills related to the performance of daily living activities (Clare et al., 2004). Importantly, in neurocognitive rehabilitation, technology is an effective tool in reducing the negative impact of everyday living difficulties in people with cognitive impairment (Maresca et al., 2020; Patterson, 2021). Many authors highlighted the role of Computerized Cognitive Training (CCT) in improving global cognition in the elderly (García-Casal et al., 2016; Gates et al., 2019; Hu et al., 2019; Zhang et al., 2019).

In addition, it has been demonstrated that CCT improves global cognition and individual cognitive domains (especially attention and memory), as well as psychosocial functioning (Travers-Hill et al., 2017) in people with mild cognitive impairments. Furthermore, CCT implementation showed several advantages over traditional techniques (Zokaei et al., 2017). Mainly, CCT programs can be built for specific cognitive functions stimulation (i.e. memory, attention). The use of technology (i.e. CCT) allows instantaneous quantitative feedback and is directly accessible via portable devices. Moreover, a key feature of computer-based programs is that they are designed to be fun and enjoyable.

Specifically, cognitive rehabilitation software is able to increase user motivational engagement and avoid repetition (Hirazoki et al., 2020; Matamala-Gomez et al., 2020). So far, the motivational engagement seems to be very relevant within the rehabilitation process and is fully incorporated into current models of health (Schwarzer, 2013). The motivational engagement has been operationalized as a biologically-driven impulse that compels an organism to act or as a set of processes to achieve personal goals (Berridge., 2004; Yee and Braver., 2018). Interestingly, in elderly patients, difficulties in terms of compliance with rehabilitation protocols are frequently present (Clare et al., 2019).

For this reason, rehabilitation protocols that integrate motivational strategies could prove particularly useful in favoring greater compliance in MCI people. In addition, motivational engagement strategies seem to be particularly useful in driving and promoting self-efficacy, self-control, and well-being by confirming greater therapeutic benefits than traditional rehabilitation programs (Choi e Twamley, 2013). A key concept in this framework of promoting patients' active involvement and motivational engagement concerns *gamification*. The aim of *gamification* is to implement game-like features (competition, narrative, leaderboards, graphics, and other game design elements) to transform a frustrating task into something engaging and possibly fun (Lumsden et al., 2016). Importantly, beyond motivational benefits, using game-design protocols to provide neurocognitive training may also be beneficial on many outcomes, including working memory, associative spatial memory, attention, problem-solving ability, emotional control, and prosocial behaviors (Lumsden et al., 2016). Furthermore, in the e-Health field, the use of gamification is directed toward the increase of physical and mental health and it is often employed for the treatment of neurodegenerative disorders (Sardi, Idri & Fernández-Alemánet, 2017). Thus, the implementation of neurocognitive training programs through a gamification-based protocol could provide several benefits and, for this reason, it has been implemented in the rehabilitation of mnestic, attentional, and frontal/executive functions by increasing patients' compliance and motivation (Lumsden et al., 2016). In this thesis, this gamification approach will be extensively discussed through the testing of an innovative protocol.

1.3 The role of associative spatial memory in MCI: implications and clinical applications

Spatial memory is essential for *route learning* and *navigation.* From an evolutionary perspective, being able to successfully explore an environment (i.e. *spatial navigation abilities*) is crucial for survival. Spatial memory involves the processes of encoding, storage and recall spatial information about the environment, objects and agents within it (APA, 2007). More specifically, spatial memory relies on the capacity to remember the position and location of objects or places, which may include orientation, direction, and distance. It is well known that spatial memory depends on mental representations constructed within a dual system of spatial coordinates: egocentric and allocentric (Klatzky, 1998; Burgess, 2008). On the one hand, the egocentric system refers to an individual location in space and is based on subject-object relations. On the other hand, the allocentric coordinate system refers to object relations independently of the individual's position in space, with the aim of creating an environment-centered representation. Interestingly, to successfully navigate the environment, it is essential to switch flexibly between one and the other coordinate system, depending on the environmental demand (Lester et al., 2017). At the neurobiological level, the two systems are supported by different neural substrates, which mediate different spatial strategies (Poulter, Hartley & Lever, 2018; Hartley et al., 2014; Byrne et al., 2009). Specifically, the development of representations by an egocentric system seems to be supported by the parietal cortex and the dorsal striatum functioning (Chersi & Burgess, 2015). A prominent role in the allocentric coordinate system is played by place cells, present in the hippocampus (O'Keefe and Nadel, 1978) that fire only when the animal takes up a specific point in space, in order to create a 'cognitive map' (Tolman, 1948) of that space (Ekstrom et al., 2003; Jacobs, 2014). A key role is also played by the medial temporal cortex (Hafting et al., 2005), the parahippocampal cortex (PHC), and the retrosplenial (RSC) (Clark et al., 2018) in the construction of spatial representation on allocentric coordinates.

Besides, RSC and the posterior cingulate cortex (PCC) also played a prominent and functional role related to the ability to switch between coordinate systems (Berns et al., 2009). Moreover, frontal regions play a key role in the processes of memory, spatial attention, and selection of egocentric/allocentric strategies (Cona & Scarpazza, 2019). Remarkably, a decline in visuospatial memory skills is frequently associated with healthy and pathological aging conditions (Amariglio et al., 2011). Importantly, deficits in spatial memory, with a prevalence of allocentric component impairments, have been documented in healthy elderly as well as in pre-clinical MCI and AD groups, where difficulty in the acquisition of map knowledge, an ability supported by visuospatial working memory and mental rotation processes, is observed (Ianchini, Ruggiero & Ruotolo, 2009). It was demonstrated that the formation of spatial representations on allocentric coordinates (Meneghetti et al., 2011) and the switching between egocentric and allocentric systems are early impaired in the first stage of cognitive decline. This finding is reinforced by the observation that elderly individuals tend to use navigation strategies based on the egocentric coordinate system (Rodgers, Sindone & Moffat, 2012). It is interesting to note that the existence of different neural bases underlying two spatial representation systems can result in patterns of dissociation at the cognitive-behavioral levels.

On the one hand, hippocampal and medial temporal damage leads to greater alterations in allocentric environmental representations. On the other hand, parietal damage leads to greater alterations in egocentric environmental representations. Finally, retrosplenial cortex and parieto-occipital sulcus impairment leads to representation switching ability alteration (Bird and Burgess, 2008; Hartley et al., 2014). In general, neural network changes underlying spatial memory ability could be a product of the decline process. The expression of spatial deficits early observed in the elderly could be the result of changes at the neural level (Boccia et al., 2019).

1.4 Research Question and aims

As previously described, this research project aims to explore different mechanisms of memory facilitation, which may be exploited to promote healthy ageing and to contrast the progression of pathological cognitive decline. Most of my thesis is focused on the validation of an innovative tool for the enhancement and rehabilitation of spatial memory skills. Specifically, through the collection of behavioral and neuroimaging data, the possibility of stimulating the ability to form allocentric maps of space in different groups of participants was explored. Furthermore, based on evidence in the literature (Dresler et al., 2017), the possible connection between spatial memory skills and verbal memory was investigated, suggesting numerous applications and clinical implications. The possibility of highlighting the connection between spatial abilities and non-spatial memory skills may have important consequences in clinical as well as purely scientific domains. In addition, the implementation of computerized protocols for cognitive enhancement could have a strong positive impact on the management of interventions by the local healthcare system.

CHAPTER 2

Memory flashes: 4Hz flickering of visual input facilitates the memorization of object locations in space

Abstract

Several studies, mostly in the animal model, have shown that the synchronization of brain oscillatory phase may play a crucial role in memory processing by regulating the activities of different sensory cortices. In humans, hippocampal theta rhythm has been demonstrated to be crucial for the formation of complex, multimodal memories. However, investigations systematically examining the role of theta oscillations in spatial memory encoding are still scarce in humans. Here, we asked participants to memorize the spatial locations of some objects in a grid (*memorization phase*) and then, following a short distraction task, to place the objects in the same spatial locations in the empty grid (*recall phase*). Importantly the luminance level of the visual stimulation was periodically modulated at two frequency rates (flickering effect): 4Hz (*Theta condition*) and 10.5Hz (*Alpha condition*) in the first experiment; and 4Hz (Theta condition) and 0Hz (Unmodulated condition) in the second experiment. Interestingly, spatial memory performances were significantly better in the Theta as compared to the Alpha condition (experiment 1) and compared to the unmodulated condition (experiment 2) thus indicating that visual stimulation flickering within the range of the theta frequency band was able to

enhance spatial memory. This finding suggests that theta oscillations may play a crucial role in spatial memory encoding even in humans.

Introduction

From an evolutionary perspective, being able to successfully explore an environment (i.e. *spatial navigation abilities*) is crucial for survival. When we try to remember a usual route, we experience the feeling of a unitary memory representation, composed by the integration of different sensory inputs. In other words, to navigate space effectively, not only do we have to combine multisensory inputs, but we are also required to associate a specific spatial location with each sensory event (Muller & Kubie, 1987). It has been proposed that these associations among events, objects and other types of information are controlled by cortical oscillations (i.e., rhythmic brain activity expressed at specific frequencies – (Clouter et al., 2017; Hanslmayr et al., 2016; Parise & Spence, 2012a). Several studies have tried to shed light on the role of specific 'brain rhythms' in memories formation. Animal studies suggest that theta frequency in hippocampal cortices plays a key role in spatial memory (Jacobs, 2014). Disrupting hippocampal theta in rodents abolishes spatial learning in Morris water maze, which can then be restored by intra-cortical stimulation at theta frequency (McNaughton et al., 2006). Furthermore, the reduction of hippocampal theta rhythm power correlates with memory impairments (Lacruz et al., 2010). In non-human primates, recent evidence has shown that associative-memory representations, such as the matching between two usually unrelated stimuli (e.g. a pseudoword and an abstract image), seem to arise as common spatial patterns of theta activity across the temporal cortex (Nakahara et al., 2016).

In humans, the hippocampus exhibits oscillations that closely resemble the 4-10 Hz theta oscillations seen in rodents. However, these rhythms seem to be expressed at a slower frequency range of 1-4 Hz (Berens & Horner, 2017; Jacobs, 2014). An acknowledged view proposes that, even in humans, the hippocampus and associative areas cooperate during the formation and the following recall of memories through theta oscillations (Buzsáki & Draguhn, 2004; Clouter et al., 2017). Theta rhythms are thought to coordinate the precise timing of neurons in hippocampal-neocortical networks, affecting the representation and long term encoding of information (Fuentemilla, 2018). Through an EEG study, Fell & Axmacher (2011) showed that a theta phase synchronization between the prefrontal cortex and temporal lobe oscillations can be observed during memory encoding and recall. Furthermore, theta coherence between frontal and temporal-parietal regions predicts individual working memory capacity (Kopp et al., 2006).

It has long been presumed that, similarly to the animal model, theta activity should play a crucial role in associative spatial memory formation even in humans. However, evidence of such an effect in humans appears still controversial (Herweg et al., 2020). On the one hand, some intracranial EEG studies exploring the activity across different brain regions, including frontal e medial-temporal lobes, reported the presence of a decrease of theta power matched with an increase in high frequency power (> 30Hz; i.e., *spectral tilt*) during successful memory encoding and retrieval (Burke et al., 2015; Long & Kahana, 2015). On the other, different scalp EEG research described increases in theta power oscillations within the medial-temporal lobe positively associated with memory performances (Hanslmayr, Spitzer, & Bäuml, 2009; Khader et al., 2010). As a supporting evidence of the pivotal role of theta rhythm for human associative memory, Clouter and colleagues (2017) demonstrated that the memory for bimodal audio-visual associations (such as some specific sounds matched with different videoclips) relies on the synchronization of inputs in the theta band. By periodically modulating the luminance of visual stimuli and the intensity of auditory stimuli, the authors were able to directly affect both the frequency and the degree of phase synchrony between the two sensorial inputs. Through an EEG study (Wang et al., 2018), the same authors demonstrated that this stimulation protocol was actually effective in inducing a neural resonance mechanism (i.e., that the brain regions involved in the processing of the stimuli oscillated at the same frequency and with the same phase as the corresponding sensory stimulus). Importantly, when the bimodal stimulation was delivered synchronously and at the same theta frequency (i.e., 4 Hz) during the memorization phase, an enhancement in memorization performances was observed in the recall phase. In other words, subjects more easily associated each videoclip with the correct sound. As a possible interpretation, Clouter and collaborators (2017) proposed that theta synchronization (described as a sort of neuronal "glue") play a key role in the formation of multimodal associative memories.

Capitalizing on this finding, we hypothesized that theta oscillations might also affect the formation of spatial memory in humans, similarly to what is observed in the animal model.

In a way, spatial memory may be considered as a form of associative memory, matching a given stimulus to a specific location in space (Arleo & Rondi-Reig, 2007; Mayes, Montaldi, & Migo, 2007). Therefore, here we verified the presence of a theta-driven enhancement of spatial memory performances. To this aim, we developed a modified version of the task exploited by Clouter and colleagues (2017), selectively employing flickering visual stimuli. Participants were administered with an object-location task. As a first step, subjects were asked to learn the spatial location of different visual stimuli included in a grid (i.e., *memorization phase*). Then, following a distraction task, the same visual stimuli were presented one by one and participants had to place them in the exact position previously displayed in the *memorization phase* (i.e., *recall phase*). In each phase, the luminance of the visual stimuli was modulated by rhythmical increases and decreases at two different frequencies: 4 Hz (*theta condition*) and 10 Hz (*alpha control condition*). In the *theta condition*, visual stimulation periodical modulation reproduced the endogenous rhythm observed across temporal cortices, during the encoding and retrieval of associative memories. Therefore, we expect enhanced spatial memory performances in the theta condition as compared to our control alpha condition. Conversely, if memory performances were similar across conditions, we should assume that rhythmical visual stimulation at theta frequency does not affect spatial memory.

Experiment 1

Materials and Method

Participants

26 healthy young adults (16 women; age – average±SD: 25.2 ±1.6), with no history of psychiatric or neurological disorders, volunteered to take part in the study.

All participants gave their written informed consent to participate in the study, which conformed to the standards required by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Turin (Protocol Nr. 121724). Participants were not compensated for taking part in the experiment.

Stimuli and Apparatus

A 3D modeling software (*Blender* - https://www.blender.org/) was used for the graphical rendering of the background. A neutral environment, depicting an essential sitting room was created, with the only aim of reproducing a familiar background, with the goal of putting the user at ease. The visual stimuli employed in the paradigm were 16 everyday-life objects presented on white square panels (all having the same size) on the room wall (see Figure 1 Panel A). The images of the everyday-life objects were randomly extrapolated from a pool of stimuli, typically used in traditional neuropsychological test (i.e., FCSRT, Free and Cued Selective Reminding Test; Frasson et al., 2011) and, after, elaborated using Photoshop. The experiment task (i.e. locating some of the objects in some specific locations and recording subjects' responses) was developed using Unity (https://unity3d.com/). Graphics and the software for stimulus presentation were realized by SynArea Consultants Srl (Turin, Italy).

Experimental procedures

In the Experiment, subjects were seated at a desk in a dimly lit room, at a distance of 60 cm from the PC screen. The experiment consisted of a simple memory recall task. Subjects were asked to remember the exact locations of the objects appearing on the screen. Within the experiment stimulus luminance was rhythmically increased and decreased at a specific frequency. In the first experiment, the experimental condition (Theta condition) stimuli (e,g., 16 objects) flickered at 4 Hz, whereas in another condition (Alpha Condition) stimuli flickered at 10.5 Hz. This specific choice of frequencies is motivated by the findings presented by Clouter et al., 2017.

The "flicker effect" has been created by modulating the luminance of visual stimuli (see Figure 1 Panel B) as shown by Clouter and colleagues (2017). Also, in their study it was demonstrated that the phase of synchrony between different sensory input, during the encoding phase, has an impact on later recall improving the subject' memory performance. Furthermore, they have established that this facilitating memory effect is specific to the theta frequency band. Additionally, this specific effect was not found in slower (1.7 Hz) or faster (10.5 Hz) frequencies (Clouter et al., 2017). For these reasons, here we aimed to investigate whether the object locations learning can be facilitated by

4Hz flickering of visual input by using 10.5Hz flickering of visual input as control condition (Experiment 1). Moreover, to avoid an effect due to rhythmic modulation that could reduce perception of stimulus (VanRullen et al., 2019) we investigated the theta-inducing flickering condition to a condition with unmodulated stimuli (below, Experiment 2).

The two experimental sessions in both experiments were carried out in two different days separated by at least seven days of break. The session order was counterbalanced across participants. Before the beginning of each session, participants were asked to stay still and fixate the computer screen. Each session included four experimental trials, for a total duration of 36 minutes. Each experimental trial started with the memorization phase (duration: 2 minutes), where subjects were asked to pay attention to the spatial configuration of objects with the aim of learning and remembering it. Following the memorization phase, subjects were asked to perform a distraction task (see below) for 5 minutes, to avoid the effect of rehearsal on subsequent memory performance. Finally, the subjects underwent the recall phase, where they had to place 10 objects, drawn at random, in the exact position displayed in the memorization phase, and, in this case, we did not flicker the screen. Each object had to be placed in a maximum of 10 seconds. A green bar showed time progression towards the end of the available time. The experimental trial (memorization phase, distraction task, recall phase) was repeated four times, each time presenting a different random object layout but using the same everyday-life objects over the four trials. This specific choice of stimuli selection is motivated by the associative novelty task request (i.e. objects presented in updated spatial positions). Here, participants were asked to perform a spatial location task and pay attention to the specific spatial layout each time presented. Thus, when the session is closed, the software generates a performance .xlsx file. This .xlsx file shows a list of objects presented for each recall phase indicating the correctness of placement for each located object (correct placement=1; wrong placement= 0). Between the memorization and the recall phases, participants performed two distraction tasks (two for each condition, administered in a counter-balanced order within subjects). In the first task, participants were presented with a sequence of two tone with different pitch (200Hz and 260Hz) and they were asked to determine whether the higher tone was the first or the second one, pressing two different buttons on the keyboard. In the second task, participants were presented with a sequence of two tones (a radio-like static noise and a beep-sound); they had to detect target stimuli (i.e. the beep sound), pressing the spacebar on the keyboard as fast and accurately as possible. Throughout the experiment, participants’ response accuracy in the recall phase was recorded.

