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PRODROMAL STAGES OF NEURODEGENERATIVE DISEASES: PROPOSALS FOR NEW APPROACHES IN DIAGNOSIS AND INTERVENTION

Doctoral Thesis

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Dedicato a mamma, e alla zia Eliana,
e a tutti coloro che hanno perso una persona cara
a causa di una malattia neurologica.

Se il mio lavoro è servito, o servirà, ad alleviare anche solo momentaneamente il dolore di qualcuno, posso dire che i miei obiettivi sono stati orgogliosamente raggiunti.

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ABSTRACT

The study of aging is a central topic in the current societal debate, as life expectancy is increasing, and new ways to maintain a good quality of life and to prevent neurodegenerative diseases are fundamental. In these terms, it is necessary to pay attention to the prodromal stages of cognitive decline, before it actually appears, in order to enhancing the accuracy of diagnoses and try to maximize interventions.

The first chapters of this thesis focus on exploring a new technological intervention for amnesic Mild Cognitive Impairment (aMCI) patients. In particular, after an excursus on cognitive aging and existing available interventions (chapters one and two), the third chapter presents Study 1, which aimed at investigating both behavioral and neurofunctional effects of a 5-weeks treatment for patients with single and multiple-domain aMCI. There is evidence that non-specific domain computerized trainings might be beneficial for patients with MCI, and a non-invasive modulation technique, Prismatic Adaptation (PA), has been shown to entail a diffuse effect on higher cognition as well. Therefore, we decided to implement a digital treatment involving the use of PA combined with Serious Games. To date, we have recruited 10 patients, who underwent neuropsychological assessments and resting-state fMRI exams, before and after the treatment. They were divided into two groups, one who received PA with real lenses (experimental group), and the other who received PA with neutral lenses (control group). Our results suggest that the 5-weeks treatment was beneficial in preventing cognitive deterioration in that timeframe, and in sustaining long-term memory and attention, in both groups. Moreover, we observed an increased anti-correlation between the Default Mode Network (DMN) and the Dorsal Attention Network (DAN) during resting-state in the experimental group, as compared to the control group, after the treatment. This result is not only in line with current literature, but it also reflects the potential neurofunctional effects of PA.

In the fourth chapter, Study 2.1 and 2.2 focus on the attention capabilities of healthy elderlies and their differences from aMCI patients. In Study 2.1 we explored the characteristics of attentional subcomponents, namely alerting, orienting, and executive control, in healthy individuals older than 65 years old, and investigated whether PA could modulate them. To do so, we recruited 20 participants and administered them with the Attention Network Test (ANT) before and after one single session of PA. Results suggest that only the alerting component was modulated by PA. A reduction in RTs was seen in both the experimental and the control groups. Moreover, we compared the performances at ANT of the healthy participants matched with the aMCI patients of Study 1. We found a significant difference in

RTs and numbers of errors, with patients being more slowly and less accurate than healthy elderlies. Taken together, Study 1, 2.1, and 2.2, demonstrated the pivotal role of attention in aging; the importance of delving into its function in the transition from healthy to pathological aging should be considered both in the diagnosis process and in designing cognitive stimulation treatments.

Finally, the fifth chapter introduces Study 3, presenting a single case of unilateral right tactile agnosia, in the context of a rare neurodegenerative disease, namely Cortical Basal Syndrome (CBS). The patient, a 55-year-old woman, initially presented with a complex neuroanatomical correlate, with left frontoparietal atrophy and the outcome of the surgical removal of a right parietal oligodendroglioma. She referred difficulties in haptic object recognition and in right-hand sensitivity. We performed an extensive neuropsychological assessment and an experimental evaluation of somatosensory functions and tactile agnosia, targeting every level of tactile processing, from elementary to higher-order tactile recognition processes: sensory deficits (i.e., tactile perception), hyloagnosia (i.e., weight, texture, and materials), morphoagnosia (meaningless-shapes test), and associative tactile agnosia (real object test). Since a standardized battery for tactile agnosia is missing, we also recruited 18 healthy controls age- and education-matched. Furthermore, we followed the patient's evolution for three years, both neuropsychologically and neurologically. The initial neuropsychological assessment revealed apraxia for the right hand, in the context of an otherwise intact cognitive profile. The patient showed normal tactile sensitivity and she was accurate for most hylognosis functions. Conversely, she was impaired with the right hand in exploring geometrical shapes and in the meaningless-shapes test. She could not recognize real objects either. Three years after symptoms onset, a DaTSCAN, previously negative, became positive, showing reduced integrity of the presynaptic dopaminergic system in the left putamen. The MR showed a progression of the left frontoparietal atrophy in the absence of lesion recurrences of the right oligodendroglioma. Behaviourally, apraxia and morphoagnosia appeared also in the left hand, while cognitive functions remained stable. The patient's clinical profile is consistent with the diagnosis of CBS and unilateral tactile agnosia as the primary symptom onset, in the absence of cognitive decline. This is the third case described in the literature manifesting morphoagnosia without hyloagnosia and the first description of such dissociation in a case with CBS.

Overall, our studies demonstrate that the understanding of physiological changes in the elderly needs further exploration, as well as the distinction between these modifications and pathological ones. Such knowledge can be indispensable for early diagnoses and for the

development of feasible and easily accessible treatments, both in the context of most common conditions, e.g., MCI, and even more in rare or poorly understood neurodegenerative diseases, e.g., CBS.

CHAPTER ONE - From healthy to pathological aging

1.1 Cognitive aging

The study of aging is currently a central theme for society, as in 2022 in Europe the median age of the population reached 44.4 years, steadily increasing over the past decade. The range varies from 38.3 years in Cyprus to 48 years in Italy, which stands out as the European Country with the oldest population. Italy also has the highest old-age dependency ratio (37.5%) in Europe, defined as the ratio of the number of people aged 65 years and over, compared to the number of people between 15 and 64 years old (Eurostat, 2022). These data imply an increase in years of life not dedicated to work, during which it is important to maximize the quality of life by ensuring good maintenance of physical, psychological, and cognitive well-being, while minimizing the length of time during which persons are functionally impaired (Hertzog et al., 2008; Rowe & Kahn, 1997). Although aging is stereotypically associated to negative traits, particularly to inevitable cognitive decline and memory loss (Lineweaver & Hertzog, 1998), studies have shown that neural plasticity is possible during the entire lifespan and that cognitive performance can be improved in the eldest despite biological cognitive constraints (Baltes, 1987; Hertzog et al., 2008). Evidence exists for gradual declines in processing speed, central sensory functioning, white matter integrity, and brain volume as individuals age (Lindenberger et al., 2001; Raz et al., 2005). However, research on higher cognitive functions reveals that a considerable portion of the elderly population experiences only modest declines or even maintains their cognitive abilities as they grow older (Greenwood, 2007; R. S. Wilson et al., 2002). Greenwood (2007) proposed a model to explain the interaction between brain volume loss (biological cognitive constraints) and the preservation of cognitive performance in healthy elderly individuals. His model suggests that brain and cognitive plasticity, through the learning of cognitive strategies, allows for the recruitment of brain areas adjacent and contralateral to the atrophic ones to maintain cognitive functions, with the only consequence of a slowdown in processing speed and an enhanced activation of those contralateral areas (Greenwood, 2007; Gutchess et al., 2005).

On the other hand, advanced age is the primary risk factor for the onset of degenerative diseases, primarily Alzheimer's Disease (AD); this underscores the vital importance of developing preventive strategies. AD is the most prevalent form of dementia and its incidence in Europe is estimated at 5.05% of the total population (Niu et al., 2017); in Italy, in 2018 the 2.12% of the population lived with AD and this percentage is estimated to grow

up to 4.13% by 2050 (*Prevalence of Dementia in Europe*, s.d.). However, cognitive decline is not only caused by AD, and it is important to differentiate between different forms of dementia in order to properly diagnose and create a care plan. The gold standard diagnostic criteria for dementia have been developed by The National Institute on Aging and Alzheimer's Association (NIA-AA) and they comprise: (1) presence of cognitive or behavioral symptoms that interfere with the ability to function at work or dailies activities; (2) the symptoms represent a decline from a previous level of functioning; (3) symptoms are not explained by delirium or other psychiatric disorder; (4) cognitive impairment is detected and diagnosed through a combination of history-taking from both the patient and an informant, and an objective neuropsychological assessment; (5) the cognitive or behavioral impairment involves at least two of the following domains: memory, reasoning and decision-making, visuo-spatial abilities, language, and changes in personality or comportment (McKhann et al., 2011). For what concerns AD, the diagnostic criteria differentiate between “Probable AD”, “Possible AD”, and “Probable or Possible AD with evidence of the AD pathophysiological process”. Probable AD is diagnosed when the patient meets the criteria for the aforementioned dementia, and in addition he/she has an insidious onset and a progressive worsening of the symptoms, presented with an initial amnestic deficit (most frequently) or an initial language or executive-functioning deficit; the diagnosis of “Probable AD” should not be applied when there is evidence of a cerebrovascular disease temporally related to the cognitive decline, or the presence of core features of other dementias (i.e. dementia with Lewy Bodies, frontotemporal dementia, primary progressive aphasia, etc.) or other diseases or medications that could have an influence on cognition (McKhann et al., 2011). In the cases when there are insufficient anamnestic data to document a progressive decline or there are comorbidities with cerebrovascular disease, other dementias, or medication that affect cognition, the diagnosis of "Possible AD" is more appropriate (McKhann et al., 2011). Finally, in the patients who meet the “Probable AD” criteria, biomarkers evidence could increase the probability that the AD pathophysiological process is the cause of the cognitive decline. The major biomarkers for AD are brain amyloid-beta (Ab) protein deposition (detected through analysis of cerebrospinal fluid (CSF) or a PET scan), an elevated CSF-tau, and a disproportionate atrophy on structural magnetic resonance imaging (MRI) in medial, basal, and lateral temporal lobe, and medial parietal cortex (McKhann et al., 2011). Between healthy aging and dementia, there is a particular condition that is gaining increasing attention from both researchers and clinicians, namely Mild Cognitive Impairment (MCI) (Cherbuin et al., 2010; Petersen, 2004). This condition involves cognitive decline in

the absence of an impact on daily life, and appears to be an intermediate stage that augments the probability, but not necessarily leads to, the development of dementia (Cherbuin et al., 2010; Gillis et al., 2019). Recognizing this continuum from healthy aging to dementia opens up opportunities for prevention that parallel the achievements in heart disease, stroke, and various forms of cancer; thus, prioritizing MCI studies should be on the same level as the efforts directed towards diagnosing and providing care for individuals who have already developed dementia (G. E. Smith, 2016).

1.2 Mild Cognitive Impairment

In the 1980s the National Institute of Mental Health (NIMH) introduced the term “Age-Associated Memory Impairment” (AAMI) referring to memory deficits that do not interfere with daily activities. According to the NIMH, these observed limitations must be confirmed through memory test performance that falls at least one standard deviation (SD) below the established average (Crook et al., 1987; Golomb et al., 2004). However, AAMI had limitations that involved confining impairment solely to the memory domain and comparing memory function in older adults to the performance of young adults, thus being unable to distinguish between individuals at risk of developing pathological conditions and those experiencing the natural aging process (Petersen & Negash, 2008). For this reason, scholars from the International Psychogeriatric Association introduced the term "Age-Associated Cognitive Decline" (AACD) to encompass multiple cognitive domains presumed to decline during normal aging (Golomb et al., 2004; Levy, 1994). During those years, many dementia assessment scales (for example the Global Deterioration Scale and the Clinical Dementia Rating) and many constructs were used, such as “isolated memory loss”, “mild cognitive disorder”, “mild neurocognitive disorder”, “cognitive impairment–no dementia”, without clinical and scientific consensus on the best term to use and on this diagnostic category (Golomb et al., 2004). It was only in 1995 that Mild Cognitive Impairment (MCI) became an independent diagnostic category, referred to subjects who retained normal global cognitive function without impairment on tasks of daily living but had subjective memory complaints and scored below age-adjusted norms on memory tests (Golomb et al., 2004; Petersen, 2004; Petersen et al., 1995). At present, the diagnostic criteria are those of the NIA-AA, which, building upon the foundations laid by Petersen and colleagues and subsequent studies and revisions, has expanded and detailed this diagnosis (Albert et al., 2011; McKhann et al., 2011; Petersen et al., 1999). The core clinical criteria for individuals with MCI (Albert et al., 2011) are:

(1) **Concern regarding a change in cognition**, in terms of evidence, from the individual, an informant, or a skilled clinician of a change in comparison to a previous level of cognition;
(2) **Impairment in one or more cognitive domains**, evidenced by a reduced performance at the objective assessment that is greater than would be expected for the patient's age and educational background;
(3) **Preservation of independence of functional abilities**; persons with MCI may have difficulties in complex daily tasks, but they generally maintain their independence of function in daily life;
(4) **Not demented**; the cognitive changes should be sufficiently mild so that there is no evidence of a significant impairment in social or occupational functioning.

Once the core criteria have been fulfilled, a more detailed clinical characterization can be undertaken. Indeed, the classification of MCI includes two subcategories: Amnestic MCI (aMCI), characterized by the primary cognitive impairment in memory, and Non-amnestic MCI (naMCI), where the predominant impairment involves cognitive functions other than memory, such as attention, language, or visuospatial skills (Petersen, 2004; Winblad et al., 2004). In both forms of MCI, these impairments can either manifest in isolation (Single-domain MCI) or in combination with other cognitive deficits (Multiple-domain MCI) (Petersen & Morris, 2005; Saunders & Summers, 2011; Winblad et al., 2004). Finally, in order to carry out a proper diagnosis, the clinician should determine if the likely cause of the MCI syndrome is degenerative (i.e., gradual onset, insidious progression), vascular (i.e., abrupt onset, vascular risk factors, history of strokes, transient ischemic attacks), psychiatric (i.e., history of depression or anxiety), or secondary to concomitant medical disorders such as congestive heart failure, diabetes mellitus, systemic cancer (Petersen & Negash, 2008). Although the presence of MCI doesn't necessarily imply a prognosis of cognitive decline, individuals with MCI have a 3-5 times higher likelihood of developing dementia compared to their peers without MCI (Campbell et al., 2013). The understanding of the MCI subtype and etiology would help in predicting the type of dementia the patient could evolve (Petersen & Morris, 2005). For example, both single and multiple-domain amnestic-MCI have a highly likelihood to progress in AD, while non-amnestic MCI has major probability to progress in Frontotemporal Dementia (FTD) or Lewy Bodies Dementia (LBD), mostly when a single domain is affected (Gillis et al., 2019; Petersen et al., 1999; Petersen & Morris, 2005). However, there is a significant heterogeneity in the outcomes of MCI, regardless of the initial symptoms that appear. Even aMCI has shown to increase the risk of conversions in

dementia different from AD (Fischer et al., 2007; Summers & Saunders, 2012), and it has been suggested that a more precise assessment of other cognitive domains could provide more insightful information about outcomes compared to memory alone. Indeed, even in the very early stages of Alzheimer's disease, deficits in other cognitive domains, particularly executive functions and attention, have been observed (Storandt, 2008). The predictive accuracy for the conversion from MCI to AD considering more cognitive variables, including episodic memory and processing speed measures, has been reported to be as high as 86%; additionally, it has been discovered that the evaluation of executive function and functional capacity were better predictors of conversion from MCI to AD after 2 years compared to biomarkers, such as MRI and cerebrospinal fluid (Gomar et al., 2011; Reinvang et al., 2012). Therefore, it appears crucial to conduct more in-depth and longitudinal studies of the disease's progression, with a focus on cognitive functions that have been relatively overlooked compared to the memory domain in the past.

1.3 The Attention Network Test (ANT) as informative tool in MCI

Focusing on executive functions and attention in order to study the progression trajectories of MCI, it seems crucial to find a proper tool that serves the need of both experimental and clinical practice to delve into these components. Neuropsychological models of attention propose a division of attention into three primary subcomponents: alerting, orienting, and executive control (Fan et al., 2002a; McDonough et al., 2019; Posner & Petersen, 1990; Posner & Rothbart, 2007). "Alerting" refers to the ability to increase vigilance and response readiness to an external cue; "orienting" involves selecting specific information from various sensory inputs and directing attention to it, while "executive control" pertains to the monitoring and resolution of complex mental operations, particularly involved in decision-making, planning, and error detection (Fan et al., 2005).