Data Analysis

The aim of the experiment was to evaluate participants’ memory performance across sessions (i.e., Theta vs Alpha), to verify any performance modulations due to visual stimulus specific frequency of oscillation. To explore the presence of such modulation, we summed participants' response accuracy in each experimental trial, thus obtained an accuracy value for each session for each participant. Therefore, we directly compared the accuracy values for each session through a paired sample t-test. Alpha level was set at 0.05.

Results

Data analysis revealed that participants' accuracy values were significantly greater in the Theta vs Alpha sessions (Theta average±SD: 26,96 ±6,48; Alpha average±SD: 23,76 ± 7,95; t_{25}= 2.06, p= 0.01, *d* =0.04). Specifically, the accuracy values were better in experimental condition of 74 % (See figure 1 Panel C for details),

thus, indicating that the frequency of oscillation of the visual stimulation presented during the experiment is able to affect participants' memory performance in this specific task.

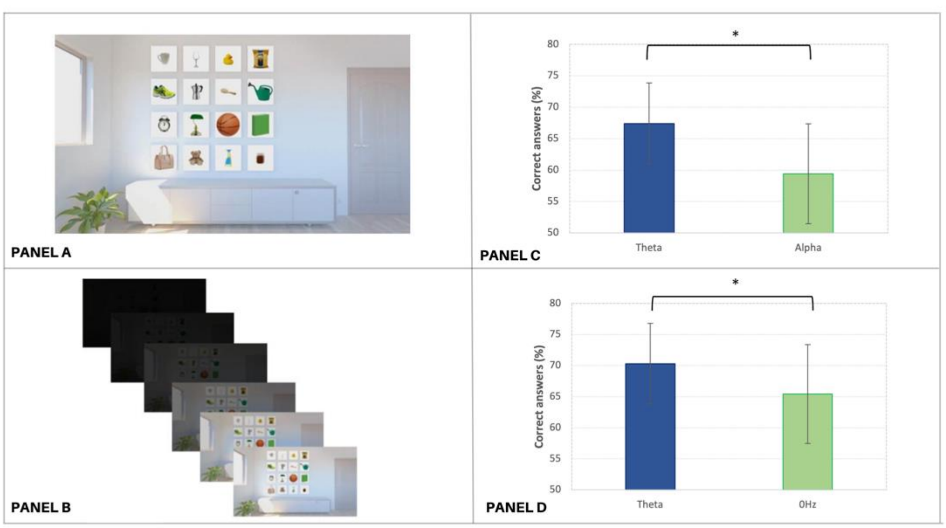

*Figure 1. Experiment 1: Panel A Luminance Modulation; Panel B Screen Display; Panel C Accuracy measure: Memorization accuracy in Theta (blue) and Alpha (green) conditions. Error bars represent standard deviations; *=p<0.05; Panel D Experiment 2 Accuracy measure: Memorization accuracy in Theta (blue) and Unmodulated (green) conditions. Error bars represent standard deviations; *=p<0.05.*

Experiment 2

The experiment 2 was conducted to measure the behavioral effects of frequency of oscillation on memory performance. For this purpose, 26 healthy right-handed young adults (14 women; age – average ±SD: 25.35 ± 2.07), with no history of psychiatric or neurological disorders, were recruited. All participants gave their written informed consent to participate in the study, which conformed to the standards required by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Turin (Prot.n.121724 – 01/03/18). Participants were not compensated for taking part in the experiments.

Experimental procedures

The experimental procedures were identical to those of Experiment 1, except for the control condition in which stimuli are unmodulated (i.e., 0 Hz). Thus, for investigating whether the memory performances can be facilitated by 4Hz flickering of visual input, each participant performed two conditions, respectively one stimuli flickered at 4Hz (Theta condition) and another at 0 Hz.

Data analysis

To verify the modulations due to visual stimulus at 4Hz oscillation (experimental condition), compared to a 0 Hz (control condition), it was recorded the accuracy value for each session for all participants. Paired-samples t-test were used to compare memory performances made in experimental condition vs. control condition. Alpha level was set at 0.05.

Due to software problems that did not save the accuracies, 3 participants were excluded from the analysis.

Results

Similarly to experiment 1, data analysis revealed that participants' accuracy value performed in 4Hz condition (Experimental: average ± SD: 28.13 ± 5.96) is significantly higher than 0 Hz (control: average ± SD: 26.17 ± 5.73 ; $t_{22} = -2.11$, $p = 0.046$). Specifically, the accuracy values were better in experimental condition of 70 % (See figure 2 for details).

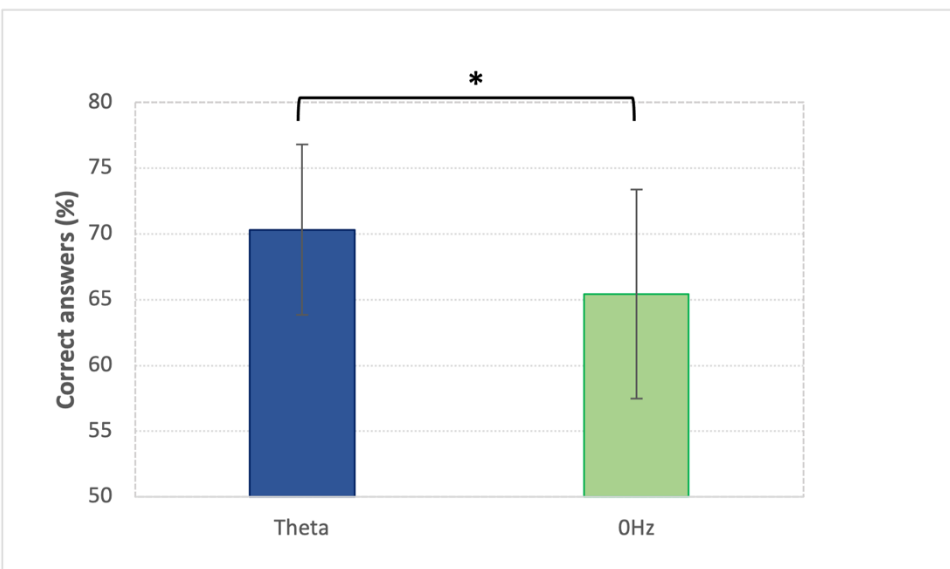

*Figure 2. Experiment 2 Accuracy measure: Memorization accuracy in Theta (blue) and Unmodulated (green) conditions. Error bars represent standard deviations; *=p<0.05.*

Discussion

In the present study, we carried out a behavioural experiment aimed to explore the effect of rhythmical modulations of visual stimulus luminance on spatial memory. Previous studies suggested that theta frequency plays a key role in associative memory formation (Clouter et al., 2017a) (Buzsáki & Moser, 2013; Cruzat et al., 2021). Consequently, we hypothesized that the flickering of visual stimulation within the theta frequency band (i.e., 4 Hz) might have also enhanced the memorization of objects' locations in space, when compared to a control condition where stimuli flickered at a different frequencies, 10 Hz (in Experiment 1) and at 0Hz (in Experiment 2). Indeed, as we find on experiment 2, it's not only the flickering of stimuli to enhance the memory performances, thus it seems that theta oscillations could have a role in improving or even facilitating memory. The present results confirmed our hypothesis, highlighting significantly higher memorization performances following the theta as compared to the alpha condition.

But *how* can visual information flickering at the theta rhythm improve spatial memory? We believe that this effect may be due to two different factors.

First, active exploration has been often associated with theta oscillations in several mammalian species (Herweg et al., 2020), thus indicating their direct involvement in spatial cognition. Second, spatial memory may be considered as a form of associative memory, and as such, similar to other kinds of associative learning (Clouter et al., 2017), may be subjected to the influence of theta frequency ((Mayes et al., 2007b)). Spatial behaviour, indeed, is typically regarded as a product of complex memory, based on the interaction of multiple parallel processes at different levels (Arleo & Rondi-Reig, 2007). At the sensory level, the input of different perceptual modalities is integrated to provide the navigator with a coherent description of the spatial context. The processing of these integrated multimodal representations of the explored environment may be considered the core of spatial cognition (Arleo & Rondi-Reig, 2007). Moreover, even at the action-selection level, navigating relies on multiple concurrent processes, and demands the ability of the individual to adapt its goal-directed strategy to the specific situation (Mayes et al., 2007b). As suggested by Gallistel (1990), spatial memory is based on both low-level sensory-motor learning and more abstract context representations, thus representing by definition a form of associative learning. Coherently, at the anatomical level, the cerebral structure thought to be responsible for the association of the different memorized sensorial inputs is the hippocampus (Meister & Buffalo, 2016). Not surprisingly, evidence from animal studies showed that the hippocampal area similarly supports spatial memory recall using environmental items, such as spatial landmarks, as cues to retrieve other associated elements (such as specific routes). Furthermore, evidence from human studies showed that associative novelty (i.e. objects presented in updated spatial positions) and related memory retrieval mechanisms are tied to the hippocampal theta (Jeewajee et al., 2008).

According to the above, the visual stimulation periodical modulation at 4hz may reflect the endogenous rhythm observed across temporal cortices, during the encoding and retrieval of associative memories, this may explain the observed memory effect. Although this mechanistic explanation underlying the observed effect is hard to detect in a behavioral study, these results could represent a first step toward understanding the formation, updating, and retrieval of spatial information.For instance, Jensen (2001) better clarified that Theta oscillations play a central role in coordinating neural activity during spatial information processing. Specifically, their results suggested Theta oscillations could act like carrying waves for spatial information transfer between associative areas via synchronized oscillations at the same frequency (Jensen, 2001). Furthermore, other evidence indicates that theta oscillations modulate sensory and motor brain activity in various brain regions to facilitate spatial learning and navigation planning (Caplan et al., 2003). Particularly, Theta oscillations have been linked to the induction of long-term potentiation (LTP) and it was demonstrated stimulation that mimics the Theta rhythm is effective in inducing LTP (Larson et al., 1986). In particular, the type of learning that Theta oscillations facilitate may necessarily involve learning synchronised interactions between different brain regions (Caplan et al., 2003). For instance, Buzsaki (1996) proposed that learning is supported by the transfer of information from the hippocampus to the different associative cortices, mediated by cortical theta oscillations. Instead, other evidence from human recordings reveals greater synchronisation of hippocampal and parahippocampal theta activity during successful learning (Fell et al., 2003). Overall, the previously presented findings in the animal model suggest that the regulation of the hippocampal theta may be considered the pivotal mechanism for associative and spatial memory encoding. Importantly, recent studies demonstrated that hippocampal theta may support similarly associative functions even in humans. Through an intracranial EEG study, Kragel and colleagues (2020) demonstrated that hippocampal theta coordinates memory processing during visual exploration. More specifically, theta rhythm has been shown to regulate both spatial positions' encoding, updating, and retrieval (Kragel et al., 2020). Moreover, previous electrophysiological studies (Jutras et al., 2013) showed that memory representations in hippocampal area guide eye-movements towards behaviorally relevant locations (Kragel et al., 2020; Meister & Buffalo, 2016); particularly the visual exploration of novel spatial layout, and not repeated layout, induces a reset of hippocampal theta oscillations (Jutras et al., 2013). Kaplan and colleagues (2014) suggest that human mPFC theta temporally coordinates aMTL theta during spatial memory retrieval.

By identifying an increase in mPFC theta power during the cued retrieval of learned spatial representations compared to a preceding baseline period of fixation and by revealing increased coupling between the phase of this theta signal and both the phase of ongoing theta oscillations in the right aMTL (Kaplan et al., 2014). In line with these findings, an ECoG study (Nakahara et al., 2016) has shown that associative encoding is facilitated for stimuli that are modulated by a synchronous theta rhythm. Furthermore, similarly to the study by Clouter et. al. (2017), through a series of behavioural experiments, Parise &

Spence (2012), demonstrated the presence of better information processing when auditory and visual flickering stimuli are presented synchronously versus asynchronously (Parise & Spence, 2012a).

The present study, by showing that 4Hz flickering of visual input alone is able to enhance the memorization of object locations in space, is in line with the presented previous research, and supports the pivotal role of theta oscillation in spatial memory encoding in humans. Following the above, the possible neural mechanism able to clarify our behavioral results could be that the memory advantage is related to the synchronization of different inputs arising from different associative cortices during the retrieval memory phase and transmitted to the hypothalamus in order to retrieve a unitary and integrated memory representation.

Future electrophysiological research could further clarify the mechanistic basis underlying the theta-induced memory potentiation effect. In addition, further investigations could explore whether the results replicate in a similar experiment, with different manipulation (i.e. the “room wall” appearing at a variably - manipulated angle), or other manipulations on a hippocampal - dependent spatial memory paradigm.Importantly, if our findings will be confirmed, the flickering of visual stimuli at theta frequency could be exploited for the rehabilitation of memory deficits as well as in the educational field.

CHAPTER 3

MindtheCity! a virtual navigation training promotes the remapping of space in allocentric coordinates: evidence from Behavioural Data

Abstract

Successfully exploring the environment we live in is crucial for survival. Organisms need to remember previous navigation attempts to form safe and successful interactions with the outer world. In this line, allocentric space representations are demonstrated to be crucial to improve visuospatial skills, pivotal in everyday life activities, and for the development and maintenance of other cognitive abilities.

Here, we present a series of experiments in which we propose a virtual-navigation training with an innovative tool designed for the present project. Specifically, we investigated whether virtual navigation stimulates the ability to form spatial allocentric representations in healthy young subjects, elderly people, and people with Mild Cognitive Impairment (MCI). In Experiment 1 we used a novel 3D videogame (MindTheCity!), focused on the navigation of a virtual town. We verified whether playing at MindTheCity! enhanced the performance on spatial representational tasks and a spatial memory test. Our preliminary behavioral results suggest that the training can promote an improvement in subjects' spatial and memory skills. It is well known that spatial location represents a physical feature that can arrange the processing and mental representation of different types of

information, even those that are not typically spatial. In the Experiment 2, we investigated whether virtual-navigation training can improve even non-spatial information through a word-pair memorization task. Additionally, given that previous evidence (Amedeo et al., 2018; Sacco et al., 2022) demonstrated the effectiveness of MindtheCity! training in improving spatial memory abilities in healthy people, in the Experiment 3 and the Experiment 4, we investigated whether a four-week training with MindTheCity! could stimulate the ability to use survey navigation strategies and create allocentric cognitive maps, leading to an improvement in cognition and spatial memory skills in elderly people and people with MCI.

Following a MindtheCity! period of training, we verified the possible behavioral changes (training-induced) on spatial memory performance. Moreover, the general focus was to collect feedback on usability to implement possible modifications to the video game with a potential use within clinical rehabilitation contexts.

Introduction

When we navigate a space, we build an egocentric representation of the surrounding environment, i.e. the memory trace of the sequence of elements and landmarks encountered along a route. However, through further explorations, we may also develop allocentric representations, capturing the spatial relationships between environmental elements, independently from individuals' subjective perspective (Latini-Corazzini et al.

2010, Thorndyke and Hayes-Roth 1982). Previous studies suggested that the retrosplenial cortex is the region supporting the conversion of spatial information from an egocentric perspective to allocentric coordinates. This ‘re-coding’ is crucial to improve visuo-spatial skills since, thanks to allocentric representation high level of plasticity, it allows space remapping when necessary. Not surprisingly, the ability to map the space in allocentric coordinates seems to progressively decline in healthy ageing (Bates and Wolbers 2014, Klencklen et al. 2012), and its deterioration represents an early clinical marker of prodromal forms of dementia (such as Mild Cognitive Impairment) and Alzheimer’s Disease (AD) (Coughlan et al, 2019; Markova et al. 2015, Pengas et al. 2010, Serino et al. 2014). Potentiating the ability to shift from egocentric to allocentric representations is thus a central goal in the fields of learning and memory and may constitute a fundamental challenge to enhance learning mechanisms in young people, preventing visuo-spatial ability detriment in healthy elderly, and contrasting topographical disorientation in AD.

Virtual reality (from now on VR) is becoming rather popular in spatial exploration studies (Coutrot et al. 2019, König et al. 2020). First, compared to other spatial navigation trainings and tests, it represents a more ecological option. Its better adherence to real-life navigation makes VR a sensitive assessment tool for visuo-spatial ability impairments (Markova, Laczo, Andel, Hort and Vlcek 2015, Plancher et al. 2012), as well as an effective rehabilitative training (Faria et al. 2016). Furthermore, it allows safer and more controlled space explorations as compared to real-life ones, at the same time granting the opportunity to match virtual navigation with the measurement of behavioural and neural activity parameters (Serino, Cipresso, Morganti and Riva 2014).