One task that has been developed to investigate these subcomponents is the Attention Network Test (Fan et al., 2002a). This simple task, lasting about 20 minutes, can provide insights into the efficiency of each of these three subcomponents individually. It has been demonstrated that these attentional subcomponents can decline independently over the course of a person's life, and performance on the ANT could potentially serve as an indicator of an early stage of cognitive decline (Sarrias-Arrabal et al., 2023; Van Dam et al., 2013). However, the direction of attentional changes during lifetime remains somewhat unclear, as some studies show broader alerting in older individuals (Fernandez-Duque & Black, 2006), while others find reduced alerting (Gamboz et al., 2010; Jennings et al., 2007). On the other

hand, it has been suggested that impairment in the executive control network might be a prodromal symptom of degeneration, as selective executive control dysfunction has been observed in patients with aMCI through ANT (Zhang et al., 2015).

The ANT requires participants to determine whether a target (central arrow) presented on a computer screen points to the left or to the right, by pressing the left or right shift keys. They are instructed to answer as quickly and accurately as possible. The central arrow may appear alone (neutral condition), or with two flanker arrows on both its left and right side. The flankers are either congruent (pointing to the same direction as the target) or incongruent (pointing to the opposite direction). Therefore, the executive control of attention is measured by subtracting the mean reaction time (RT) of the congruent condition from the mean RT of the incongruent condition. Alerting and orienting components are instead derived from the four possible cue conditions before target appearance (no-cue, center-cue, double-cue, and spatial-cue – when the cue appears in the same location as the target). The difference between no cue and double cue conditions provides the index of the efficiency of the alerting network. The difference between center cue and spatial orienting cue conditions provides an index of the efficiency of the orienting network (Fan et al., 2002a).

1.4 Neurofunctional aspects in MCI

The evidence that alterations in attention and executive functions occur in the early stages of degenerative diseases and in MCI is consistent with neurofunctional evidence regarding the connectivity of brain networks in MCI patients. While most fMRI studies on MCI have traditionally focused on brain activity during episodic memory tasks (for a review: Ries et al., 2008), recent scientific interest has broadened to include resting-state fMRI (rs-fMRI), a technique that examines brain region activation in the absence of a specific task or stimulus (Lee et al., 2013). One of the most extensively studied networks is the Default Mode Network (DMN), which comprises widespread cortical and subcortical networks, including the posterior cingulate cortex (PCC), the medial prefrontal cortex (mPFC) with its dorsomedial (dmPFC) and ventromedial (vmPFC) subdivisions, the middle temporal gyrus (MTG), the medial temporal lobe (MTL), and the angular gyrus (AG) in the lateral parietal cortex. The subcortical nodes are the mediodorsal thalamic nuclei and the nucleus accumbens (Alves et al., 2019; Menon, 2023; Raichle et al., 2001; Raichle & Snyder, 2007). The DMN is referred to as the “task-negative network” because it is typically deactivated during execution of attention demanding tasks and serves as a self-centered predictive model of the world, being active during periods of “rest” and quiet wakefulness (Alves et al., 2019; for a review:

Menon, 2023). On the contrary, the “task-positive networks” are those associated with goal-directed attention and mental control tasks, and they comprise the Dorsal and the Ventral Attention Network (DAN and VAN, respectively) (Corbetta & Shulman, 2002; Szczepanski et al., 2013; Vossel et al., 2014). The DAN includes the dorsolateral PFC (dlPFC), the Frontal Eye Fields (FEF), the Inferior Precentral Sulcus (IPS), the Superior Occipital Gyrus (SOC), and the superior parietal lobule (SPL). The VAN comprises the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC) (Fox et al., 2006; Spreng et al., 2013; Vossel et al., 2014).

The DMN and the VAN/DAN are functionally anti-correlated to permit a segregation of neuronal processes subserving opposite goals or competing representations (Fox et al., 2005; Hampson et al., 2010). An alteration of both the default mode and the attentional networks have been found in patients with aMCI and AD; indeed, changes in low-frequency blood oxygen fluctuations have been seen in patients with aMCI in terms of decreasing regional homogeneity in bilateral PCC (DMN nodes) compared to healthy controls (Bai et al., 2008; Sorg et al., 2007), and alterations of PCC, mPFC, and IPS functioning have been associated with both early and advanced degeneration (Andrews-Hanna et al., 2007; He et al., 2007; Sorg et al., 2007). However, at present, the pattern of altered DMN in MCI is variable across studies, making it inadequate to be considered a biomarker, although it remains promising if further investigated as a potential means to distinguish individuals with MCI from healthy older adults (Eyler et al., 2019).

Furthermore, recent studies suggest that the anti-correlation between DMN and DAN/VAN, with its pivotal role for the integrity of attentional abilities, is attenuated in aging, and that patients with aMCI and patients with AD have functional connectivity of PCC decreased within DMN, but increased with the DAN in an inverse way (Esposito et al., 2018; Spreng et al., 2016; J. Wang et al., 2019; K. Wang et al., 2007; Zhang et al., 2015). Hence, the abnormal functional connectivity within and between DMN and DAN/VAN nodes may explain the behavioral changes observed in cognitive degeneration and should been taken into consideration to better understand neurofunctional modification at early stage of dementia (Andrews-Hanna et al., 2007; Eyler et al., 2019; Zhang et al., 2015).

CHAPTER TWO - Cognitive intervention for MCI

2.1 The importance of cognitive intervention

Despite individuals with MCI being able to maintain their independence, they still undergo changes in their psychological and daily functioning, as well as in their quality of life (QOL) (Huckans et al., 2013; Teng et al., 2012). Areas of daily functioning most frequently impacted are appointment scheduling, transportation issues, and financial management (Huckans et al., 2013; Teng et al., 2012), while psychological changes encompass an increased vulnerability to anxiety, depression, and sleep disturbances (Gold, 2012; Huckans et al., 2013). Moreover, as previously stated, patients with MCI have higher probability to convert to dementia, thus intervention seems crucial to manage the symptoms and to prevent more severe functioning and cognitive changes. Cognitive Rehabilitation Therapy (CRT) is defined as any systematic behavioral therapy with the explicit purpose of enhancing cognitive performance, assisting individuals in compensating for cognitive deficits, or facilitating adaptation to such deficits; the assumption is that cognitive stimulation could promote structural and functional brain reorganization. CRTs involve various approaches, such as lifestyle interventions, psychotherapy, and traditional cognitive training, as long as they are employed as treatments to address cognitive impairments (Cruz Gonzalez et al., 2018; Huckans et al., 2013). The main intervention encompasses:

a. Restorative cognitive training, which employs structured and repetitive cognitive tasks with the goal of enhancing neuroplasticity;
b. Compensatory training, primarily aimed at improving an individual's functioning by teaching compensatory strategies;
c. Lifestyle interventions, specifically targeting the reduction of risk factors through the promotion of physical activity, healthy nutrition, and the reduction of alcohol and tobacco consumption;
d. Psychotherapy, particularly focused on managing neuropsychiatric symptoms (for a review: Huckans et al., 2013).

Focusing on cognitive training programs, they mostly employ memory or attention techniques in combination with training for other cognitive functions. Current evidence states that the effectiveness of these programs shows promising but inconclusive results in terms of both objective and subjective cognitive measures. Consequently, there is insufficient data to establish standard treatment guidelines (Akhtar et al., 2006; Belleville et al., 2006; Butler et al., 2018; Ge et al., 2018; Greenaway et al., 2008; Huckans et al., 2013; Jean et al., 2010).

2.2 Technology-based intervention

In line with the technological advancements of recent years, several studies have sought to implement new cognitive intervention techniques by testing the effectiveness of virtual reality, computerized exercises, and interactive video games (for a review: Ge et al., 2018). Technology-based therapy permits real-time feedback to the patient, and it allows for a greater number of difficulty levels and proposed activities, thereby enabling the creation of highly individualized treatments. It also seems to deliver better outcomes than traditional trainings in improving QoL (Faucounau et al., 2010; Ge et al., 2018). The plethora of therapeutic possibilities offered by this type of intervention has prompted a reflection on the effectiveness of specific-domain *vs* non-specific domain treatments (Green & Bavelier, 2012; Park & Park, 2018). A recent randomized control-trial with a sample of 78 MCI patients (Park & Park, 2018) has proven that patients who underwent the non-specific treatment (not-specific computer training, NCT) for ten weeks, 30 minutes per day, three times a week, demonstrated a significantly greater improvement in visuospatial skills and quality of life compared to the group that engaged in cognition-specific computer training (CCT). Moreover, NCT improved motivation and compliance as well, which are related to better treatment outcomes (Park & Park, 2018).

Within the context of non-specific domain, technology-based treatments, there has been a growing focus in recent years on Serious Games (SG). SG refer to digital applications designed to extend beyond pure entertainment, with the aim of assisting in the assessment, stimulation, treatment, and rehabilitation of patients dealing with cognitive disorders (Robert et al., 2014). Some authors argue that while traditional cognitive rehabilitation targets specific domains, with the expectation that improvement in one cognitive capacity may extend to others, computerized training programs that favor cognitive engagement offer the opportunity to acquire new skills while simultaneously training a variety of cognitive functions, including memory, attention, and reasoning (Chan et al., 2016; Manca et al., 2021; Vaportzis et al., 2017). The use of SG in aging has garnered significant attention from researchers and clinicians particularly after a 2013 study (Anguera et al., 2013), which demonstrated both behavioral and neurofunctional modifications in executive functions in a healthy elderly population following video game usage (60-85 years old). Subsequently, the use of SG in MCI and AD has been extensively explored by many authors, although rigorous feasibility and efficacy studies are still lacking (Chan et al., 2016; Manca et al., 2021; Manera et al., 2015; McCallum & Boletsis, 2013; Muscio et al., 2015; Robert et al., 2014; Savulich et al., 2017; Vaportzis et al., 2017). Findings are promising, but further research is needed,

including larger sample sizes and the development of intervention protocols. Currently, it is suggested not to entirely replace traditional rehabilitation but to integrate it with the use of SG (Abd-alrazaq et al., 2022).

2.3 Neuromodulation techniques and Prismatic Adaptation

Another line of research for the treatment of MCI has recently focused on investigating the effectiveness of neuromodulation techniques, either individually or in combination with classical cognitive therapy (for a review: Birba et al., 2017). Neuromodulation is a technique which involves the modulation of brain activity and nervous system, through both implantable and non-implantable technologies, whether electrical or chemical, to enhance the QoL and functionality. When addressing neurodegenerative diseases, one of the primary goals of various neurostimulation protocols is to promote neuroplasticity, which can be achieved through the direct stimulation of specific brain regions (Marson et al., 2021). The most commonly implemented neuromodulation techniques in aging studies are non-invasive transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), which have shown promising but highly heterogeneous and inconclusive results in the long term (Cruz Gonzalez et al., 2018; Xu et al., 2019). The lack of uniform stimulation parameters across studies and the intrinsic need, inherent to these tools, to select specific areas for stimulation, prevents from both a comprehensive understanding of effectiveness, and the possibility of broader cognitive modulation (Cruz Gonzalez et al., 2018). Indeed, studies primarily focus on the stimulation of temporal areas and the dorsolateral prefrontal cortex (DLPFC), given their respective importance in memory processes (Kaye et al., 1997) and in higher-level cognitive functions (Tremblay et al., 2014), although failing in determining the outcome for other cognitive domains related to different brain regions (Cruz Gonzalez et al., 2018).

Furthermore, these neuromodulation techniques have limitations regarding their applicability criteria. Although their safety has been widely demonstrated (Russo et al., 2017; Utz et al., 2010), their use is contraindicated for individuals with a clinical history of migraine, epilepsy, scalp diseases, or those with metallic implants or pacemakers, which complicates subject recruitment for clinical studies and their practical application in everyday clinical practice (Potter-Baker et al., 2016; Russo et al., 2017; Thair et al., 2017).

Interestingly, there is a bottom-up behavioral technique that, although not traditionally considered a neurostimulation procedure, may have a neuromodulatory effect at cortical level, known as Prism Adaptation (Clower et al., 1996; Redding et al., 2005). Prism

adaptation (PA) is an experimental paradigm that, by the means of prismatic lenses, alters the visual scene perception through the shift the visual field by 10º or 20º to the right or left (Redding et al., 2005; Welch et al., 1974). Importantly, PA has been shown to induce modulation at both motor and attentional networks (Luauté et al., 2009). PA has proven highly effectiveness in rehabilitating visuospatial disorders and unilateral spatial neglect (De Wit et al., 2018; Luauté et al., 2009; Pisella et al., 2006) and recent evidence suggests its efficacy in other cognitive abilities, such as phonemic fluency (Turriziani et al., 2021), numbers representation (Loftus et al., 2008), and treatment of chronic pain (Christophe et al., 2016). PA involves a dynamic reorganization that occurs at the central level in response to the perceived sensory mismatch (Clower et al., 1996). This reorganization comprises two main independent processes: (1) the *recalibration*, involving the reprogramming of movements in space, which is primarily strategic and cognitive in nature (Redding et al., 2005), and (2) the *realignment*, an automatic reorganization of sensorimotor spatial maps to align the visuomotor frame with the visuoperceptual frame (Redding et al., 2005).

While there is no complete understanding of the underlying brain mechanisms of PA, a recent literature review proposes an integrated explanatory model by combining evidence from neuroimaging and neurostimulation studies (Panico et al., 2020). This model (Figure 2.1) involves (i) cerebellar-parietal activation, primarily related to recalibration and realignment, followed by (ii) a bottom-up temporo-frontal cortical activation that reflects motor cortex activation and higher-level cognitive effects (Panico et al., 2020).

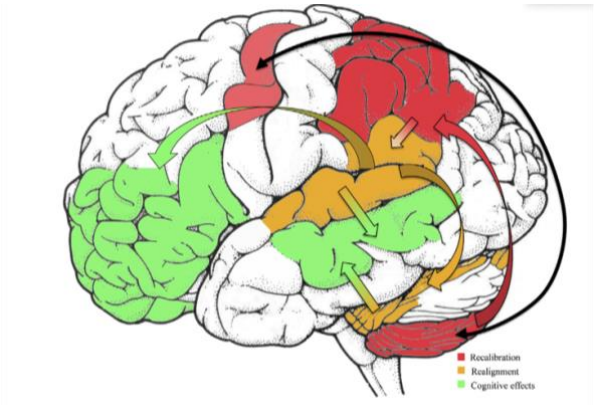

Figure 2.1. An interpretative framework for PA (adapted from Panico et al., 2020).

If Panico's model and recent evidence are correct, it could be argued that PA may have positive effects not only on visual-spatial orientation and attention, as already demonstrated in its application in neglect rehabilitation, but also for stimulating higher-level attentional

functions. Indeed, PA in healthy populations can modulate the resting-state functional connectivity of certain nodes within the DAN and the DMN, namely the Frontal Eye Field (FEF), Medial Prefrontal Cortex (MPFC), and Posterior Parietal Cortex (PPC), even after one single session (Schintu et al., 2020; Tsujimoto et al., 2019; Wilf et al., 2019). The activity of these networks, essential for attentional functions, is anticorrelated in the healthy brain and it supports better performance in attention tasks (see chapter 1.4 for details) (Fox et al., 2005; Spreng et al., 2013; Zhang et al., 2015). Given the alteration in functional brain connectivity in the elderly, as discussed in the previous chapter, PA may prove to be a useful tool for neuromodulation in the early stages of cognitive decline and MCI.

CHAPTER THREE - Experimental Study 1

In this chapter I will present the preliminary results (N = 10) of a larger experimental project that is being carried out at ASST Grande Ospedale Metropolitano Niguarda in Milan, in collaboration with the University of Pavia, which aims to collect a total of 40 aMCI patients.
The study is a Randomized Controlled Trial (RCT) where aMCI patients underwent a technology-based treatment protocol, preceded and followed by behavioral and neurofunctional assessments.
All patients were recruited, assessed, and administered the treatment protocol at Center for Cognitive Neuropsychology of the hospital while they underwent rsfMRI in the neuroradiological department of the same hospital.
A power analysis was carried out to establish the sample size of the whole study using G*Power 3.1.9.2 software (http://www.gpower.hhu.de/). Cohen's standard values were used. Assuming an effect size of 0.5, a power of 0.8, and an alpha value of 0.05, it is necessary to include a total of 34 patients (17 per group) to obtain a significant interaction effect between conditions. Since it is not possible to precisely estimate the magnitude of the effect at issue, not having been investigated in previous studies, and that the experimental designs include fragile patients at risk of drop-out, we decided to opt for a conservative approach including 40 patients.
The study's procedures are in accordance with the 1975 Helsinki Declaration and the project was approved by the Ethical Committee of the ASST G.O.M. Niguarda (Milano, Area 3).