Here, we used a novel 3D videogame, MindTheCity!, specifically realized to train the ability to build allocentric space representations from first-person perspective navigation. The VR environment represented a town that participants had to repeatedly explore in order to locate and retrieve specific objects. Importantly, the environment might be explored with the only help provided by visual information, since auditory cues were excluded from the game. In the Experiment 1, in the Experiment 3 and 4 , we investigate whether focused navigation (one hour for five consecutive days) in a virtual environment without explicit local landmarks stimulates the ability to form allocentric representations, thus increasing performance on spatial allocentric representational tasks (such as pointing to a specific location in space); and whether improvements may be captured by a spatial memory test (i.e., asking participant to remember the location of specific objects placed in a rows-columns pattern), whose realization is known to be grounded on allocentric coordinates (Mou and McNamara 2002, Pasqualotto, Spiller, Jansari and Proulx 2013). Experiment 3 was conducted to verify and replicate the possibility to enhance the ability to form allocentric spatial representations in a group of elderly people. Given that, our behavioral results are considered promising, in the Experiment 4 we aimed at verifying the effect of MindtheCity! training on cognitive functioning in a group of people with MCI.

Besides, it is well known that early signs of topographic disorientation can predict cognitive impairment. The key role of navigation skills in humans on global cognition is amply demonstrated by brain damage outcomes and healthy adults with poorer allocentric spatial processing than their co-equals tend to develop greater risk factors for cognitive impairment and dementia (Ritchie et al., 2018). It is assumed that human cognition can be improved throughout the lifespan with physical exercise and neurocognitive training, but specific interventions based on spatial skill enhancement may also result in effectiveness (Raichlen et al., 2017; Waddington & Heisz, 2023).

Waddington & Heisz (2023) in their study demonstrated that orienteering experts have a better hippocampus-dependent cognitive function when compared to non-orienting controls. Looking at the cellular substrate of the spatial representation system, it is important to note that spatial encoding cells support a wide range of behavioral actions in addition to spatial coordinates (Wood et al., 1999).

Altogether, this evidence suggests a connection between memory and spatial navigation.

As an example, if we consider declarative memory as a relational processing system, the similarities applicable to the domain of spatial memory are more immediately apparent. Several authors propose an interesting perspective in this regard by pointing out the role of the hippocampal system in encoding events based on a relational representation between objects and actions within spatial contexts (Cohen and Eichenbaum, 1993; Eichenbaum & Cohen, 2014). Specifically, evidence suggests a fundamental role of the neural substrate of spatial navigation in representing paths as episodes by associating spatial episodes with semantic maps of space (Eichenbaum, 2004). Two contrasting views on the hippocampal role and functioning predominate in the literature. On the one hand, the declarative memory view argues for the fundamental role of the hippocampal system in supporting the processing and organization of declarative memory, our capacity to remember facts and events of daily life (Cohen and Squire, 1980; Eichenbaum et al., 2014). On the other hand, the spatial navigation view argues for the fundamental role of the hippocampal system in supporting the formation of spatial maps based on Euclidean space. Although these two contrasting views dominate the literature, in the Experiment 2 we try to further investigate a possible connection between memory and spatial navigation. For better reading and clarity, an Experiments Summary Tables (Table ST 1; Table ST 2) are reported below.

* Study 2	Subjects	Methods	Neuropsychological and Behavioural Assessment	Results
Experiment 1	**23 Healthy young male (mean age: 25; SD: 2.93)**	***Virtual navigation* training or Control Condition for:** • 5 days / 1 hour each day • Spatial memory task ** 2 week break* ***Virtual navigation* training or Control Condition for:** • 5 days / 1 hour each day • Spatial memory task	1. Pointing task 2. Tracking Exploration Strategies 3. Spatial memory Task	1. Mean angular errors performed in the second half of training **were significantly lower** than those occurred in the first half of training. 2. Time spent in searching objects in the first half of the training was **significantly greater** that in the second half of the training. 3. Performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition.*
Experiment 2	**14 Healthy young male (mean age: 25; *SD*: 3.56)**	***Virtual navigation* training or Control Condition for:** • 5 days / 1 hour each day • Verbal memory task ** 2 week break* ***Virtual navigation* training or Control Condition for:** • 5 days / 1 hour each day • Verbal memory task	1. Pointing task 2. Verbal memory Task	1. Mean angular errors performed in the second half of training **were significantly lower** than those occurred in the first half of training. 2. Performances in the verbal memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition.*

Table ST1. SUMMARY TABLE STUDY 2; Experiment 1 and Experiment 2. Subjects, Methods, Neuropsychological and Behavioural Assessment, Results were reported.

* Study 2	Subjects	Methods	Neuropsychological and Behavioural Assessment	Results
Experiment 3	**29 healthy elderly subjects (mean age: 63,86 ; *SD*: 5,93)**	***Virtual navigation* training or Control Condition for:** • Spatial memory task **(t0)** • 20 min. for 5 days / 4 Weeks • Spatial memory task **(t1)** ** 2 week break* ***Virtual navigation* training or Control Condition for:** • Spatial memory task **(t2)** • 20 min. for 5 days / 4 Weeks • Spatial memory task **(t3)**	1. Pointing task 2. Spatial memory Task	1. Mean angular errors performed in the second half of training **were significantly lower** than those occurred in the first half of training. 2. Performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition*
Experiment 4	**30 subjects with *MCI* (mean age:73,03; *SD*: 5,35)**	***Virtual navigation* training or Control Condition for:** • Spatial memory task **(t0)** • 20 min. for 5 days / 4 Weeks • Spatial memory task **(t1)** ** 2 week break* ***Virtual navigation* training or Control Condition for:** • Spatial memory task **(t2)** • 20 min. for 5 days / 4 Weeks • Spatial memory task **(t3)**	1. Neuropsychological Assessment ***(According to Caltagirone et al., 1995)*** 2. Pointing task 3. Spatial memory Task 4. Ad hoc Enjoyment Questionnaire	1. Significant results were found in **Raven's Coloured Progressive Matrices; TMT (A);** 2. Mean angular errors performed in the second half of training **were significantly lower** than those occurred in the first half of training. 3. Performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition.* 4. Patients reported an overall satisfaction rate of over 65% (mean=39.38; SD=12.23)

Table ST 2. SUMMARY TABLE STUDY 2; Experiment 3 and Experiment 4. Subjects, Methods, Neuropsychological and Behavioural Assessment, Results were reported.

Experiment 1 - MindtheCity! as an innovative tool to improve spatial memory abilities in healthy young people

Subjects

Healthy young male students from the University of Turin volunteered to take part in the experiments: 23 subjects (mean age: 25; SD: 2.93) participated in the present study.

Sample size was a priori determined according to a power analysis applied to the results of a pilot experiment (N = 5) testing the effect of MindTheCity! training on a directional pointing task (dependent variable: pointing angular errors).

Because behavioral studies have shown that there are gender differences in navigational task performances, a gender homogenous group (i.e., male only) was chosen (Astur et al., 1998). Only right-handed subjects were selected, and the evaluation was made with the Edinburgh Handedness Inventory (Oldfield, 1971). Moreover, usual videogame users were excluded, especially for videogames in which the creation of mental maps of virtual environments is required for playing to avoid contamination effects on memory formation processes. All participants were medication free with no history of psychiatric or neurological disorders. All participants gave their written informed consent to participate in the study, which conformed to the standards required by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Turin (Prot. n. 121724—01/03/18). Participants were not compensated for taking part in the experiments.

Experiment 2 - **The effects of** ***MindtheCity! in improving non - spatial memory abilities in healthy young people***

Subjects

Healthy young male students from the University of Turin volunteered to take part in the experiments: 14 subjects (mean age: 25; *SD*: 3.56) participated in the present study.

Because behavioral studies have shown that there are gender differences in navigational task performances, even in this experiment a gender homogenous group (i.e., male only) was chosen (Astur et al., 1998). Only right-handed subjects were selected, and the evaluation was made with the Edinburgh Handedness Inventory (Oldfield, 1971). Moreover, usual videogame users were excluded, especially for videogames in which the creation of mental maps of virtual environments is required for playing to avoid contamination effects on memory formation processes.

All participants were medication free with no history of psychiatric or neurological disorders. All participants gave their written informed consent to participate in the study, which conformed to the standards required by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Turin (Prot. n. 121724—01/03/18). Participants were not compensated for taking part in the experiments.

MindtheCity! - The Training

MindTheCity! is a 3D-videogame set in a fictional town, developed using Unity.1 Graphics and the software for data collection were realized by *SynArea Consultants Srl* (Turin, Italy). MindTheCity! is divided into five districts, with progressively increasing dimensions (and therefore progressively increasing navigation difficulty), from the first to fifth. The town includes only few environmental landmarks: A central garden (the starting point for each district exploration), a church, a skyscraper, a telecommunication tower. All other buildings and streets present the very same characteristics, in order to encourage users to adopt a survey strategy of navigation and to create their own cognitive map of the environment (Ishikawa and Montello, 2006). The main aim of the game is to complete a wayfinding task. Particularly, participants, while exploring the town with their virtual avatars (by pressing PC arrow keys), were asked to assemble five components of a bicycle (wheels, handlebars, pedals, rear frame and front frame), which were scattered around each district. In a first phase, participants had to explore the neighborhood freely in order to locate all bike components without collecting them (free exploration phase). In a second phase, participants were asked to remember where the previously identified components of the bike were located, in order to find the shortest path to retrieve them (object search phase). In this phase, anytime players collected one bike component, they had to perform a pointing task through their avatar (see **Figure 1**). They were requested to point an arrow toward the direction where they started the exploration (for the first retrieved component) or toward the previously retrieved bike component (from the second component on).

Two parallel versions of the game were designed (A and B) differing only in bike components positioning, in each district of the virtual town. This was done to exclude that training results might be related to a specific distribution of the objects within the virtual town, instead of the training itself. Each participant was presented with both versions of the game during the training. Version order (A–B; B–A) was counterbalanced across subjects, to avoid any sequence effects on results.

Furthermore, all participants played MindTheCity! one hour per day, for five consecutive days, in accordance with previous literature showing that this time is sufficient to improve spatial orientation (Kober et al., 2013; Claessen et al., 2016). During each session, at least two districts (of increasing dimension) were explored, with a 10–15 min break between them, for a total time of 50 min of training per day. Besides, here, the active training with Mindthecity! was contrasted with a passive navigation control condition, through a within-subject design.

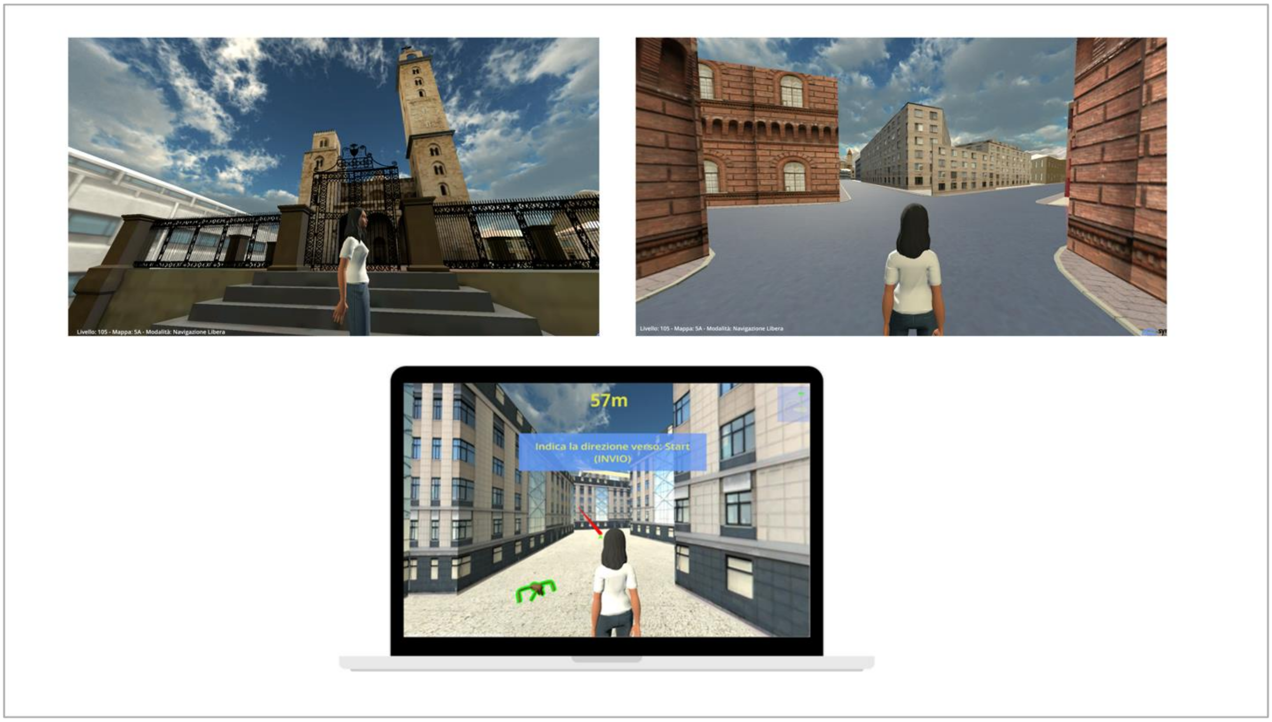

*Figure 1. **MindtheCity! virtual environment and Avatar** (Top panel)- **Pointing task** (Bottom panel): in the videogame, subjects were asked to point to specific locations in the virtual space.*

Experimental Procedures

The present study was conducted to measure the behavioral effects of MindTheCity! on spatial representations and memory.

Participants were randomly assigned to the experimental condition (training with MindTheCity!) or to a control condition (Passive Navigation with MindTheCity!) (i.e., passively observing an avatar exploring the same virtual town). Importantly, both conditions were carried out at the university laboratory, in presence of the experimenter.

For five consecutive days (a first day of familiarization followed by 4 days of actual training), participants were asked to play MindTheCity! (Experimental condition) or to undergo the Passive Navigation (control condition). The order of these two conditions was counterbalanced across subjects. The two experimental conditions (i.e., active training with MindTheCity! vs. Passive navigation control condition) were separated by a break of 14 days (see **Figure 2**). On the last day of MindTheCity! training and of Passive Navigation, participants received the post-training assessment on the spatial memory task (***Experiment 1***) and on the verbal memory task (***Experiment 2***), specifically designed for the present study.

The Spatial Memory Task – Experiment 1

Following the training with MindTheCity! and following the control condition (passive navigation), participants were asked to perform a *spatial memory task* (i.e., a *spatial object-location memory task* (Postma et al., 2008; Zimmermann and Eschen, 2017), where subjects had to locate some objects in their correct locations in space and recording subjects' responses), developed using Unity.

Graphics and the software for stimulus presentation were realized by *SynArea Consultants Srl* (Turin, Italy). The visual stimuli employed in the paradigm were 16 everyday-life object images (elaborated using Photoshop), presented on a rows– columns pattern (4 × 4), composed of white square panels (all of identical dimensions). The background of the square panel was a fictional room wall (see **Figure 2**).

The task consisted of a simple memorization and recall test. Each session included four blocks, for a total duration of 36 min. Each block started with the Memorization Phase (duration: 2 min), where subjects were asked to pay attention to the spatial configuration of the objects with the aim of learning and remembering it. Following the Memorization Phase, subjects were asked to perform a distraction task (a pitch discrimination task similar to Sarasso et al., 2019; Sarasso et al., 2021, see also Sarasso et al., 2020) for 5 min, to avoid a rehearsal effect on subsequent memory performance. In the final Recall Phase, subjects were asked to place 10 (out of 16) objects in the exact position displayed in the Memorization Phase. Each object placement had to be completed in a maximum of 10 s. A green bar showed time progression toward the ending of the available time. The block (Memorization Phase, Distraction task, Recall Phase) was repeated four times, each time presenting a different random-generated object layout.

This task was used to assess whether participants' visuospatial abilities were modulated by the realization of the training with MindTheCity! vs. Passive Navigation, and, more specifically, whether participants' skills in forming allocentric spatial representations were affected. The present spatial memory task particularly promotes the use of allocentric representations. The objects to be remembered are positioned in a grid, thus promoting the adoption of allocentric coordinates (Postma et al., 2008).