3.1 Introduction and Rationale

As mentioned in the previous chapters, MCI is a clinical condition that needs to be increasingly attentioned, in order to delay or even prevent conversion to dementia. Although various intervention techniques have been studied, methodologies and results are highly heterogeneous. Thus, to date, no definitive approach can be applied with certainty (Huckans et al., 2013). However, technology-based intervention, as well as non-specific domain CRTs, seem to be rather promising (Ge et al., 2018). Moreover, given that mechanisms underlying PA hint at an impact on higher-level cognitive functions, with a reorganization of resting-state neurofunctional connectivity (Panico et al., 2020; Wilf et al., 2019), this neuromodulatory technique could prove useful in clinical practice, as it is non-invasive and easily applicable. Yet, no study to date has attempted to use PA as a modulatory technique in association with CRT in patients with MCI.

Considering that (i) aMCI patients show a selective impairment in executive control at the Attention Network Test (ANT) and altered neurofunctional connectivity in the DMN-DAN, that (ii) PA seems to influence those same brain networks in healthy persons, and that (iii) generic computerized cognitive stimulation has shown greater promise than specific-domain training, we hypothesized that the use of PA in combination with computerized cognitive exercises might induce a modification of DMN-DAN connectivity and, consequently, an improvement in attention in patients with aMCI.

Thus, the present study aims at investigating whether prism adaptation associated with Serious Games can positively modulate cognitive functions, both at behavioral and neurophysiological (rsfMRI) level, in patients with single- and multiple-domain aMCI. This study also assesses the feasibility of a novel cognitive stimulation treatment for aMCI, and to investigate the effects of this protocol on mood, QoL, and subjective perception of memory processes.

3.2 Procedure and Methods

3.2.1 Participants

The study was proposed to all patients who autonomously arrived at the Centre of Neuropsychology for a neuropsychological assessment and received a diagnosis of aMCI (both single and multiple domains), following Petersen criteria (Petersen & Morris, 2005). In particular, we selected patients with a Mini Mental State Examination (MMSE, Measso et al., 1993) corrected score ≥ 23, daily activities indexes (ADL/IADL, Katz, 1983) within the normal range, and a deficit score in at least the Free and Cue Selective Reminding memory Test – image version (Frasson et al., 2011). This neuropsychological assessment had to precede the start of the experimental protocol by a maximum of six months.

Exclusion criteria were (i) age < 18 or > 85, (ii) presence of a psychiatric or neurological disorder explaining the cognitive performance obtained at tests, (iii) pharmacologically treated, (iv) substance abuse, (v) untreated primary sensory disorders or worsening sensory disturbances (i.e., not-corrected vision and hearing impairments), and (vi) contraindications to fMRI examination (i.e., pacemakers, fixed hearing implants, presence of foreign metallic bodies such as intrauterine implants, metal splinters or fragments, screws, spikes, fixed dental prosthesis, and claustrophobia).

Twelve patients with aMCI, both single- and multiple- domains, were consecutively recruited and gave their informed consent to participate in the study, of whom 2 drop-out due to (non-neurological) illnesses that prevented attendance to all cognitive stimulation sessions.

Thus, the final sample included 10 participants (5 males, 5 females), mean age = 78.9, SD = 5.84 (min. 71, max 85); mean education level = 13.4, SD = 4.14 (min. 9, max 19). Half of the sample was randomly assigned to the experimental group (N = 5, age: M = 79.80, SD = 6.14; education level: M = 16, SD = 2.83) and the other half to the control group (N = 5, age: M = 78, SD = 6.08; education level: M = 10.8, SD = 3.70). Table 3.2.1 shows the corrected score at tests included in the clinical neuropsychological assessment.

Test	*Group*	*Mean*	*SD*	*Min.*	*Max.*
MMSE	experimental	25.36	1.40	23.85	27.60
	control	26.58	0.95	25.20	27.77
Phonologic fluency	experimental	33.60	15.13	21.91	57.88
	control	30.54	10.31	12.88	39.00
Semantic fluency	experimental	35.21	8.572	26.53	48.91
	control	36.41	5.14	31.91	44.92
Short story	experimental	5.167	4.805	0	9.5
	control	7.18	2.03	5.3	9.9
Digit span forward	experimental	5.388	0.759	4.51	6.13
	control	5.76	1.61	3.96	7.65
Digit span backward	experimental	4.53	0.62	3.57	5.19
	control	4.77	0.92	3.68	5.89
Corsi Span forward	experimental	5.95	0.67	4.94	6.62
	control	5.12	1.15	3.98	6.66
Corsi Span backward	experimental	4.91	0.87	3.73	6.03
	control	4.78	0.73	4.22	6.03
TMT A	experimental	43.39	24.04	13.9	73
	control	41.04	8.87	35	56
TMT B	experimental	176.33	101.16	40.25	317
	control	94	77.82	2	212
Stroop (time)	experimental	31.55	15.35	13.19	50.75
	control	13.73	21.12	-11	37.5
Stroop (errors)	experimental	1.65	1.799	0	4
	control	0.4	0.652	0	1.5
SDMT	experimental	38.33	7.85	29.5	49.77
	control	45.97	6.77	36.9	53.9
Raven's matrices	experimental	35	2.04	32	36.5
	control	33.92	2.51	31.1	36.5

Table 3.2.1. **Neuropsychological tests used to diagnose the patients.** The table reported the corrected mean scores obtained by the experimental and the control groups. MMSE: Mini Mental State Examination (Measso et al.,1993); Phonemic Semantic fluency (Novelli et al., 1986); Short story (Carlesimo et al.,2002); Digit Span (Monaco et al., 2012); Corsi Span (Monaco et al., 2012); TMT: Trail Making Test, A and B versions (Giovagnoli et al.,1996); Stroop Test (Caffarra et al., 2002); SDMT: Symbol Digit Modalities Test (Nocentini et al., 2006); Raven's matrices, colored version (Basso et al., 1987).

3.2.2 Experimental procedure

The experimental group and the control group differed based on the PA treatment type, whereas all participants were submitted to SG.

PA was carried out either with real prismatic lenses 20º rightwards shifted, for the experimental group, or with sham lenses, for the control group. SG were administered via the "MindLenses" device (https://www.restorativeneurotechnologies.com/mindlenses-dispositivo-medico-riabilitazione-ictus-adhd), which comprises a digital transposition of the PA procedure and seven SG (see paragraph 3.2.3 for details). The MindLenses device (prismatic lenses and tablet) comes with a CE mark, and it was used according to the manual indications.

Both groups performed (i) 2 test sessions, one before and one after the PA treatment, and included the administration of the outcome cognitive tests of the study (see paragraph 3.2.4 for details), (ii) one PA treatment divided in 10 sessions, and (iii) 2 rsfMRI examinations, one before and one after the PA treatment.

The required commitment for each participant consisted of 5 weeks (see Table 3.2.2). The first week was dedicated to the definition of the clinical picture and the recruitment, followed by the acquisition of behavioral and functional baseline data. The following weeks were dedicated to the 10 treatment sessions. During the final week, after the 10th treatment session, patients underwent again the cognitive outcome tests and the rsfMRI scan. All collected data were recorded in the appropriate case report form (CRF).

The stimulation sessions were administered 3 times per week, in 3 consecutive weeks, on Monday, Wednesday, and Friday, and they lasted around 30 minutes each. Finally, rsfMRI examinations were carried out on Wednesdays before the first-week treatment and in the last week, lasting 20 minutes each.

3.2.2.1 Functional data acquisition

The fMRI data were collected via a 1.5 Tesla Philips Achieva, equipped with an Echo-speed gradient and amplification hardware. Patients were asked to lay down without moving, keep their eyes closed, and not to think about anything. Foam padding was used to minimize head movement.