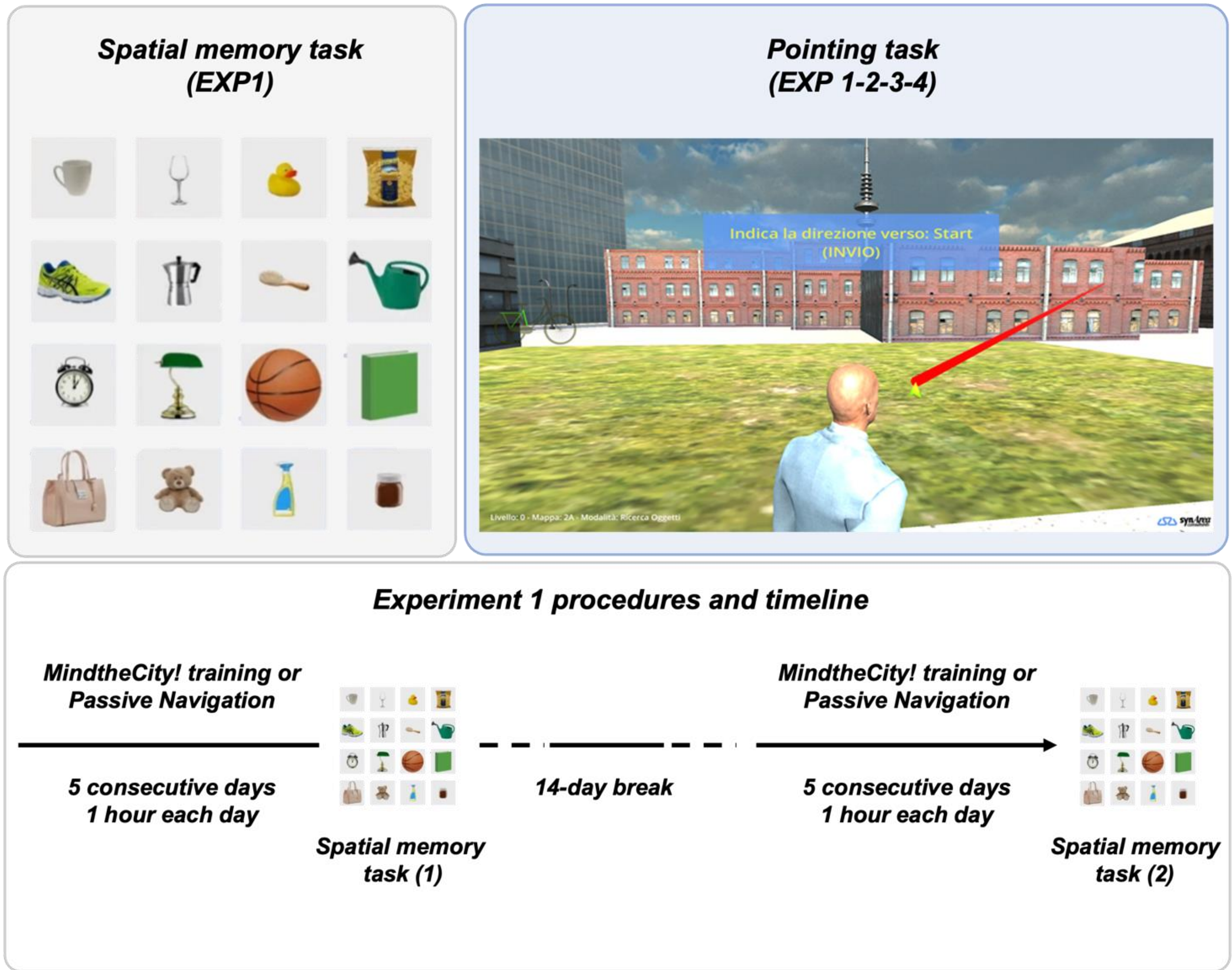

*Figure 2 Experimental tasks. Spatial memory task **(top left panel)**: subjects were asked to remember the location of the objects presented in figure (Experiment 1). Pointing task **(top right panel)**: in the videogame, subjects were asked to point to specific locations in the virtual space (Experiments 1-2-3-4). Experiment 1 procedures and timeline **(bottom panel)**: the figure describes the experimental design of Experiment 1.*

The Verbal Memory Task – Experiment 2

The *Verbal memory task* consisted of a word- pair memorization and recall test. Participants were asked to memorize (duration of the memorization phase: 50 s) a list of 7 different pairs of abstract, semantically unrelated words.

Importantly, following the training and the control condition, participants had to memorize a different list of words. After a distraction task (which replicated the procedures of Experiment 1), participants were then asked to recall the 7 word-pairs, one by one. Corrected responses and errors (intended as both missed elements and uncorrected associations) were recorded.

Assessment

During the training, participants were asked to point an arrow toward the direction where they started the exploration (for the first retrieved component) or toward the previously retrieved bike component (from the second component on). This pointing task aimed to verify whether participants were successful in representing the map of the district in allocentric coordinates. In immersive VR training, pointing tasks usually require the access of a mix of egocentric (to establish the position of the own body in the virtual space) and allocentric representations (to map the environment independently from their own point of view). However, in MindTheCity!, differently from an immersive virtual environment, the avatar is always visible as an external object during the pointing task, thus likely decreasing the reliance on egocentric representations.

Degrees of angular error between the avatar’s pointing and targets’ actual positions were used as a performance measure and were recorded throughout the experiment. Importantly, the actual direction of the pointing was always retained in the computation of the angular error. During the game, no feedback of angular errors was given to participants.

Moreover, with the aim of further investigating whether and how *MindTheCity!* training might promote participants' abilities to map the virtual environment, we tracked subjects' navigational strategies during the training. As described above, in the first free exploration phase, participants might freely explore the town to locate the bicycle components. In the second, object search phase, participants were asked to collect all the previously identified bicycle components. Here, participants' exploration strategies in the free exploration and in the object search phases were tracked (see **Figure 3**).

Importantly, the specific sequence in which the bicycle components were found were recorded. In each day, we verified how many subjects found and collected the objects in the same vs. a different order.

Furthermore, we recorded the time spent to find the objects in both phases. If participants collected the objects in the same sequence and in a similar time between the free exploration and the object search phases, we should assume that they were employing a route strategy (mainly based on environmental landmark) to navigate the virtual environment, which would promote the adoption of the same path between exploration and object search. Conversely, if participants collected the objects in a different sequence and in a shorter time between the free exploration and the object search phases, the adoption of a survey strategy (mainly based on Euclidean relationship between different locations) appeared more likely, allowing them to select the most convenient path to cover to collect all the objects as quickly as possible. Importantly, the adoption of a survey strategy, as opposed to a route strategy, has been proposed to mainly rely on allocentric representations, which similarly to survey maps, are focused on the spatial relationships between objects (see Carelli et al., 2011; even though also egocentric representations may contribute to cognitive map realization). Therefore, the employ of a survey strategy would support the hypothesis that MindTheCity! training actively promotes the development of allocentric representations. Conversely, the adoption of a route strategy would indicate that participants mainly relied on path- based, egocentric information.

Analysis

Pointing Task & Tracking Exploration Strategy – Experiment 1

To evaluate subjects' performance at *MindTheCity!*, angular errors in the pointing task were recorded. Single subject angular errors were averaged in order to obtain one single measure for each session. We therefore summed the measurements collected in the first half (days 2–3) and in the second half (days 4–5) of the training, respectively, thus resulting in two distinct values for each subject. Paired-samples *t*-tests were used to compare angular errors made in the first half of the training vs. those made in the second half of the training.

Furthermore, with the aim of exploring whether participants' improvements were constant across the training days or whether instead they were focused on a specific day, we investigated daily participants' performance, from days 2 to 5. We therefore performed a linear mixed model analysis including angular errors as the dependent variable, with day of training (Day) as fixed repeated-measure factor, plus random effects intercepts and slopes for Day. The model used Satterthwaite's method for the estimation of degrees of freedom and the covariance structure for random effects was first-order autoregressive (AR1). *Post hoc* pairwise comparison *p*-values were corrected using Sidak's method.

Regarding the tracking exploration strategy, participants' exploration strategies in the free exploration and in the object search phases were tracked. The specific sequence in which the bicycle components were found were recorded. In each day, we verified how many subjects found and collected the objects in the same vs. a different order. Furthermore, the time necessary to find the objects in the free navigation phase and in the object search phase was measured. Then, we averaged the time spent in exploration and in the object search, respectively, between days 2 and 3 (first half of the training) and between days 4 and 5 (second half of the training. Paired-samples *t*-tests were used to compare the time spent in searching the bicycle components in the first half of the training vs. in the second half of the training.

Furthermore, through paired-sample *t*-tests, we verified whether on a daily basis, the time spent to find the objects in the free navigation phase was different (possibly greater) than the time spent to find the same objects in the object search phase. Bonferroni correction was applied to *t*-test alpha level: 0.05/4 = 0.0125. Finally, with the aim of exploring whether participants' exploration and object search times were constant across the training days, we investigated daily participants' performance, from days 2 to 5, by performing the same linear mixed model analysis, exploited for the pointing task.

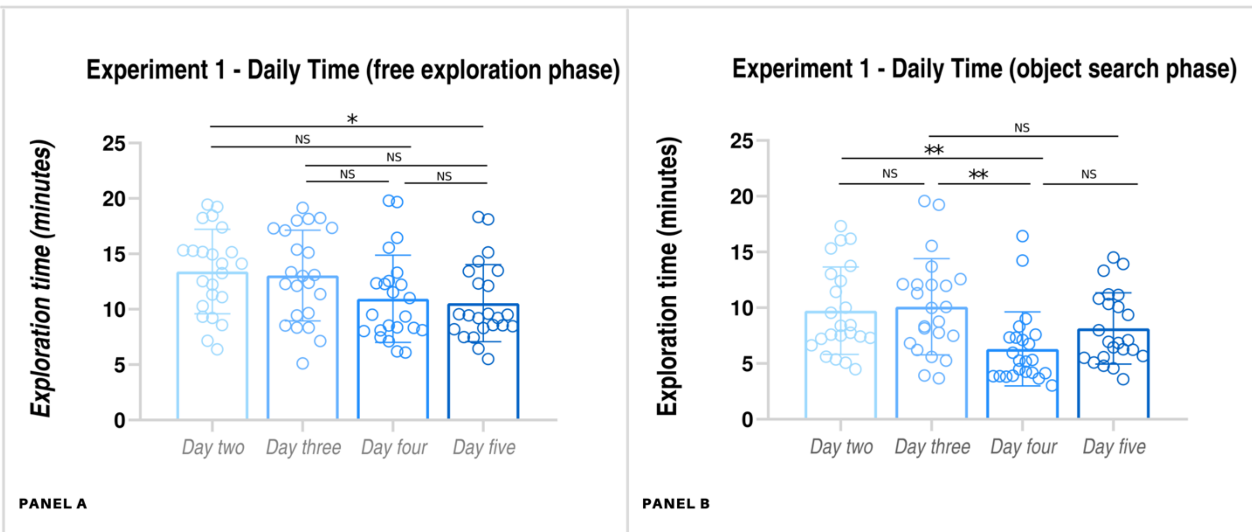

Figure 3 Tracking of navigational strategies in Experiment 1. Daily performance in the Free exploration phase ***(A)****: subjects' time needed to find the bicycle components. Daily performance in the Object search phase* ***(B)****: subjects' time needed to find and collect the bicycle components.* $*p < 0.05$; $**p < 0.01$.

Spatial Memory Task – Experiment 1

To evaluate subjects' performance on the memory task, participants' accuracy values were recorded and analyzed. Two subjects were excluded from subsequent analyses for a technical problem occurred during data recording. Paired-samples *t*-tests were used to compare participants' accuracy values following the experimental condition (*MindTheCity!*) vs. following the control condition (Passive Navigation).

At the end of each testing session, we asked participants which strategies they employed to remember objects' disposition. Importantly, all participants adopted the same strategies in both sessions (i.e., the employed strategies were the same following *MindtheCity!* and the Passive Navigation). The most common memorization strategies were based on color similarities between objects and on the spatial disposition of the objects in rows and columns. Some participants also tried to associate some objects according to their functions.

Pointing Task – Experiment 2

These analyses fully replicated those employed in *"Experiment 1 - MindtheCity! as an innovative tool to improve spatial memory abilities in healthy young people."*

Verbal Memory Task – Experiment 2

Participants' accuracy values were recorded and analyzed by means of number of errors to evaluate subjects' performance on the memory task.

A paired-samples *t*-test was used to compare participants' accuracy values following the experimental condition (*MindTheCity!*) vs. following the control condition.

Results – Experiment 1

Regarding the pointing tasks' data analysis, mean angular errors performed in the second half of training were significantly lower than those occurred in the first half of training (First Half: average ± *SD*: 146.76 ± 66.57 degrees; Second Half: average ± *SD*; 103.92 ± 42.10 degrees; $t22 = 3.42$, $p = 0.001$, $dz = 0.76$). Furthermore, participants' daily performances (**see Table 1A**) were as follows: day 2 68.69 ± 35.36 degrees; day 3 78.08 ± 40.07 degrees; day 4 51.37 ± 25.31 degrees; day 5 55.10 ± 29.68 degrees (see **Figure 4**). Through the linear mixed model analysis, we found a significant effect of Day ($F = 6.489$, $p = 0.002$). *Post hoc* pairwise comparisons revealed that performances of day 4 were significantly improved as compared to day 2 ($p = 0.032$) and day 3 ($p = 0.003$). A marginally significant improvement was found between days 5 and 3 ($p = 0.062$). It is interesting to note that, despite the slight difficulty increase, no significant difference was found between days 2 and 3 ($p = 0.745$) and between days 4 and 5 ($p = 0.994$).

For what concerns the tracking exploration' data analysis, on average, only 4 (± 1.41) out of 23 participants collected the bicycle components in the same sequence as the objects were found in the free exploration phase, thus indicating that the large majority of the subjects covered a different path between the exploration and the object search phase Furthermore, we averaged the time spent in the exploration and in the object search phases, respectively, between days 2 and 3 (first half of the training) and between days 4 and 5 (second half of the training). Paired-samples *t*-tests revealed that the time spent in searching the bicycle components in the first half of the training was significantly greater that in the second half of the training for both exploration and object search phases (free exploration phase: first half, 13.22 ± 3.22 min; second half, 10.75 ± 2.87 min, paired-samples *t*-test, $t = 3.41$, $p < 0.001$, $dz = 0.81$; object search phase: first half, 9.91 ± 3.21 min; second half, 7.22 ± 2.79 min, paired-samples *t*-test, $t = 4.78$, $p < 0.001$, $dz = 0.89$). Overall, these findings seem to indicate the adoption of a survey strategy to navigate the virtual environment, as suggested by the different covered paths between exploration and object search phases and by the shorter time needed to collect the bicycle components in the object search phase as compared to the exploration phase.

When looking at day-by-day performances (see **Figure 4** and **Table 1B**), we observed that the time spent to find the objects in the free navigation phase was always significantly greater than the time spent to find the same objects in the object search phase (Day 2: free exploration, 13.40 ± 3.81 min; object search 9.73 ± 3.91; paired-samples *t*-test, $t = 5.46$, $p < 0.001$; Day 3: free exploration, 13.04 ± 4.09 min; object search 10.09 ± 4.30; paired-samples *t*-test, $t = 3.06$, $p = 0.005$; Day 4: free exploration, 10.95 ± 3.94 min; object search 6.31 ± 3.32; paired-samples *t*-test, $t = 6.01$, $p < 0.001$; Day 5: free exploration, 10.55 ± 3.48 min; object search 8.14 ± 3.19; paired-samples *t*-test, $t = 3.22$, $p = 0.003$). Finally, when comparing subject exploration performances on a daily basis, we found a significant effect of Day ($F = 4.420$, $p = 0.011$). *Post hoc* pairwise comparisons revealed that performances of day 5 were significantly improved as compared to day 2 ($p = 0.026$). Conversely, object search time results paralleled the daily accuracy pattern observed for the pointing task (see **Figure 4**), with a significant effect of Day ($F = 9.747$, $p < 0.001$). *Post hoc* pairwise comparisons revealed that the greatest improvement (expressed as a reduction of object search time) was observed between day 3 and day 4 (day 2 vs. day 3: $p = 1$; day 2 vs. day 4: $p = 0.003$; day 3vs.day4:p=0.001;day2vs.day5:p=0.375;day3vs. day 5: $p = 0.132$; day 4 vs. day 5: $p = 0.068$). Notably, as for the pointing task, despite the slight difficulty increase, we did not find a significant difference between the performances of day2 and day3.

Finally, data analysis revealed that participants' memorization performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition (Mindthecity!: average ± SD: 28.76 ± 6.40; Passive Navigation: 25.81 ± 7.00; t22 = 2.60, p = 0.017, dz = 0.45).* Notably, one of the limits of this Experiment is the gender of the participants (only male). Given that behavioural studies have highlighted gender differences in a navigational task (Astur et al., 1998), a gender - homogenous group (i.e. male only) was chosen for this step of *MindtheCity!* validation.

Generally, it could be interesting to investigate the possibility of replicating the effects of *MindtheCity!* in a healthy young female group. Effectively, this possibility could open new opportunities for intervention in the neuropsychological and the cognitive enhancement fields.

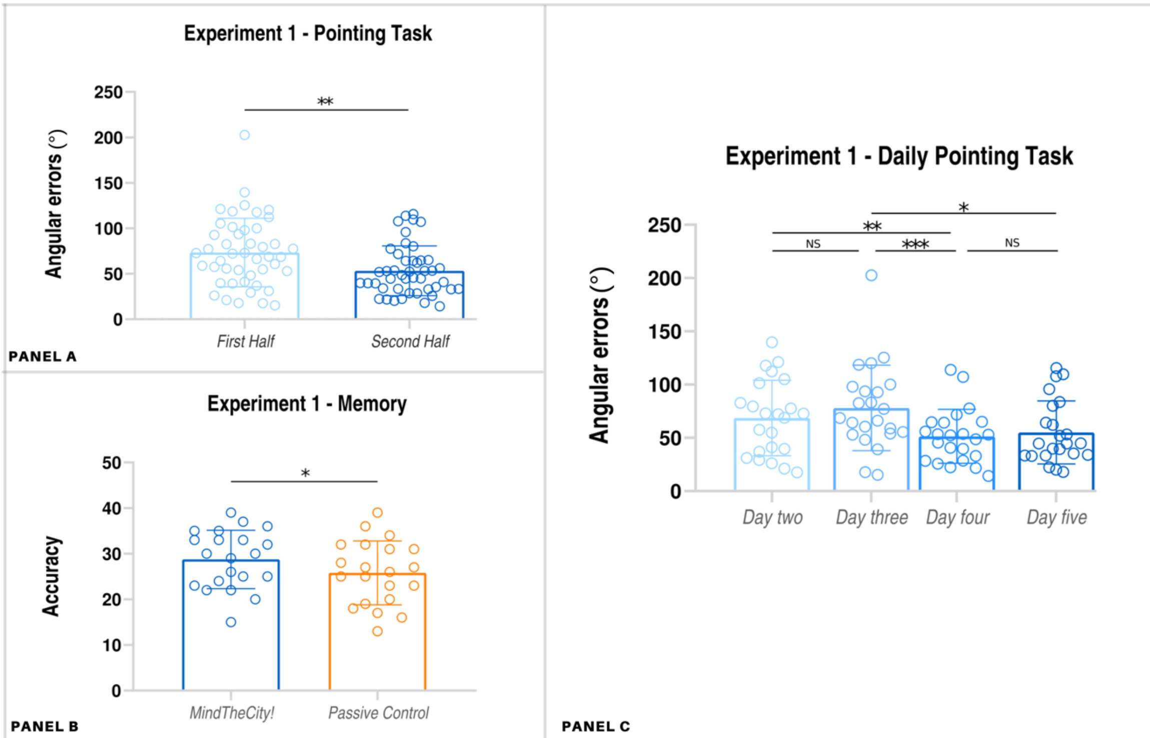

Figure 4 Results of Experiment 1. Pointing task ***(A)****: subjects' angular errors made in the first and in the second part of the MindTheCity! training. Spatial memory task* ***(B)****: subjects' accuracy (absolute scores) following MindTheCity! and following Passive Navigation. Daily performance at pointing task* ***(C)****: subjects' angular errors made in each day of MindTheCity! training. *p < 0.05; **p < 0.01.*

Results – Experiment 2

Regarding the pointing tasks' data analysis, mean angular errors performed in the second half of training were significantly lower than those recorded in the first half of training (average ± *SD*, First Half: 249.56 ± 133.55 degrees; Second Half: 189.49 ± 119.90 degrees; $t13 = 3.13$ $p = 0.004$, $dz = 0.47$). Furthermore, participants' daily performances were as follows: day 2 110.37 ± 82.94 degrees; day 3 139.18 ± 59.48 degrees; day 4 112.12 ± 69.06 degrees; day 5 77.35 ± 57.97 degrees (see **Figure 5**). Through the linear mixed model analysis, we found a significant effect of Day ($F = 16.526$, $p < 0.001$). *Post hoc* pairwise comparisons revealed that performances of day 5 were significantly improved as compared to day 3 ($p < 0.001$) and day 4 ($p = 0.024$). No other significance was found. Despite the slight difficulty increase, no significant difference was found between day 2 and day 3 ($p = 0.248$).

For what concerns verbal memory task's analysis, results revealed that participants' memorization performances were significantly enhanced following *Mindthecity!* training as compared to following the control condition (number of correct responses, *Mindthecity!*: 4.43 ± 1.39; control: 3.43 ± 1.09; $t13 = 2.87$, $p = 0.013$, $dz = 0.79$).

Remarkably, even in this case, including the female gender could have important and very strong implications in terms of generalizing the results and applying our protocol in the clinical practice.

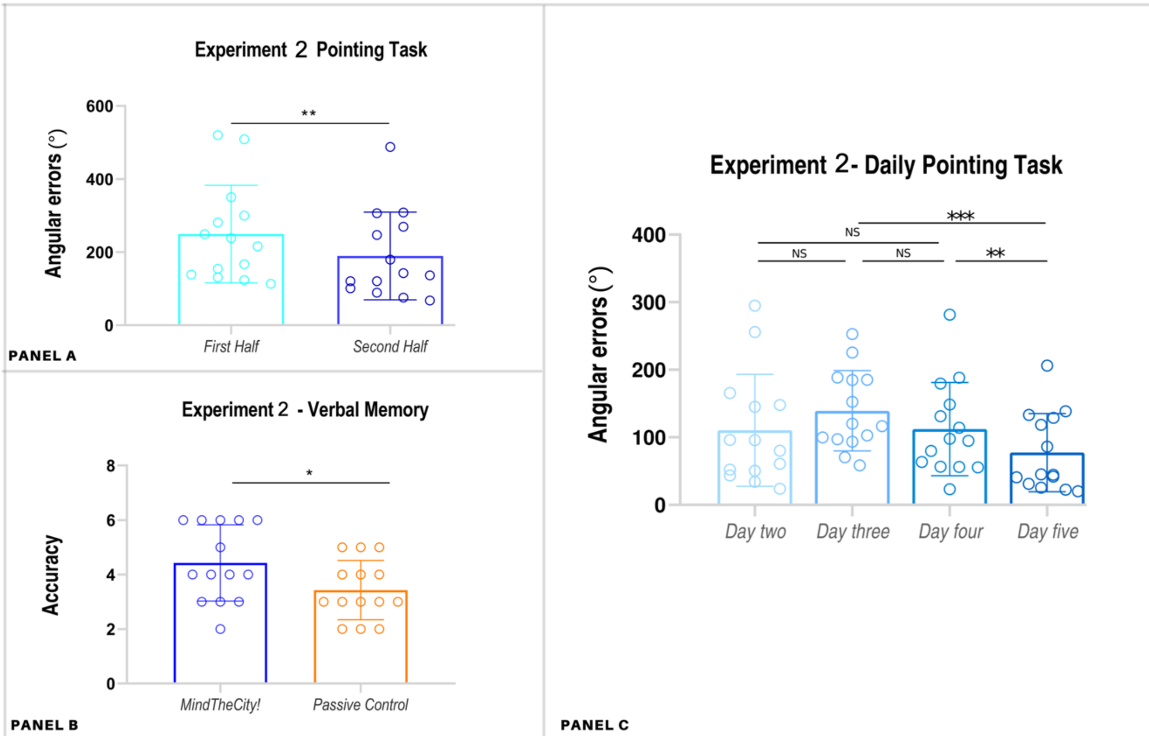

*Figure 5 Results of Experiment 2. Pointing task **(A)**: subjects' angular errors made in the first and in the second part of the MindTheCity! training. Verbal memory task **(B)**: subjects' accuracy (absolute scores) following MindTheCity! and following Passive Navigation. Daily performance at pointing task **(C)**: subjects' angular errors made in each day of MindTheCity! training. *p < 0.05; **p < 0.01.*

TABLE 1A | Experiment 1— Pointing Task

	Day 2	Day 3	Day 4	Day 5
Average (°)	68.69	78.08	51.37	55.10
Main Effect of Day	*F= 6.489*		*p= 0.002*	
Pairwise Comparisons	Day 2 Vs Day 3 p= 0.745	Day 4 Vs Day 2 p= 0.032	Day 4 Vs Day 3 p= 0.003	
	Day 4 Vs Day 5 p= 0.994		Day 5 Vs Day 3 p= 0.062	

TABLE 1B | Experiment 1—tracking exploration strategies.

Free Exploration Average (min)	Day 2	Day 3	Day 4	Day 5
	13.40	13.04	10.95	10.55
Object Research Average (min)	Day 2	Day 3	Day 4	Day 5
	9.73	10.09	6.31	8.14
Main Effect of Day (Free Exploration)	*F= 4.420*		*p= 0.011*	
Main Effect of Day (Object Research)	*F= 9.747*		*p < 0.001*	
Paired samples ttests	Day 2	Day 3	Day 4	Day 5
	p< 0.001	p= 0.005	p< 0.001	p= 0.003
Pairwise comparisons	Day 2 vs Day 3	Day 2 vs Day 4	Day 2 vs Day 5	
	p= 1	p= 0.003	p= 0.375	
	Day 3 Vs Day 4	Day 3 Vs Day 5	Day 4 Vs Day 3	
	p= 0.001	p= 0.132	p= 0.068	

Experiment 3 - The effects of MindtheCity! in improving spatial memory abilities in elderly populations

Materials and Methods

Subjects

29 healthy elderly subjects (mean age: 63,86 ; *SD*: 5,93) participated in the present study. All participants took part in the study voluntarily, after reading the information sheet and signing the written informed consent for participation, in accordance with the standards required by the Declaration of Helsinki. The experimental protocol was approved by the Ethics Committee of the University of Turin (Prot. no. 121724 - 01/03/18). Participants did not receive compensation for participating in the experiments.

Experiment 4 - Testing MindtheCity! training on Mild Cognitive Impairment populations

Materials and Methods

Subjects

30 subjects with *Mild Cognitive Impairment*s *(Minor Neurocognitive Disorder DSM-5)* (mean age:73,03; *SD*: 5,35) with 11-year average schooling, referred to the S. C. Geriatria U - Centro Disturbi Cognitivi e Demenze (CDCD) and the SSD Psicologia Clinica, at the Presidio Molinette di Torino (Azienda Ospedaliera Universitaria Città della Salute e della

Scienza di Torino) participated in the present study. All participants took part in the study voluntarily, after reading the information sheet and signing the written informed consent for participation, in accordance with the standards required by the Declaration of Helsinki. The experimental protocol was approved by the Ethics Committee of the University of Turin (Prot. no. 121724 - 01/03/18). Participants did not receive compensation for participating in the experiments.

Experimental Procedures – Experiment 3 and Experiment 4

According to the cross-over experimental design (see **Figure 6**), each participant underwent four weeks (20 min/day for 5 days/week) of training using MindTheCity! (*Experimental condition*) and a further four weeks (20 min/day for 5 days/week) of passive viewing o video documentaries on natural environments (*Control condition*). A two-week wash-out period was scheduled between the two conditions. After an initial familiarisation session with the video game, carried out in the hospital under the supervision of the neuropsychologist, the remaining training sessions (as well as those in the control condition) were carried out by the patients at home, autonomously, with the possibility of daily telematic monitoring of the data by the clinician, via the REHOME-MP platform, as well as the guarantee of telephone assistance when needed. Further, subjects were divided into two groups by random assignment. Within each group, the two parallel versions, A and B, of each quarter of the virtual city are presented in *MindTheCity!*

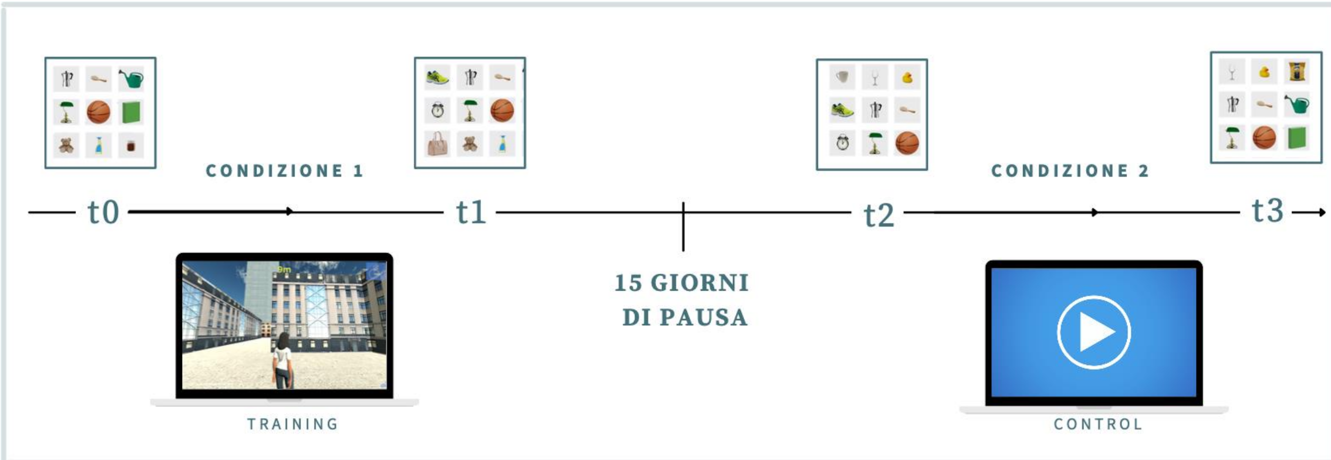

*Figure 6 Experiment 4 procedures and timeline **(bottom panel)**: the figure describes the experimental design of Experiment 4.*

Inclusion Criteria – Experiment 4

The inclusion criteria involved:

- Evidence of a modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor function, or social cognition), based on the concern of the individual, a credible informant or the clinician; evidence of a slight decline in cognitive function and a modest impairment of the cognitive performance, should preferably be documented by standardized neuropsychological tests or, in their absence, by another quantified clinical assessment (DSM-5).
- Cognitive deficits do not interfere with independence in daily living activities (e.g. complex instrumental activities of daily living are preserved, but require increased effort, compensatory strategies, or adaptation) (DSM-5).

- Age over 55.
- Schooling over 5 years.
- No changes in drug therapy -if any- for the entire duration of experimentation.
- Absence of psychiatric disorders and medical disorders of various kinds (e.g. neurological, motor, sensory) capable of impairing the use of a tablet.

Neuropsychological Assessment – Experiment 4

Enrolled patients underwent neuropsychological assessment (*screening and second level*) at the beginning and the end of the protocol, and 6 months afterward (*follow up*); pre (t0, t2) and post (t1, t3) experimental and control condition assessment, with the use of psychological questionnaires and spatial (Spatial Memory Task) learning tests; assessment of enjoyment and usability of the video game (Ad hoc Enjoyment Questionnaire).

Specifically, intending to investigate their global cognitive state, including attention and executive functions domains, verbal learning and memory, and visuospatial learning and memory, patients underwent two neuropsychological assessments through the following battery:

- Montreal Cognitive Assessment (MoCA)
- Attentional Matrices (Della Sala, 1992)
- Trail Making Test (Giovagnoli, 1996)
- Rey's 15-word test (Caltagirone et al., 1995; Carlesimo et al., 1995, 1996)

- Direct and reverse Digit Span (Monaco et al., 2013)
- Direct and reverse Corsi Block-tapping test (Monaco et al., 2013)
- Phonemic Verbal Fluency (FAS) (Costa et al., 2014)
- Semantic Verbal Fluency (colors-animals-fruit) (Costa et al., 2014)
- Raven's Coloured Progressive Matrices (CPM) (Caltagirone, 1995)
- Short Stroop Test (Caffarra et al., 2002)
- Rey's Complex Figure Test (Caffarra et al., 2002)

Further, to explore the perceived usability of *MindtheCity!* and the level of activity enjoyment by patients an *Ad hoc Enjoyment Questionnaire* was built and implemented. In the self-report questionnaire, patients were asked to answer questions related to the use of the video game, indicating a score on a Likert scale from 0 to 10.

Here, are some examples of questions participants were asked to answer:

"*While using MindTheCity! how often did you think about something else?"*

"During the weeks of training, how gratified did you feel?"

Particularly, the Ad hoc enjoyment questionnaire investigates 6 items:

1. level of distractibility
2. level of gratification
3. level of engagement
4. level of entertainment
5. level of anxiety

6. perception of usability

Interestingly, the usability data collection provided promising insights about patients' level of satisfaction and engagement. Overall, rates of satisfaction are higher than 65% (mean=39; SD=12). Table II shows a summary of the main results.

Spatial Memory Task – Experiment 3 and Experiment 4

In the pre-and post-condition experimental/control phases, the Spatial memory task was used (see *Experiment 1)*. The task designed based on the Location Learning Test (LLT - Bucks and Willison; 1997) takes the form of a 'spatial object-location memory task' (Postma et al., 2008; Zimmermann and Eschen, 2017), for the assessment of spatial learning ability.

In the task, participants were asked to re-locate a series of objects to the correct spatial location within a previously observed grid. The visual stimuli used are objects from everyday life (processed in Photoshop), presented on a row-column pattern (3x3 or 4x4), consisting of white square panels on the background of a wall of a virtual room. The task settings are customizable according to the subject's performance and the experimenter's objectives.

Globally, the following parameters can be modified via the settings:

- *number of items (3x3 or 4x4 grid)*
- *number and duration of memorization shifts*

- *maximum time for re-locating individual items in the recall phase*
- *waiting time for delayed recall.*

In the present experimental design, the use of a 4x4 grid was employed, with five memorization rounds lasting 60 seconds. Additionally, in order to avoid the roof-and-floor effect, a basal session was scheduled for all participants to set the appropriate number of stimuli.

Based on the screening, the following were planned:

1. with screening scores ≥ 64: switching to a 4x4 grid, with 5 rounds of 30 s memorization
2. with screening scores ≤16: switching to a 3x3 grid, with five rounds of 60 s memorization.

The Spatial Memory Task was used to assess, in the elderly and in the patient group, a possible effect MindTheCity! training-induced on learning ability and spatial memory.

Importantly, we aimed at verifying the effect of MindtheCity! on the ability to form allocentric spatial representations. Specifically, the Spatial memory task was built to favour the use of allocentric representations (Sacco et al., 2022): the objects to be memorized are arranged neatly within a grid (instead of being dispersed in a larger virtual environment).

Analysis

Pointing task – Experiment 3 and Experiment 4

To evaluate subjects' performance at *MindTheCity!*, angular errors in the pointing task were recorded and analyzed. The pointing tasks' data analysis revealed an improvement in performance between neighbourhoods 1 and 2 and between neighbourhoods 4 and 5. Particularly, a decrease in angular errors degrees and a concomitant increase in the number of objects collected were relieved.