First, spin-echo sagittal images were acquired (Flip angle: 90°, TE: 60msec, TR: 300msec, FOV: 280x280 mm) to visualize the anterior and posterior commissures on the sagittal medial section and to facilitate the data acquisition along the bicommissural plane. The chosen volume included the entire brain and the cerebellum. Secondly, a weighted-T1

anatomical scan was acquired using a 3D-SPGR sequence (Flip angle: 20°, TE: 3.2 msec, TR: 7.2 msec, acquisition matrix: 256x232, slice thickness: 1 mm, interslice gap: 0 mm and voxel dimension: 1x1x1 mm). The volumetric MRI scans included 200 slices acquired on oblique sections parallel to the AC-PC line to cover the entire brain volume. The T1 acquisition time lasted 7 minutes.

Resting state functional images were acquired over a period of 10 minutes. Functional volumes consisted of 35 parallel slices, acquired with a volume TR of 3000 ms, TE 60 ms, matrix size 64x64, FOV 280x280, voxel size 4x4x4 mm, for a total of 200 volumes.

Experimental procedure	T0			T1-T10	T2	
	1st examination (T0a)	2nd examination (T0b)	3rd examination (T0c)	10 days/ 10 sessions	4th examination (T2a)	5th examination (T2b)
Standard neuro-psychological test battery	X					
Checking of inclusion and exclusion criteria	X					
Demographic data collection and anamnesis	X					
Study description and informed consent		X				
Pre-treatment outcome tests		X				
Pre-treatment rs-fMRI			X			
"Mind Lenses" stimulation protocol				X		
Post-treatment outcome tests					X	
Post-treatment rs-fMRI						X

Table 3.2.2. Flowchart of the experimental procedure.

3.2.3 Materials: MindLenses protocol

The first activity of each treatment session was the PA, with real (experimental group) or sham (control group) lenses. This procedure was administered through the MindLenses tablet (Samsung Galaxy Tab A7). Patients were comfortably seated, and the position of the

tablet was at a distance equal to the maximal extension of each participant's arm. During this phase, the patient was asked to point as fast and as accurate as possible to the black squares that randomly appeared at the center, left, or right side of the blank screen. Patients were asked to touch the black squares with the index finger of the right hand, moving from the center of the trunk towards the target in every trial. The pointing phase comprised three conditions: 30 pointings before wearing the prisms (pre-exposure, visible pointings), 90 pointings wearing the (real or sham) lenses (exposure, visible pointing), and 30 pointings after lenses removal (post-exposure, visible pointing). Right after the adaptation phase, patients played the SG.

MindLenses SG consist of 7 games related to three different cognitive areas (see Table 3.2.3). The games are characterized by a dynamic difficulty adjusting mechanism (augmenting or diminishing difficulty), adapting to the patient's performance during gameplay. Specifically, there are four levels of increasing difficulty – from 0 to 3 –, each having its own score multiplier. Correct answers provided during greater difficulty levels ensure a higher score. Before the start of each game, the patient could try an example proof.

Cognitive function involved	**Game's name**	**Game time duration (in seconds)**
Attention	*"Occhio alla bomba"*	200
	"The Cafè"	120
	"Trova l'intruso"	90
Language	*"Associazioni Semantiche"*	90
Executive functions	*"Ragionamento Matematico"*	120
	"Sono uguali?"	90
	"In ordine inverso"	120

Table 3.2.3. Cognitive domains; Serious Games of MindLenses protocols. 1) Mind the bomb 2) The Café 3) Find the outsider 4) Semantic associations 5) Are they the same? 6) Reverse order. 7) Mathematical reasoning; Maximum time (seconds) given to the patient to perform each game.

Specifics of each game is described hereafter:

1) "*Occhio alla bomba"* (Mind the bomb)

This game aims at enhancing patients' ability to:

- Pay attention to stimuli for a long time (sustained attention);

- Pay attention to several stimuli simultaneously (divided attention);
- Inhibit the interference.

Several stimuli (circles, hexagons, hearts, and bombs) fell from the top to the bottom of the screen with increasing number and speed. The patient was asked to touch the target stimuli (circles, hearts, and bombs) only when they entered an indicated target area. On the contrary, they had to ignore the hexagonal stimuli and desist from touching them. The final score corresponded to the number of correctly identified and touched stimuli.

2) "The Café"

This game aims at enhancing patients' ability to:

- Pay attention to several stimuli simultaneously (divided attention);
- Plan their own actions.

Patients were asked to prepare the orders of a coffee shop. Required orders were shown on the screen with increasing difficulty, i.e., of amount and number of requests presented at once. According to the directions received, the participant had to decide which drink to prepare (coffee, milk, chocolate, or mixed drinks) and the quantity (one, two, or three dispenses). The successful completion of more complex orders resulted in a higher score.

3) Trova l'intruso (Find the outsider)

This game aims at enhancing patients':

- Selective attention;
- Visual spatial exploration;
- Ability to inhibit interferences.

Patients were asked to search for the odd-one-out figure within a matrix composed of several identical figures. With the increase in difficulty, more and more similar (to a perceptual level) stimuli were presented. Although the final score corresponded to the number of correct answers, it could vary according to the level of difficulty.

4) "Associazioni semantiche" (Semantic associations)

This game aims at enhancing patients' ability to:

- Perform semantic associations;
- Reason.

Patients were asked to associate professional figures with the most appropriate working tool. With the increase in difficulty, more and more distracting stimuli were presented. Although the final score corresponded to the number of correct answers, it could vary according to the level of difficulty.

5) "Sono uguali?" (Are they the same?)

This game aims at enhancing patients' ability to:

- Inhibit the interference;
- Maintain the attention for a long time (sustained attention);
- Control the impulses.

Patients were asked to focus on the center of the screen, where couples of figures were presented. If the two figures were identical (with respect to shape, color, and texture), they had to press a button. On the contrary, when the two figures were different, they did not have to perform any actions. Each pair of stimuli remained on the screen for 1 second only and there were no breaks between one trial and the other. With increasing difficulty, more and more similar figures were presented. Although the final score corresponded to the number of correct answers, it might vary according to the level of difficulty.

6) "Ordine inverso" (Reverse order)

This game aims at enhancing patients':

- Short-term memory;
- Working memory.

Series of figures were presented, one at a time. Each figure remained on the screen for one second. Patients were asked to remember the order of the presentation of the icons and to reorder them in the reverse order (from the last presented to the first). With the increase of the difficulty, distractors appeared among the list of correct items to select and reorder, and the length of the series was progressively longer. Although the final score corresponded to the number of correct answers, it could vary according to the level of difficulty.

7) "Ragionamento matematico" (Mathematical reasoning)

This game aims at enhancing patients':

- Computing capacity;
- Working memory.

Patients were asked to perform basic calculations, keep the result in mind, and continue to take further calculations, always starting from the last written result. With the increase of the difficulty, more and more complex operations were presented. Although the final score corresponded to the number of correct answers, it could vary according to the level of difficulty.

3.2.4 Behavioral outcome tests

The Free and Cued Selective Reminding Test (FCSRT)-words version (Grober & Buschke, 1987; italian version: Girtler et al., 2015), the Attention Network Test (ANT, Fan et al., 2002), the Modified Taylor Complex Figure (MTCF, Hubley, 1999; italian version: Casarotti et al., 2014), and the Visual Naming test are the neuropsychological and cognitive tests chosen as outcome measures. Moreover, we decided to monitor depression, quality of life, and subjective memory functioning, through the Geriatric Depression Scale 15-items (Sheikh & Yesavage, 1986; italian version: Isella et al., 2002), the Quality of Life in Alzheimer's Disease (QoL-AD, Logsdon et al., 1999; italian version: Bianchetti et al., 2017), and the Prospective and Retrospective Memory Questionnaire (PRMQ, G. Smith et al., 2000), respectively. None of these tests was used during the initial clinical neuropsychological assessment based on which the patients received the diagnosis. These outcome tests were administered to the patients twice, before and after the treatment protocol. The raw score of FCSRT, MTCF, and of the Visual Naming test were corrected considering gender, age, and education level of each participant.