Further, in order to evaluate whether there was a real improvement in the use of the MindtheCity!, the overall average of angular errors degree (weighted by the number of objects collected) was calculated by distinguishing, for each neighbourhood, between the measures collected in the first half (version A) and those collected in the second half (version B) of the training week.

Interestingly, we found a statistically significant decrease (p value<0.05; p value$= 0.02$) between the averages of the first half of the week and those of the second half pointing out an improvement in the patients' performance at the video game.

Spatial memory task – Experiment 3 and Experiment 4

To evaluate participants' performance on the spatial memory task, subjects' accuracy values were recorded and analyzed.

Neuropsychological Assessment – Experiment 4

In order to investigate possible training effects on patients' performances on neuropsychological assessment, scores obtained in the pre-training condition and those obtained in the post-training condition were compared through a paired-sample t-test.

Results – Experiment 3

Regarding the pointing tasks' data analysis (see **Figure 7**), mean angular errors performed in the second half of training were significantly lower than those occurred in the first half of training (p= 0.000).

Finally, data analysis revealed that participants' memorization performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition (p = 0.02).*

Results – Experiment 4

Regarding the pointing tasks' data analysis (see **Figure 8**), mean angular errors performed in the second half of training were significantly lower than those occurred in the first half of training (p= 0.04). For what concerns neuropsychological assessment analysis, on the other hand, no statistically significant changes were detected. On the other hand, results showed a significant increase in the scores on the abstract reasoning test (Raven's Progressive Matrices; p=0.02; Figure 9) Furthermore, a significant change was also found in the TMT test A (p=0.02; Figure 10). However, this result must be interpreted as a decrease: an increase in test scores indicates a negative change in performance. Despite this, from a qualitative point of view, there are positive increases in the scores obtained in several tests. Although not significant, the scores in the Rey's 15-Word Test both on immediate and delayed recall (Figure 11) are favorable pointing out a qualitative performance increase.

Finally, data analysis revealed that participants' memorization performances in the spatial memory task were significantly enhanced following *Mindthecity! training as compared to following the control condition (p = 0.02).*

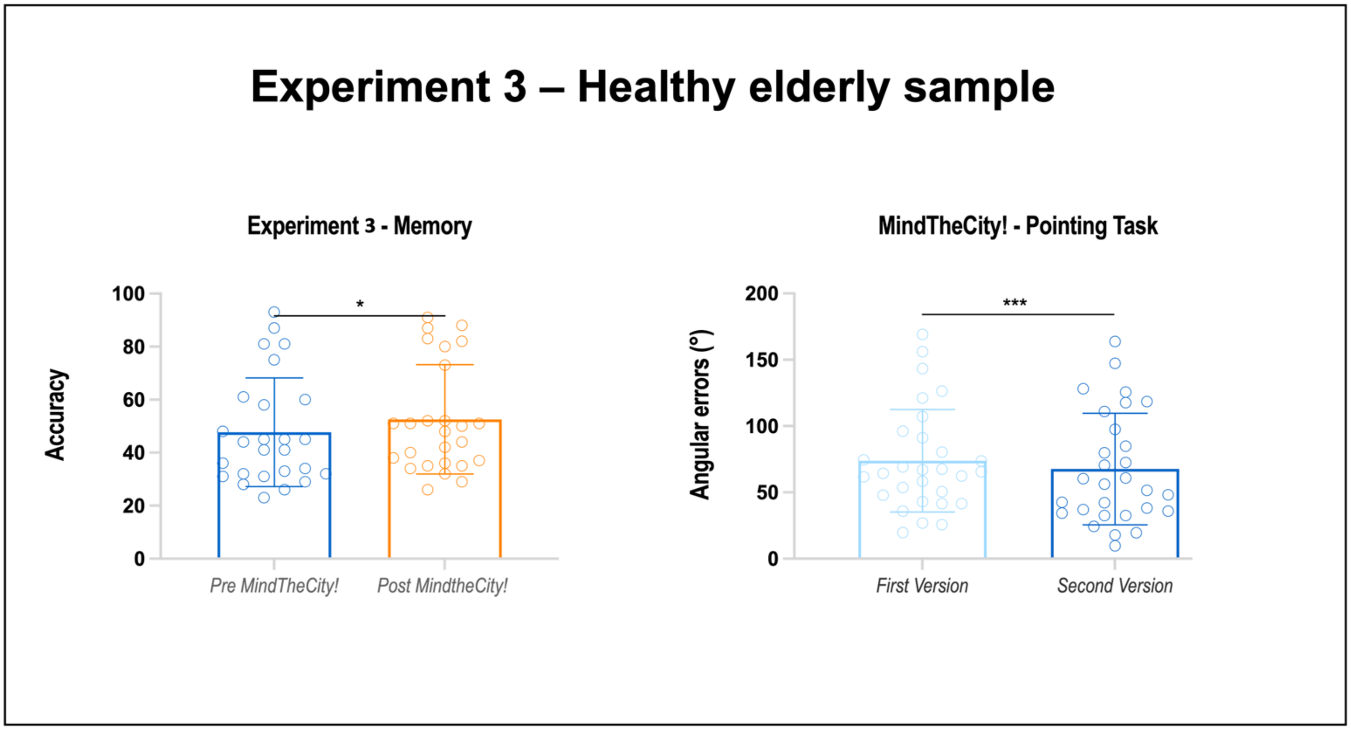

*Figure 7 Results of Experiment 3. Spatial memory task **(left panel)**: subjects' accuracy (absolute scores) pre MindTheCity! and following MindtheCity!. Pointing task **(right panel)**: subjects' angular errors made in the first and in the second part of the MindTheCity! training.*

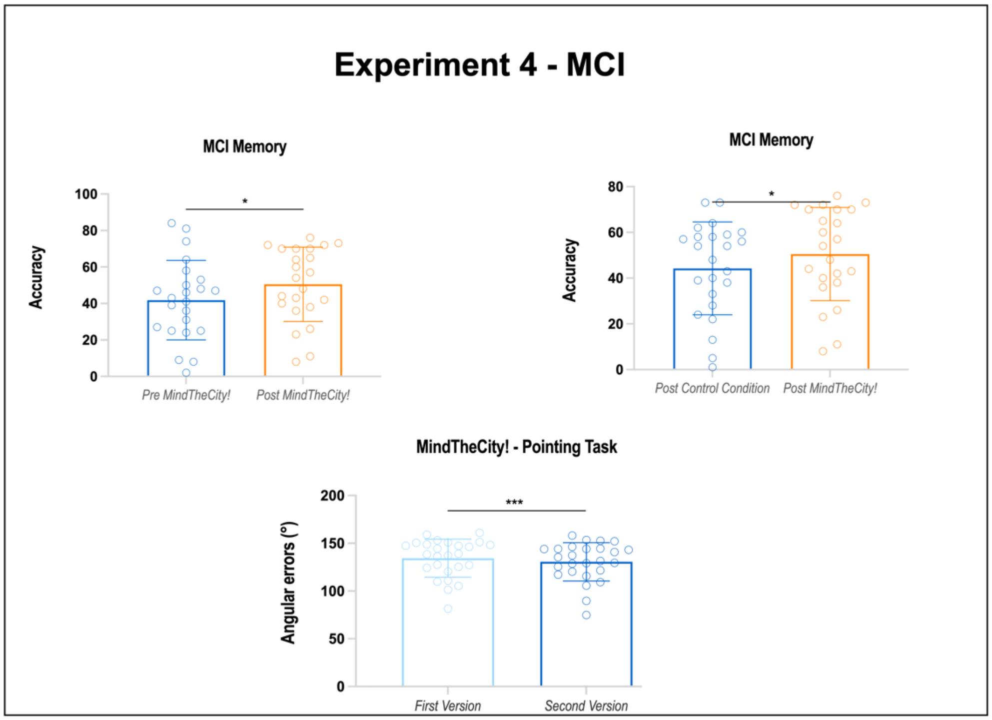

*Figure 8 Results of Experiment 4. Spatial memory task **(left top panel)**: subjects' accuracy (absolute scores) pre MindTheCity! and following MindtheCity!. Spatial memory task **(right top panel)**: subjects' accuracy (absolute scores) following control condition and following MindtheCity! Pointing task **(bottom panel)**: subjects' angular errors made in the first and in the second part of the MindTheCity! training.*

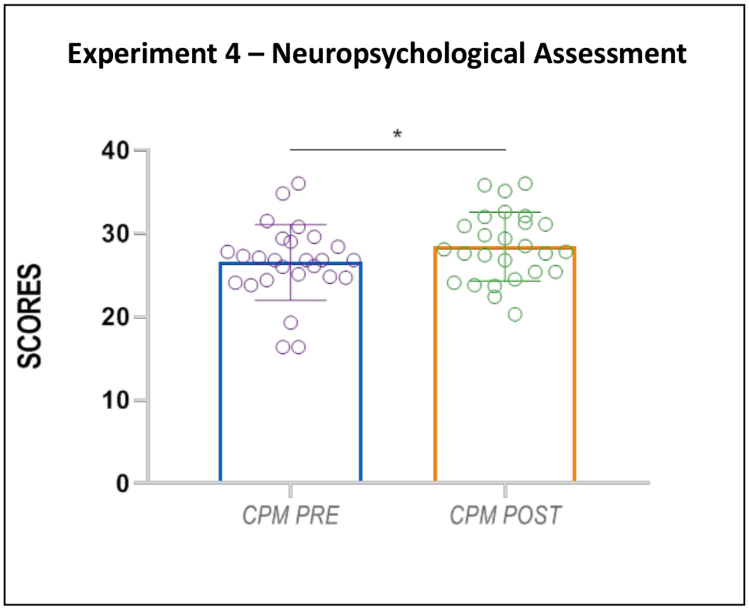

Figure 9 Experiment 4. Neuropsychological Assessment. Raven's Progressive Matrices (cpm): participants' scores pre MindtheCity! and post MindtheCity!

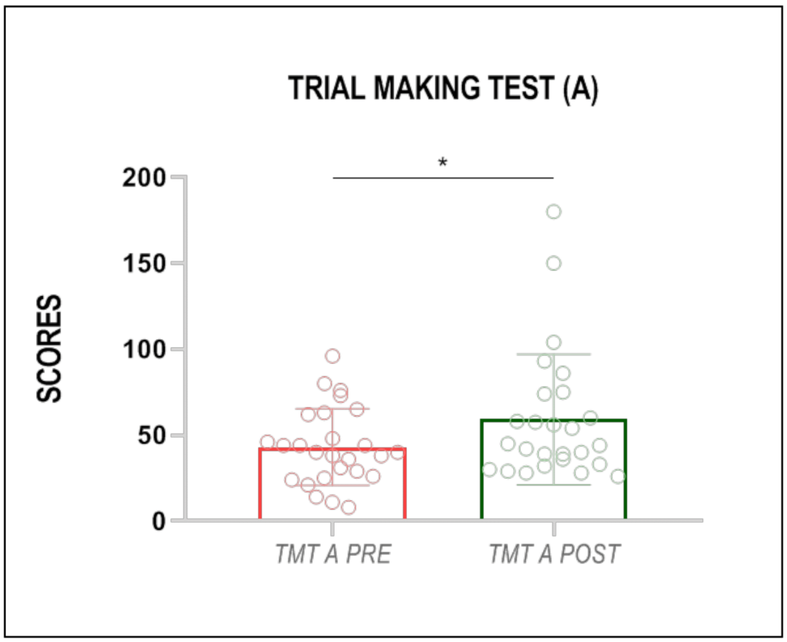

Figure 10.Experiment 4. Neuropsychological Assessment. Trial Making Test (TMT - A): participants' scores pre MindtheCity! and post MindtheCity!

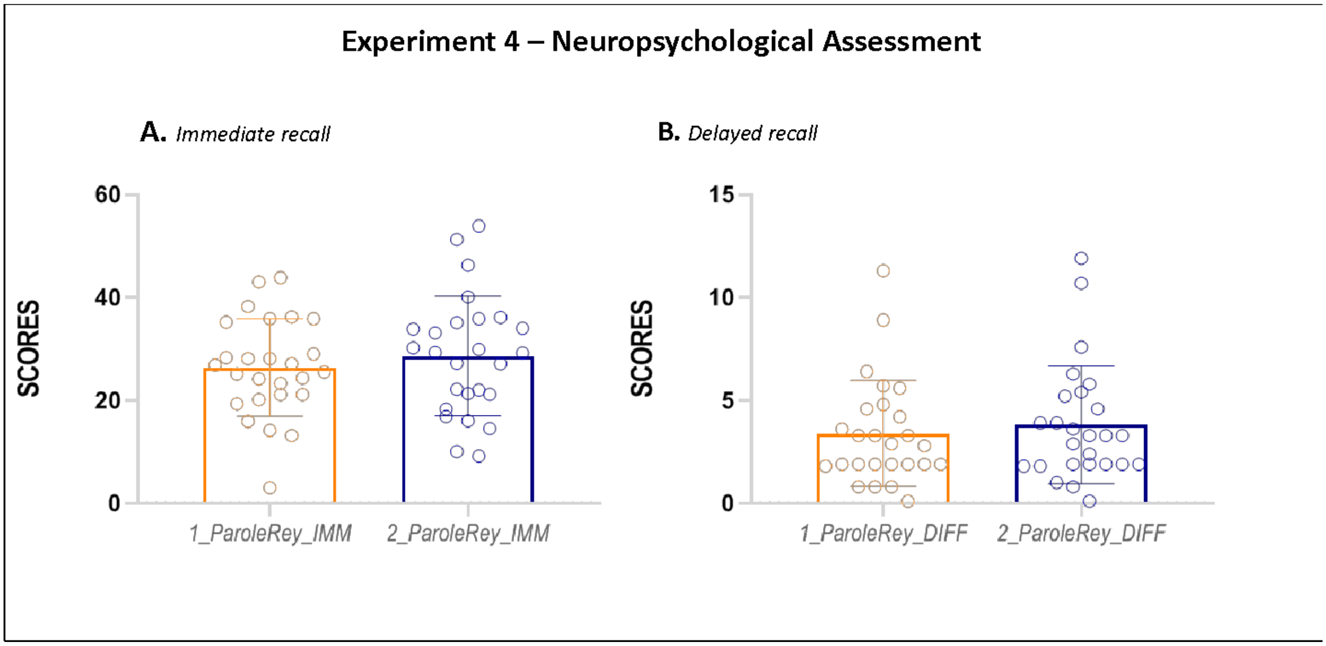

Figure 11. Experiment 4. Neurpsychological Assessment. Rey's 15 Words Test. Qualitative trend in participant's scores pre MindtheCity! and posto MindtheCity!

Table II - Summary of positive rating percentages on Ad hoc Enjoyment Questionnaire

Ad hoc enjoyment questionnaire	*% Positive Rating (N=30)*
OVERALL SATISFACTION	**> 65%**

Discussion

In the present research, with the aim of testing the presence of behavioral modulations following *MindTheCity!* training, we exploited three different measurements (i.e., *Pointing task*, *Tracking of exploration strategies*, and *Spatial memory task*), all related to the ability to map the virtually navigated space. More specifically, in each session of the training (in Experiment 1, Experiment 2, and Experiment 3 and 4), we tested participants' allocentric knowledge (Latini-Corazzini et al., 2010) of the virtual environment they were navigating, by asking them to point to different places within the virtual town (e.g., the starting point). Importantly, angular errors of such pointing task demonstrated that, in the second half of the training, participants' performance was significantly improved as compared to the first half of the training. This finding is important since it demonstrates that participants' ability to successfully map the virtual environment (necessary to perform the pointing task) was significantly enhanced throughout the training. Crucially, the improvement highlighted in Experiment 1 was confirmed in Experiment 2, which can be considered as a measure of internal replicability of the *Pointing task* results. Furthermore, similar results were also confirmed in Experiment 3. Results from the tracking of navigational strategies seem to indicate that most participants adopted a survey strategy to navigate the virtual environment, as suggested by the different covered paths between exploration and object search phases and by the significantly shorter time needed to collect the bicycle components in the object search phase as compared to the exploration phase. Since the employment of survey maps is considered related to the development of allocentric representations (Carelli et al., 2011), we believe that the present finding may represent supporting evidence of the ability of *MindTheCity!* training in promoting the space remapping in allocentric coordinates. When looking at participants' pointing task performances on a daily basis, we noticed that the greatest improvement was observed between days 3 and 4, in Experiments 1 and 2, and between days 3 and 5 in Experiment 3 and 4. This finding suggests that, overall, four sessions of training might be enough to improve participants' spatial navigation abilities significantly. Importantly, despite the slight difficulty increase between days 4 and 5, performances never worsened between the two sessions. A similar pattern of results was obtained when observing participants' daily performance at the object search task (see **Figure 3**). This parallel between the participants' performance at the two tasks might indicate that these two parameters might actually track the development of the same skill, possibly the ability to form allocentric representations (an aspect which seems to be crucial for the realization of both tasks). Looking at participant's performance on neuropsychological assessment, in Experiment 4, we observed a general preservation of patient's cognitive performance with *post-MindtheCity! training* scores frequently overlapping with the *pre - MindtheCity! training* scores. Considering the patients' clinical-cognitive condition, characterized by a neurodegenerative mechanism, the absence of a significant decrease in the scores on neuropsychological assessment can be considered a positive treatment outcome. Furthermore, results of the *Spatial memory task* (Experiment 1; Experiment 3 and 4), by showing a significant difference following an active vs. a passive training, confirmed the efficacy of the *MindTheCity!* training in enhancing participants' ability to build and remember the spatial relationships between different elements, independently from participants' position in space. The *Spatial memory task* was crucial in demonstrating that this improvement in allocentric spatial encoding was not limited to the explored virtual environment but instead it may generalize to different tasks. Future research could also include a non - spatial memory task to replicate the Experiment 3 and the Experiment 4 and then investigate the clinical impact of an overall memorization enhancement in the context of neurocognitive stimulation. Overall, our behavioral results coherently demonstrated that a short training (1 h for 5 consecutive days) with *MindTheCity!* effectively potentiates young, healthy subjects' ability to translate the spatial information acquired from an egocentric perspective to allocentric coordinates.