The ANT (see chapter one and figure 3.2.3) was performed on a MacBook Pro using the software "Psychology Experiment Building Language" (PEBL) battery, version 2.1 (website: https://pebl.sourceforge.net). Original English instructions were translated into Italian and simplified. The screen size resolution was 840x525. The task consisted of 24 practice trials, followed by 3 test blocks, each one consisting of 96 trials, for a total of 288 trials. Each trial consisted of 5 events: a fixation period of a random variable duration (400-1600 ms); a warning cue (100 ms); a short fixation period (400 ms), and the target. Targets were presented until the participant responded, but for no longer than 1700 msec. Finally, the post-target fixation period had a variable duration depending on the duration of the first fixation and the patient's RT (3500 ms – 1st fixation – RT). Each trial lasted 4000 ms (Fan et al., 2005).

Once the patient completed the test, the PEBL battery provided the examiner with a TextEdit summary file, including the number of total errors, the mean accuracy, the mean RT, and data corresponding to the 3 measured variables (alerting, orienting, executive control). These data included the obtained scores for each subcomponent (total trials and only correct ones), median, means, and SD for each condition.

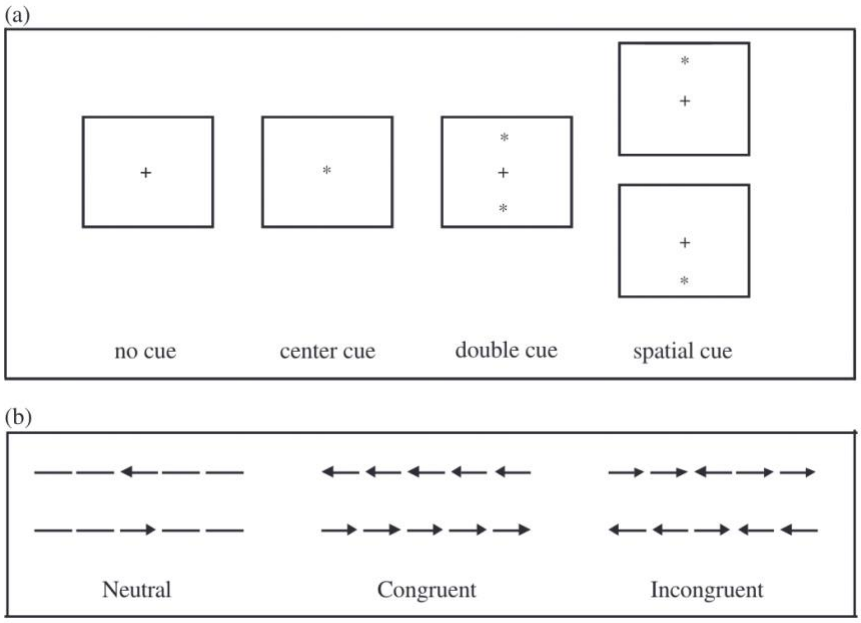

Figure 3.2.3. ANT experimental procedure from Fan et al., 2002.
a) The four cue conditions; b) The six stimuli used in the present experiment (Fan et al., 2002b)

3.3 Statistical analysis

3.3.1 Study design

The study is a RCT aimed at investigating changes in behavioral and neurofunctional responses in patients with single- and multiple-domain aMCI, following a cognitive stimulation program using prismatic lenses and SG.

The study presents a 2x2 research design with Time (Pre *vs.* Post treatment; within-subjects) and Group (Real *vs.* Sham, between-subjects) as factors.

3.3.2 Behavioral data

Behavioral data of each outcome test and PA were analyzed using JASP Statistical Software (Version 0.18.1 intel, available online at: https://jasp-stats.org/).

Data have been analyzed using a 2x2 repeated measures analysis of variance (ANOVA). Raw scores of FCSRT-words, MTCF, and Verbal Naming test were corrected using canonical procedure of neuropsychological tests correction, which encompasses the comparison with a normative sample available in the literature (Lezak et al., 2012). Thus, corrected scores were taken into consideration for the analysis. For the ANT, we analyzed RTs, numbers of errors, as well as alerting, orienting, and executive control scores of the corrected items.

PA data were extracted transforming pixel data into centimeters using the following formula: cm = pixel*(2.54/224). We checked for hardware recording errors, excluding negative RTs

(<0) and pointing deviations larger than 4 cm. Then, to determine whether the digital PA was effective, the deviations means (in cm) from the target in the x-axis was considered and compared in the following conditions: pre-exposure (mean of the 30 trials of the pre-adaptation phase), early-exposure (mean of the first 3 trials of the adaptation phase), and late-exposure (mean of the last 3 trials of the adaptation phase) (Turriziani et al., 2021). Data were analyzed through a Linear Mixed Model with deviations means as dependent variable and Condition (Real *vs.* Sham), Time (three exposure phases) and Sessions (1 to 10) as factors.

Lastly, we decided to investigate whether there were differences between the groups during the course of the treatment, thus we used a 2x2 repeated measures analysis of variance (ANOVA) to compare the mean score of each Serious Game: Group (Real *vs.* Sham) and Sessions (First two *vs.* Last two) were the main factors. Because of the difficulty and the excessively high speed of the "Sono uguali?" (Are they the same?) game, considering that no patient was able to perform the task within the required time to ensure that the actual correct responses were recorded, the scores of this game were not considered in the analysis.

3.3.3 Functional data

rsfMRI data were analyzed using the connectivity Toolbox software CONN (18th version, MathWorks, Natick, MA, USA) and SPM 12.7771 (Penny et al., 2011; Whitfield-Gabrieli & Nieto-Castanon, 2012), implemented in MATLAB Version: 9.7 (R2019b).

Preprocessing. Functional and anatomical data were preprocessed using a preprocessing pipeline including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, indirect segmentation, and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign & unwarp procedure, where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data (acquired in ascending order) was corrected following SPM slice-timing correction (STC) procedure, using sinc temporal interpolation to resample each slice BOLD timeseries to a common mid-acquisition time. Potential outlier scans were identified using ART as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations, and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were coregistered and normalized into

standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following an indirect normalization procedure using SPM unified segmentation and normalization algorithm with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 5 mm full width half maximum (FWHM).

Denoising: Functional data were denoised using a standard denoising pipeline including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors), outlier scans (below 102 factors), session and task effects and their first order derivatives (4 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries between 0.008 Hz and 0.09 Hz. CompCor noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 95.4 to 169.2 (average 145.7) across all subjects.

First-level analysis. ROI-to-ROI connectivity (RRC) matrices were estimated characterizing the functional connectivity between each pair of regions among 8 HPC-ICA network ROIs. Selected ROIs were (i) four nodes of the DMN: LP right and left, PCC, and MPFC, and (ii) four nodes of the DAN: IPS right and left, FEF right and left. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a general linear model (weighted-GLM), estimated separately for each pair of ROIs, characterizing the association between their BOLD signal timeseries. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

Group-level analyses were performed using a General Linear Model (GLM). For each individual connection a separate GLM was estimated, with first-level connectivity measures at this connection as dependent variables (one independent sample per subject and one measurement per experimental condition), and groups or other subject-level identifiers as independent variables. Connection-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of similar connections). Cluster-level inferences were based on parametric statistics

within- and between- each pair of networks (Functional Network Connectivity), with networks identified using a complete-linkage hierarchical clustering procedure based on ROI-to-ROI anatomical proximity and functional similarity metrics. Results were thresholded using an uncorrected $p < 0.05$ at the connection-level. This choice was due to the limited sample size. Yet, for the sake of completeness, we also report p-FDR at the cluster level corrected results.

3.4 Results

3.4.1 Behavioral results

Prismatic adaptation

Digital PA was effective in the Real group compared to the Sham group, as emerged from the comparison between the different exposure phases deviations. Indeed, pre-exposure and early-exposure deviations were significantly different in the Real group, compared to the Sham group, with a significant Group*Time interaction ($F(1,8.02) = 9.49$, $p = 0.015$), indicating that the deviation was larger for the Real group in the early-exposure phase (M Real = 0.44±0.41) compared to both the pre-exposure phase (M Real = -0.02±0.14 *vs.* M Sham = 0.01±0.11) and the Sham group in the same early-exposure phase (M Sham = 0.05±0.18) (Figure 3.4.1a). We also found a significant main effect of Time ($F(1,8.02) = 12.99$, $p < 0.01$), and a main effect of Group ($F(1,8.03) = 8.36$, $p = 0.02$), while Session seemed not to influence the results ($F(9,15.86) = 2.03$, $p = 0.11$).