Chapter 4

MindtheCity! a virtual navigation training promotes the remapping of space in allocentric coordinates: evidence from Neuroimaging Data

Abstract

The employment of functional spatial memory strategies improves overall memorization (i.e., even non-spatial information) (Dresler et al., 2019). From a clinical point of view, the emergence of impairments in visuo-spatial abilities may represent an early symptom of neurodegenerative diseases supporting the central role of visuo-spatial skills in supporting other cognitive functions.

Given that spatial memory skills can be improved by adaptive and extended training, here we employed an experimental paradigm intending to verify whether playing at MindTheCity! enhanced the performance on spatial representational tasks (pointing to a specific location in space) and on a spatial memory test, by replicating the same results showed in the experiment described above. Furthermore, to uncover the neural mechanisms underlying the observed effects, we performed a preliminary fMRI investigation before and after the training with MindTheCity!

Generally, our preliminary neuroimaging and behavioral results suggest that the training activates brain circuits involved in higher-order mechanisms of information encoding, triggering the activation of broader cognitive processes and reducing the working load on memory circuits.

Introduction

Is it possible that the improving of spatial skills, and especially of visuo-spatial memory allows the enhancement of overall memorization abilities?

The importance of spatial mental representation for human cognition has been deeply explored by many authors (Dahaene et al., 1993; Van Dijck et al., 2011). Particularly, Dahaene and colleagues (1993) in their work highlighted the SNARC effect (Spatial Numerical Association of Response Codes). Specifically, they employed a classic parity judgment task where participants had to decide if a number was odd or even. The left-/right-hand key assignment was mixed: the answer "even" (as the answer "odd") was assigned for half of the trials to one hand and for the other half to the other hand and results of their experimental paradigm showed a SNARC effect (Dahaene, Bossini and Giraux., 1993). Precisely, small numbers activated faster responses when participants answered with the left hand and large numbers activated faster responses when participants answered with the right hand. The authors agree that the effect was due to the representation numbers have in (semantic) long-term memory (LTM), that of a mental line, which in western cultures increases from left to right (Dehaene, et al., 1993). Interestingly, by employing a new experimental paradigm, Van Dijck and Fias (2011) challenged by proposing that the SNARC effect depends on the organization that numbers take on in working memory and not relies on Dahaene et al.'s long-term memory conception. Expressly, in this study, participants were asked to remember the correct order of five numbers randomly presented (1 to 10) appearing at the center of the screen. When a number was displayed to be remembered, after the presentation phase, participants had to perform a parity judgment task. Even in this work, the left/right button assignment was mixed, as in Dehaene and colleagues (1993). Surprisingly, in contrast to the usual SNARC effect, their results showed a SPARC effect (Spatial-Positional Association of Response Codes). In this case, left-handed responses were faster with the numbers presented in the first positions of the numbers to be remembered (instead of the small numbers in the SNARC effect) and right-handed responses were faster with the numbers presented in the last positions (instead of the large numbers) thus suggesting a spatialization effect (Van Dijck & Fias., 2011).

With this new conceptualization, the authors suggested a spatial value of processing information. It would appear that people tend to create a spatial mental line based on the order in which elements enter the immediate memory in which the initial words of a sequence have a left spatial value while the last words of the same sequence have a right spatial value (Guida & Lavielle- Guida., 2011). This is strongly consistent with the view that in immediate verbal memory, the order of elements is spatially encoded through spatialization. What does spatialization have to do with the overall processing of memorization? With the study presented here, we explored the possibility of generalizing improvements in spatial abilities, obtained after a period of training, to other cognitive functions (i.e. overall memorization). It is well known (Worthen e Hunt, 2011) that visuo-spatial processes played a central role in improving memory of verbal material (i.e. Method of Loci) (Guida & Lavielle- Guida., 2011).

Experiment 5 - MindtheCity! Replicating and Neuroimaging sample

Materials and Methods

Subjects

Healthy young male students from the University of Turin volunteered to take part in the experiments: 23 subjects (mean age: 24.21; *SD*: 2.89) participated in the present study.

Sample size was a priori determined according to a power analysis applied to the results of a pilot experiment (N = 5) testing the effect of MindTheCity! training on a directional pointing task (dependent variable: pointing angular errors).

Because behavioral studies have shown that there are gender differences in navigational task performances, a gender homogenous group (i.e., male only) was chosen (Astur et al., 1998).

Only right-handed subjects were selected, and the evaluation was made with the Edinburgh Handedness Inventory (Oldfield, 1971). Moreover, usual videogame users were excluded, especially for videogames in which the creation of mental maps of virtual environments is required for playing to avoid contamination effects on memory formation processes.

All participants were medication free with no history of psychiatric or neurological disorders. All participants gave their written informed consent to participate in the study, which conformed to the standards required by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Turin (Prot. n. 121724—01/03/18). Participants were not compensated for taking part in the experiments.

Experimental Procedures

This study was conducted to explore and uncover possible brain changes correlated with the use of MindTheCity!, by representing a preliminary investigation of the possible neural networks involved in spatial learning strategies.

An independent group of other 23 participants performed the same training with MindTheCity! and the same pointing task as described in the experiment reported above. Notably, in this experiment, none of the subjects performed the Passive navigation control condition.

Additionally, these participants underwent two fMRI sessions: one before the training (pre-training) and the other one after the end of the training (post-training), performing a preliminary investigation of the possible changes in neuronal activity associated with the training.

Data acquisition was performed at the Molinette Hospital in Turin on a 3-T Philips Ingenia with a Sense high field high-resolution head coil (MRIDC) optimized for functional imaging. Functional $T2*$-weighted images were acquired using a gradient-echo EPI sequence, with a repetition time (TR) of 2,800 ms and an echo time (TE) of 30 ms. The acquisition matrix was 96 × 96; the field of view (FoV) was 230 mm. For each paradigm, a total of 260 volumes were acquired. Each volume consisted of 31 axial slices, parallel to the anterior–posterior (AC–PC) commissure line and covering the whole brain; the slice thickness was 4 mm with a 0.5 mm gap. Two scans were added at the beginning of functional scanning and the data was discarded to reach a steady-state magnetization before the acquisition of the experimental data. In the same session, a set of three-dimensional high-resolution T 1 - weighted structural images was acquired for each participant. This data set was acquired using an Ultra-Fast Gradient Echo

3D sequence (3D TFE—Turbo Fast Echo for Philips scanners, equivalent to an MPRAGE sequence for Siemens scanners) with a repetition time (TR) of 11 ms, an echo time (TE) of 5 ms, and a flip angle of 8◦. The acquisition matrix was 384 × 384 × 229, 0.7 mm isotropic voxels.

The experiment was conducted with a block design paradigm, with 14 s of the rest condition (counting task) alternating with 28 s of the active condition (Verbal memory task). During the verbal memory task, subjects had to listen to 7 different pairs of abstract, semantically unrelated words. The same 7 pairs were repeated for the whole duration of the verbal memory task (for a total of 17 repetitions). Subjects were asked to memorize each word pair. Importantly, a completely different list of words was employed in the subsequent session of scanning. At the end of each session, outside the fMRI scan, participants were asked to recall the 7 word-pairs. Accuracy was recorded. For each session of scanning, subjects underwent two runs. Each run had an acquisition time of 12 min and 13 s.

Analysis

Pointing Task

To evaluate subjects' performance at *MindTheCity!*, angular errors in the pointing task were recorded. Single subject angular errors were averaged in order to obtain one single measure for each session. We therefore summed the measurements collected in the first half (days 2–3) and in the second half (days 4–5) of the training, respectively, thus resulting in two distinct values for each subject. Paired-samples *t*-tests were used to compare angular errors made in the first half of the training vs. those made in the second half of the training.

Furthermore, with the aim of exploring whether participants' improvements were constant across the training days or whether instead they were focused on a specific day, we investigated daily participants' performance, from days 2 to 5. We therefore performed a linear mixed model analysis including angular errors as the dependent variable, with day of training (Day) as fixed repeated-measure factor, plus random effects intercepts and slopes for Day. The model used Satterthwaite's method for the estimation of degrees of freedom and the covariance structure for random effects was first-order autoregressive (AR1). *Post hoc* pairwise comparison *p*-values were corrected using Sidak's method.

These analyses fully replicated those employed in *“MindtheCity! as an innovative tool to improve spatial memory abilities in healthy young people ”*

fMRI analysis

fMRI data were analyzed with the BrainVoyager QX (Brain Innovation, Maastricht, Holland).

Imaging data were analyzed using Brain Voyager QX (BrainInnovation, Maastricht, Holland). Functional data of each subject were preprocessed as follows: (1) Mean intensity adjustment (2) Motion correction (3) Slice scan time correction (4) Spatial data smoothing with a Gaussian kernel with full width half maximum (FWHM) of 8 mm. (5) Temporal smoothing was performed to improve the signal-to-noise ratio by removing high-frequency fluctuations: a Gaussian kernel with full width half maximum (FWHM) of 2.8 s was used for this purpose.

After pre-processing, functional scans were coregistered with their 3D high-resolution structural scans. Then, structural MRI were transformed into Talairach space (Talairach and Tournoux, 1988): Finally, using the anatomical—functional coregistration matrix and the determined Talairach reference points, each subject’s functional time course was transformed into Talairach space.

The following procedure was performed for each task condition. A single design matrix was specified and the box-car time course of the design (Rest vs. Verbal memory task) was convolved with a predefined hemodynamic response function (HRF) to account for the hemodynamic delay (Boynton et al., 1996). The resulting time courses were entered into a General Linear Model (GLM) analysis to yield beta parameter estimates for subsequent group statistics.

Afterward, a second-level GLM analysis was performed on the group to yield functional activation maps of the pre- treatment and of the difference between post-treatment and pre-treatment (post > pre).

All statistical comparisons were made on z transformed scores and were computed at a statistical threshold of $p < 0.05$ corrected for multiple comparisons using false discovery rate correction (Benjamini and Hochberg, 1995).

Activated clusters were determined through automated routines in Brain Voyager and the statistical values for the local maxima of each region were calculated. Anatomical structures were labeled using the Talairach Daemon (Lancaster et al., 2000), a digitalized version of the Talairach atlas, available online at: https://bioimagesuiteweb.github.io/webapp/mni2tal. html. Regions included in each cluster were identified using a custom Matlab script based on the Talairach atlas and confirmed by visual inspection by a trained neurologist. fMRI images were created using Neuroelf v 1.1 rc2.

Results

Regarding the pointing tasks' data analysis, mean angular errors performed in the second half of training were significantly lower than those occurred in the first half of training (First Half: average ± *SD*: 118.695 ± 54.303 degrees; Second Half: average ± *SD*; 97.434 ± 49.042 degrees; $t22 = 2.29$, $p = 0.031$, $dz = 0.46$). Importantly, behavioral data collected in Experiment 2 fully replicated the results of Experiment 1, thus confirming the validity of *MindTheCity!* training in improving subjects' ability to map the virtual space in allocentric coordinates.

Furthermore, participants' daily performances were as follows: day 2 54.85 ± 29.66 degrees; day 3 63.84 ± 35.18 degrees; day 4 46.29 ± 28.06 degrees; day 5 51.15 ± 30.06 degrees. Through the linear mixed model analysis, we found a significant effect of Day ($F = 3.544$, $p = 0.032$). *Post hoc* pairwise comparisons revealed that performances of day 4 were significantly improved as compared to day 3 ($p = 0.036$). No other significance was found. Interestingly, despite the slight difficulty increase, no significant difference was found between day 2 and day 3 ($p = 0.727$) and between day 4 and day 5 ($p = 0.963$).

For what concerns fMRI analysis, neural activation during the *Verbal memory task* before and after training (post training > pre-training) were compared. The results showed significant differences of activation in a spread network of brain areas, following MindTheCity! training. Specifically, post activations as compared to pre activations are shown in **Table 1** (see also **Figure 1**).

Following both fMRI sessions, accuracy at the *Verbal memory task* were recorded. Participants' accuracy was always at ceiling (with participants recalling on average 6 out of 7 word-pairs) and did not differed across sessions.

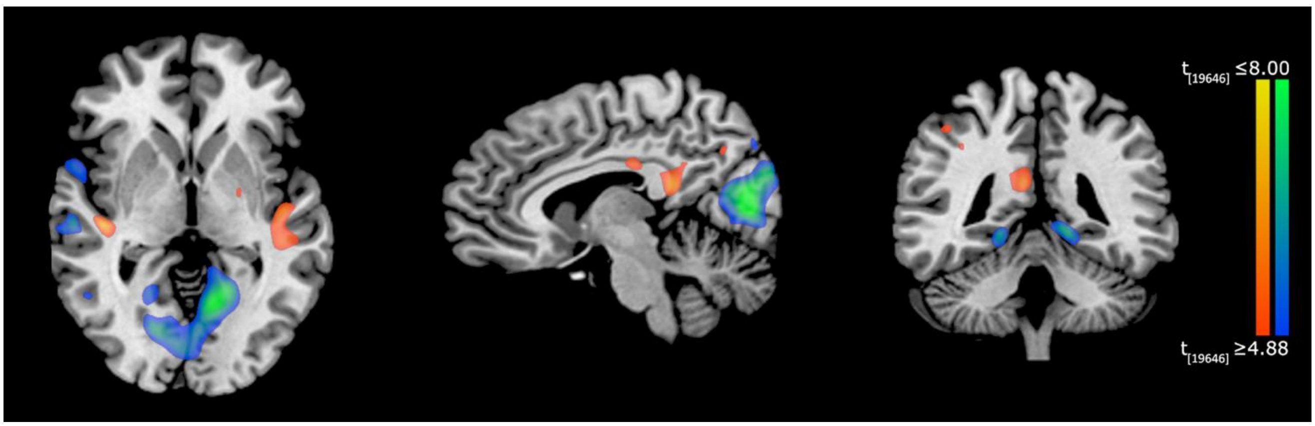

Figure 1. *Neuroimaging results of Experiment 2. Activation differences (post minus pre-training) during the Verbal memory task, superimposed on a Tailarach brain template (TAL coordinates: x = –7, y = –49, z = 3), radiological convention. Red-to-yellow blobs indicate greater activations in the post-training task compared to pre-training, whereas blue-to-green blobs represent lower activations in the post-training task compared to pre-training.*

Table 1. Post-training activations (compared to pre-training activations).

+/-		Brain region	Local maxima: x;y;z
Post +	RH	Superior Temporal Gyrus	58, -31, 9 T=6.960; p<0.001
Post +	RH	Putamen	23, 1, 11 T=6.871; p<0.001
Post +	LH	Inferior parietal lobule	-44, -38, 43 T=6.394; p<0.001
Post +	RH	Precuneus, including the inferior parietal lobule, the retrosplenial cortex and the posterior cingulate cortex (area 31)	13, -55, 34 T=7.153; p<0.001
Post +	LH	Precuneus, including the retrosplenial cortex and the posterior cingulate cortex (area 31)	-12, -58, 29 T=7.545; p<0.001
Post -	RH	Cuneus including bilateral Parahippocampal and Lingual gyri	3, -75, 16 T=-10.33; p<0.001
Post -	LH	Superior Temporal Gyrus, including the Enthorinal Cortex	-51, 1, -8

			T=-6.605; p<0.001

Discussion

Favoring the construction of allocentric representations has a pivotal role in supporting spatial memory and navigation abilities. Interestingly, recent research demonstrated that the enhancement of spatial mnemonic skills may improve overall (i.e., even non-spatial) memory performances (Dresler et al., 2017). Overall our preliminary fMRI results, focused on the difference between *pre*- and *post-training* conditions, together with the behavioral results of Experiment 1- Experiment 3 and 4, seem to indicate: (1) The involvement of less neural resources to achieve similar memorization performances, suggesting a more effective acquisition of the information to be learned; (2) the confirmation of Mindthecity! ability in improving the memorization of verbal information (Experiment 2); (3) the greater involvement of the right superior temporal gyrus and the bilateral retrosplenial cortex in the *post-training* condition, suggesting a possible shift toward visuo-spatial, imagery-based mnemonic strategies. More specifically, in the present study, after the *MindTheCity!* training, regions typically involved in memory processing— including parahippocampus, lingual gyrus and entorhinal cortex—decreased their activity. Deactivations in the memory circuits may constitute a correlate of training-induced less effortful processing. Accordingly, previous research interpreted the global activation decrease of the cerebral regions specifically involved in the training as a learning-related effect (Schiltz et al., 1999; Steele and Penhune, 2010; Howett et al., 2019). Interestingly, the parallel increase of the activity in the posterior cingulate cortex (area 31) *post* as compared to *pre-training* may be considered as supporting evidence of this interpretation, since PCC greater activation has been often related to less attentionally demanding task (Leech and Sharp, 2014). Furthermore, this specific pattern of memory-related areas deactivation paralleled with the increased activity of the regions involved in higher-level aspects of exploration and learning (such as the left supramarginal gyrus and the putamen) may also represent the neural mechanism underlying another function. A similar deactivation of the medial temporal lobe during learning has been previously found by Poldrack et al. (1999, 2001) who speculated that it may reflect an active suppression operated by other brain regions to improve performance. Hippocampal/parahippocampal regions work to retrieve declarative memories of specific previous trials: when performance does not rely upon specific episodic memories, suppression of that circuit would allow the rest of the network to work more efficiently (Mattfeld and Stark, 2015). In accordance with this view, we observed the greater activation of the left supramarginal gyrus, which is a part of the parietal memory network, contributing to both information encoding and retrieval (for a review see Gilmore et al., 2015), and the right putamen. Besides its recognized role in linguistic processing (as required by the present verbal memory task) (Viñas-Guasch and Wu, 2017), the putamen, as a part of the dorsal striatum of basal ganglia, has traditionally been associated with reinforcement learning (for a review, see Packard and Knowlton, 2002). Indeed, dorsal striatum play a critical role in processing response-contingent feedback and in maintaining information about reward outcomes (O'Doherty et al., 2004). In our *MindTheCity!*, retrieval of the bicycle's parts constitute a rewarding outcome, giving direct feedback on the participants ability to map the virtual environment. Consistently, basal ganglia have been shown to be selectively involved in the ability to learn from explicit feedback, rather than implicitly (O'Doherty et al., 2004). Therefore, we can speculate that our training increased putamen activity as part of a brain network involved in the conscious construction of cognitive maps, based on the explicit feedback provided in the training. Interestingly, in their resting-state functional connectivity study, Di Martino et al. (2008) showed that right putamen seeds hold negative relationships with parahippocampal gyrus, and predict activity in areas linked to executive control. This is in line with the idea that putamen itself, besides being directly involved in high level aspects of cognition, might have had a role in balancing the activity of the medial temporal lobe and of the regions supporting higher-level, more general learning mechanisms (such as those involved in the present task). Overall, we may interpret the post-training pattern of activations and deactivations as a result of a competing mechanism where regions involved in more general processes of memory enhance their activation to transfer the newly learned (visuo-spatial) mnemonic strategies to other learning domains. When facing a memory task which is not related to the specific skills trained, such as the word association encoding we proposed during the fMRI scanning, broader memory abilities play a crucial role. It seems that our training, directed to the enhancement of spatial mnemonic skills, was also able to improve overall (i.e., even non-spatial) memory performances (as also demonstrated behaviorally by Experiment 2, 3 and 4), by facilitating the acquisition of new information (as shown by the less effortful neural processing). This effect might also be due to the overlap in the neurocognitive systems responsible for word- pair memorization and visuo-spatial processing. Previous studies demonstrated the crucial role of parahippocampal and enthorinal regions in verbal memorization (see e.g., Goto et al., 2011; Jacobs et al., 2016; Liu et al., 2017). Therefore, it is possible that *MindTheCity!*, through its visuo-spatial training enhancing the processing of enthorinal and parahippocampal regions, concurrently improved spatial and verbal memorization. Moreover, the increase in the activation of right superior temporal gyrus might indicate the greater deployment of visuo- spatial skills after the training. Previous research exploiting intraoperative electrical stimulation in awake patients during brain surgery showed that the right superior temporal gyrus has a crucial role in serial exploratory visual search (Gharabaghi et al., 2006). Other studies confirmed this finding. Ellison et al. (2004), using repetitive transcranial magnetic stimulation, demonstrated that the right superior temporal gyrus is pivotal in human exploration behavior. It is also involved in allocentric spatial processing (Shah-Basak et al., 2018) and spatial awareness (Karnath et al., 2001). Interestingly, we also found increased activity in the inferior parietal lobules and in the precuneus. This is an interesting finding, since it might again be related to the improvement of visuo-spatial abilities following the training. Studies on brain-damaged patients demonstrated that lesions of the parietal cortices, such as those related to hemineglect (i.e., a neural pathology where patients fail to detect and respond to sensory events occurring in the controlesional space; Vallar et al., 2003; Ronga et al., 2017a,b, 2019), are often involved in the detriment of object identification and localization abilities (Trés and Brucki, 2014; Vallar and Calzolari, 2018). Therefore, it is possible that the greater activation of the parietal cortices observed in the present study might be directly related to the improvement of participants' spatial localization abilities. This interpretation of the results, suggesting that the *MindTheCity!* training enhanced the employment of visuo- spatial skills as well as the ability to remap the egocentric spatial information in allocentric coordinates, is supported by the increased activation of the retrosplenial cortex *post* vs. *pre- training*. As demonstrated by previous studies, the retrosplenial cortex is the area specifically deputed to the shift between an egocentric and an allocentric spatial frame of reference (Vann et al., 2009) and its involvement is systematically observed when visuo-spatial mnemonic strategies are employed, both in super memorizers and control participants (Maguire and Frith, 2003; Dresler et al., 2017). Overall, our preliminary neuroimaging investigation seems to indicate that our training favored the enhancement of a general learning mechanism through an increase of activation of higher order brain circuits, and a simultaneous reduction of the working load on the specialized memory circuits necessary to perform the mnemonic task. Furthermore, the *MindTheCity!* training promoted the employment of visuo-spatial strategies as suggested by the increased activation of the right superior temporal gyrus, parietal cortices, and the retrosplenial cortex. This study presents some limitations to the generalizability of the results. First of all, we recruited only male participants, thus hindering to predict the outcome of the present training for female participants. We recruited a sample of healthy, young men, and we did not perform a full neuropsychological assessment of visuo-spatial skills, omitting to explore whether some of the involved participants possessed exceptional spatial memory skills. Nonetheless, the absence of outliers in our assessment tasks suggests that this was not the case. Finally, the absence of a control task in the fMRI paradigm prevents the generalization of our neurophysiological results, which should be intended as a preliminary investigation. The present limitations should be addressed in future studies, which might further explore the possibility of *MindTheCity!* to improve visuo-spatial abilities as well as the duration of the observed effects. Altogether, our behavioral and neurophysiological results showed that *Mindthecity*! is effective in promoting the employment of visuo-spatial skills and in supporting the encoding of allocentric space representations. These findings, if confirmed by future studies, may lead to several applications. Improving visuo-spatial skills in healthy subjects is crucial to enhance their ability to navigate space in everyday life. Furthermore, the *MindTheCity!* training, supporting the egocentric-to-allocentric representation encoding, might actively contrast the aging-driven physiological decline in navigation abilities (Klencklen et al., 2012; Bates and Wolbers, 2014). Concerning the clinical domain, our training might limit the pathological deterioration typical of the prodromal forms of dementia (such as the Mild Neurocognitive Disorder) and Alzheimer's Disease (Pengas et al., 2010; Serino et al., 2014; Marková et al., 2015; Coughlan et al., 2019). Future studies should be directed to test whether *MindTheCity!* could be used as a possible clinical tool, intending to assess and possibly rehabilitate visuo-spatial impairments.

CHAPTER 5

General Discussion

This research project studies spatial memory and learning and how we can induce an improvement in these cognitive functions. With a specific focus on spatial memory abilities, a series of different experiments were conducted to implement new protocols and methodologies that are able to increase functional learning strategies. Specifically, we employed experimental paradigms intending to stimulate the implicit attentional level and motivational engagement. Memory formation is a complex process that involves the integration of different elements into a single mental representation.

Recently, it was demonstrated that the final representation of complex memories takes place in a specific time window of neural activity related to the Theta brain rhythm that would act as a binder in the integration of inputs arising from different sensory cortices (Clouter et al., 2017; Cruzat et al., 2021). Thus, given that spatial memory is intrinsically a type of multimodal and associative memory (Schott et al., 2019), we presented a behavioral study (Study 1 – CHAPTER 2) where we try to investigate the possibility of the facilitating memory effect in a spatial memory task where the luminance of visual stimuli is modulated by delivering them at Theta frequency or Alpha frequency generating a “flicker effect”.

In this study, by stimulating the implicit attentional level, we showed that the flickering of visual stimulation within the theta frequency band enhances the memorization of objects' locations in space highlighting significantly higher memorization performances following the theta as compared to the alpha condition. Specifically, our results confirm that it's not only the flickering of stimuli to enhance memory performances, it appears that theta oscillations could have a role in improving or even facilitating memory.

Following the above, the possible neural mechanism able to clarify our behavioral results could be that the memory advantage is related to the synchronization of different inputs arising from different associative cortices during the retrieval memory phase and transmitted to the hypothalamus to retrieve a unitary and integrated memory representation.

Future electrophysiological research could further clarify the neural basis underlying the theta-induced memory potentiation effect. Importantly, if our findings are further confirmed, the flickering of visual stimuli at theta frequency could be exploited for the rehabilitation of memory deficits as well as in the educational field. Additionally, given that the ability to map the space in allocentric coordinates progressively declines in healthy aging (Bates & Wolbers, 2014; Klencklen et al., 2012); and its deterioration represents an early clinical marker of prodromal forms of dementia such as MCI and AD (Coughlan et al., 2019, Markova et al. 2015, Pengas et al. 2010, Serino et al. 2014) we have tried to address acting on several perspectives: enhancing learning mechanisms in young people; preventing the deterioration of visuospatial abilities in healthy elderly people; and counteracting topographical disorientation in MCI.

Importantly, in the Study 2 (CHAPTER 3), we used a novel 3D videogame (*MindTheCity!*), involving the spatial navigation of a virtual town. We investigated whether virtual navigation stimulates the ability to form allocentric representations. We thus observed an increasing performance on spatial representational tasks (pointing to a specific location in space) and on a spatial memory test (asking participants to remember the location of specific objects). Furthermore, to uncover the neural mechanisms underlying the observed effects, we performed a preliminary fMRI investigation before and after the training with Study 3 (CHAPTER 4).

Results show that our virtual training enhances the ability to form allocentric representations and spatial memory. Additionally, our neuroimaging data confirmed the behavioral results. Furthermore, our preliminary neuroimaging results suggest that the training activates brain circuits involved in higher-order mechanisms of information encoding, triggering the activation of broader cognitive processes and reducing the working load on memory circuits.

The improvement in spatial navigation ability observed in MindTheCity! appears to be in line with what has been reported in previous studies on the effects of using exploratory-type video games (Faira et al., 2014). Additionally, it has been shown that users of exploratory-type video games show greater development of the brain areas crucial for creating spatial maps (Kühn & Gallinat, 2014) and obtain higher scores in tests of episodic and spatial memory (Clemenson & Stark, 2015). Similarly, training with MindTheCity!

promotes the use of visual-spatial strategies, as suggested by the increased activation at the level of the right superior temporal gyrus, parietal cortices, and retrosplenial cortex, areas involved in allocentric spatial processing (Shah-Basak et al., 2018) and spatial awareness (Karnath et al., 2001), which are fundamental in human exploratory behavior. Importantly, in the MCI group, the performance improvement in MindTheCity! did not show a linear and continuous trend over the four weeks of training. The absence of a linear decrease in angular errors could be partly attributable to an inexact progression in the difficulty of the neighborhoods. A further factor to be considered is probably related to the technical difficulties experienced by some patients in using technological devices. In general, it has been observed that patients with cognitive impairment show difficulties in using technological tools without help or in using specific icons and devices (González-Abraldes et al., 2010; González-Palau et al., 2013). It is important to highlight that such difficulties do not prevent them from having a positive experience with the software. In this line, according to what has been observed in the literature (for a review see Contreras-Somoza et al., 2021), MindTheCity! is a fun tool that is sufficiently practical to use and engaging, as suggested by the results regarding usability, understood as the degree to which a product can be used with a guarantee of effectiveness, efficiency, and satisfaction by users in specific contexts and with specific goals (International Organisation for Standardisation [ISO], 2019b). In line with what has been reported so far, the results of the spatial learning tests (our Spatial memory task) are also encouraging, indicating an improvement in spatial learning performance in each group, supporting the effectiveness of training with MindTheCity! in enhancing participants' ability to construct and remember spatial relationships between different elements. One possible interpretation of this finding is that the improvement in allocentric spatial coding is generalized to different spatial learning tasks, and not limited to the virtual city environment explored. Thus, promoting the construction of allocentric representations would play a key role in enhancing spatial cognition and memory skills (Sacco et al., 2022). Accordingly, previous research in healthy subjects has shown that the enhancement of spatial memory skills can also improve the performance of other (non-spatial) learning mechanisms (Dresler et al., 2017; Sacco et al., 2022). The results obtained in our Verbal Memory task (Study 2, Experiment 2) confirm this finding, opening up a possible generalization of the improvement observed in spatial learning tests at non-spatial learning processing. Finally, this research highlights several limitations in the use of telerehabilitation in people with MCI. First of all, the requirement of an Internet network for the transmission of the MindTheCity! game data led to the exclusion of all patients who, despite having suitable clinical characteristics, were nevertheless without a Wi-Fi connection. In addition, the technology gap still represents an important limitation, in terms of the digital skills deployed by the patients. Overall, future research will be needed to overcome the limitations of this research and to enable MindTheCity! to become a valid clinical tool in cognitive enhancement and the treatment of pathological aging.

5.1 Gamification, Brain Plasticity and Divergent Thinking: Future Direction for Mild Cognitive Impairment

Rehabilitative video games may capture and positively engage participants by stimulating neuroplasticity and preventing the frustration often related to distance rehabilitation (Anderson-Hanley et al., 2012.); they have a positive effect on emotions and executive functions (Anderson-Hanley et al., 2012; Rosenberg et al., 2010); and increase therapeutic compliance (van Schaik et al., 2008). The motivational engagement strategies seem to be particularly useful in driving and promoting self-efficacy, self-control, and well-being by confirming greater therapeutic benefits than traditional rehabilitation programs (Choi e Twamley, 2013). Gamification aims to apply game-like features (competition, story, leaderboards, graphics, and other game design elements) to make a frustrating task engaging and even fun (Lumsden et al., 2016).

Beyond gamification, there are new methods and constructs that assume renewed importance in counteracting cognitive decline associated with states of cognitive neurodegeneration. Given the prevalence of MCI in elderly population values, the importance of highlighting early markers of cognitive impairment becomes clear. In this regard, there is an increased focus in the literature on the development of new stimulation and rehabilitation programs to counteract the cognitive decline in these patients. In this connection, divergent thinking (DT) has recently gained increased attention for its potential in early diagnosis and rehabilitation programs in patients suffering from neurodegenerative diseases (Hart and Wade, 2006; Palmiero et al., 2012; Fusi et al., 2020). Interestingly, a positive correlation between DT and the construct of Cognitive Reserve (CR) was demonstrated by several studies (Colombo et al., 2018; Fusi et al., 2020) which plays a key role in the field of aging. Fusi and colleagues (2020), in their fascinating work, highlighted an impairment in DT abilities in people with MCI but surprisingly only in the figural indicator score suggesting that the figural DT could be considered for the early diagnosis of MCI patients and, secondly, the sparing of all other DT skills could suggest that, considering its relationship with CR, verbal DT could be considered a possible and meaningful target for prevention or early cognitive stimulation programs. (Fusi et al., 2020). Given that divergent thinking is a cognitive marker involved in major cognitive functions such as memory, attention, spatial skills and executive functions, future research could consider DT to determine the relationship between cognitive impairment and figural DT in people with MCI.

5.2 Conclusions

Looking at traditional rehabilitation protocols, they are essentially characterized by a performance-based approach. This type of approach can hurt the self-perception of the patient receiving rehabilitation treatment.

Neurocognitive rehabilitation protocols based on a traditional approach tend to create a passive view of the patient who perceives himself exclusively as the object of treatment.

The focus of rehabilitation is mainly directed at deficit enhancement rather than on the person in his (or her) entirety. It is, therefore, necessary to introduce into clinical practice a gentle approach to the rehabilitation of the person in his individuality and uniqueness by promoting an active vision of the patient. In this regard, implementing gamification elements through virtual reality, considering the aesthetic preferences, and the constructs of creativity and divergent thinking become crucial for the passage from "to cure" to "to care" in neurocognitive rehabilitation. Moreover, the experience in Virtual Reality positively affects people's self-consciousness, particularly their sense of agency and their sense of ownership. These innovative tools for clinical and rehabilitation practice are not only effective, but they are also able to shift the focus away from performance alone and promote a positive *care experience* in terms of compliance and adherence to treatment. Regarding this topic, the possibility of promoting a people's sense of agency in a rehabilitation context may have important positive implications not only for the outcomes but also to lead the individual receiving treatment to regain his (or her) identity and integrity. Moreover, through the validation of a project like MindtheCity, it is possible to provide the patient with a different and renewed treatment experience. We have already seen how the introduction of gamification elements into clinical practice positively impacts patient motivation. It is also well known that by stimulating the intrinsic motivation of treatment recipients, they will achieve favorable outcomes more easily.

Despite this, the present project, by providing a valuable and innovative tool that can be used at home, makes it possible to act directly on each patient's perception of illness. Besides, an e-health clinical tool validation may positively impact not only patients' global well-being but also in terms of resource optimization in the hospital setting.

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