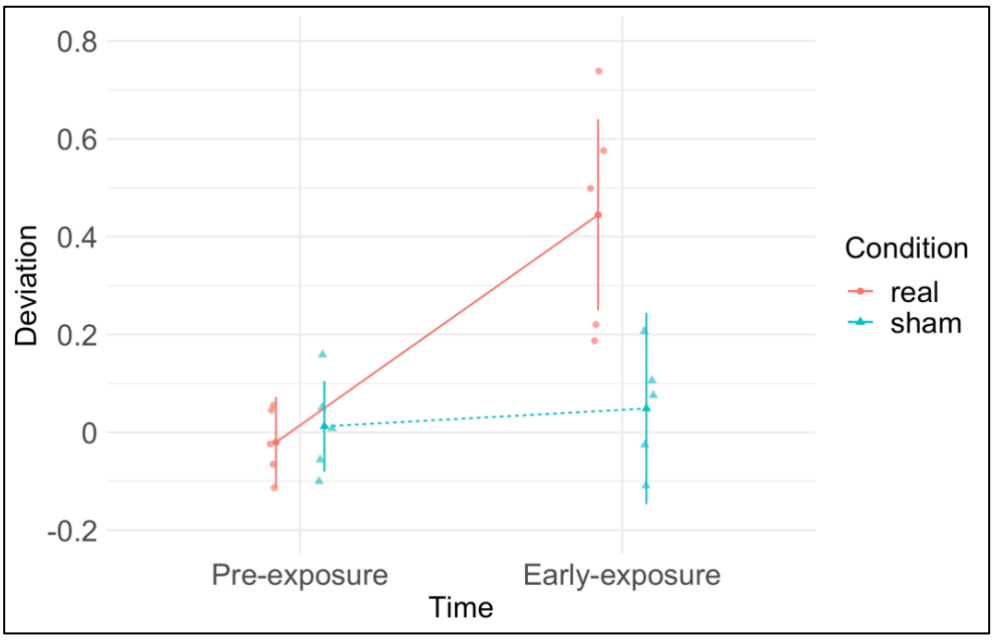

Figure 3.4.1a Deviation means in cm in the pre-exposure and in the early-exposure phases, of Real and Sham groups, during prismatic adaptation.

The same results were found when comparing early *vs.* late exposure deviations, with a significant main effect of Time ($F(1,8.24) = 21.00$, $p = 0.002$) and Group ($F(1,7.83) = 5.62$, $p = 0.05$), as well as a significant interaction Group*Time ($F(1,8.24) = 5.17$, $p = 0.05$), meaning that the deviations differences in the early-exposure phase (M Real = 0.44±0.41 vs. M Sham = 0.05±0.18) dissipated in the late-exposure phase (M Real = -0.05±0.47 vs. M Sham = -0.12±0.26) (See Figure 3.4.1b). No effect of Session ($F(9,18.23) = 0.55$, $p = 0.83$) was found.

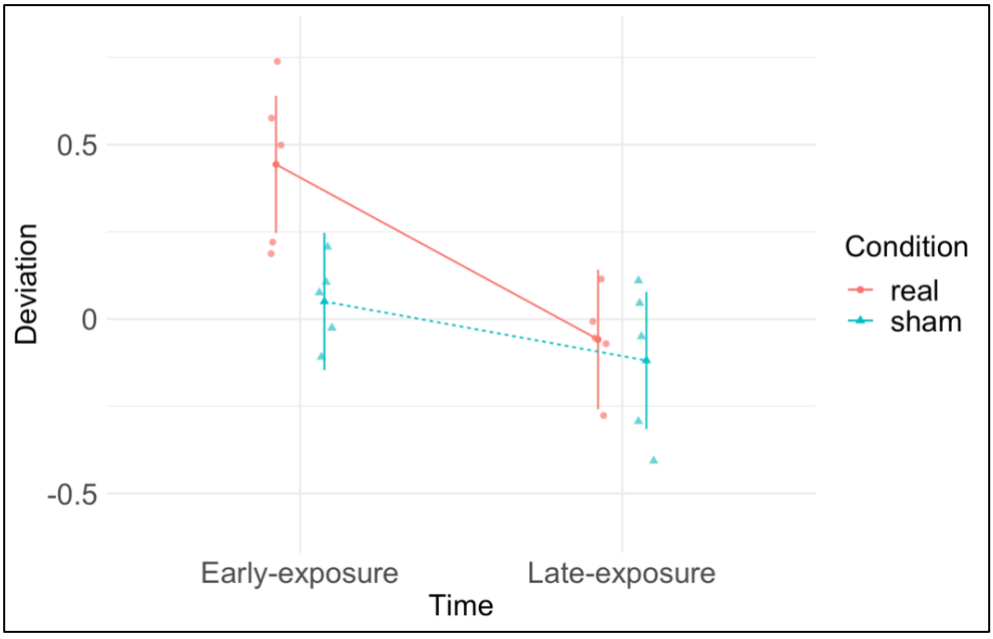

Figure 3.4.1b. Deviation means in cm in the early-exposure and in the late-exposure phases, of Real and Sham groups, during prismatic adaptation.

The above results suggest that only the group who used real lenses deviated rightwards from the target in the early phases of exposure, and then adapted to the shifting, which is in line with what expected during traditional PA. On the contrary, the Sham group remained accurate towards the target in all phases (see Figure 3.4.1c).

Finally, it is worth noting that there was no effect of Session, indicating that the effects are consistent between the 10 adaptation sessions.

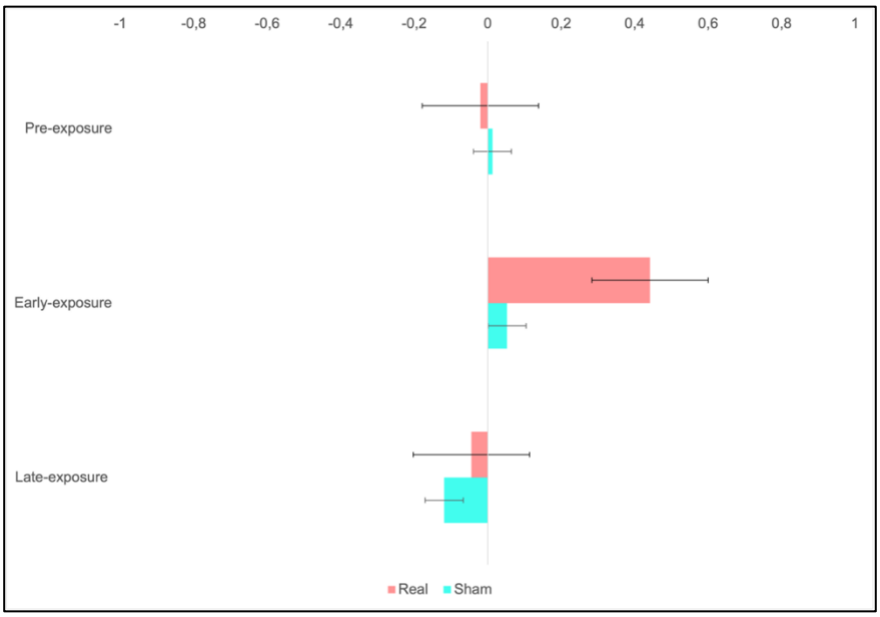

Figure 3.4.1c. X axis: Deviation means from 0 (accuracy) in cm, across the three exposure phases of prismatic adaptation procedure.

Cognitive tests

FCSRT-words. No difference between Pre (M Real = 11.59±6.732; M Sham = 13.40±3.01) and Post (M Real = 13.19±7.34; M Sham = 14.73±2.97) treatment was found in the immediate recall phase of the FCSRT test (F (1,8) = 2.472, *p* = 0.155). We checked for differences at baseline by comparing Real and Sham groups FCSRT immediate scores at the Pre treatment. An independent sample t test did not yield a significant result (t(8) = -0.55, *p* = 0.597). Likewise, no significant main effect of Group (F(1,8) = 0.261, *p* = 0.155) nor a significant interaction Time*Group (F(1,8) = 0.021, *p* = 0.887) were found (See Figure 1).

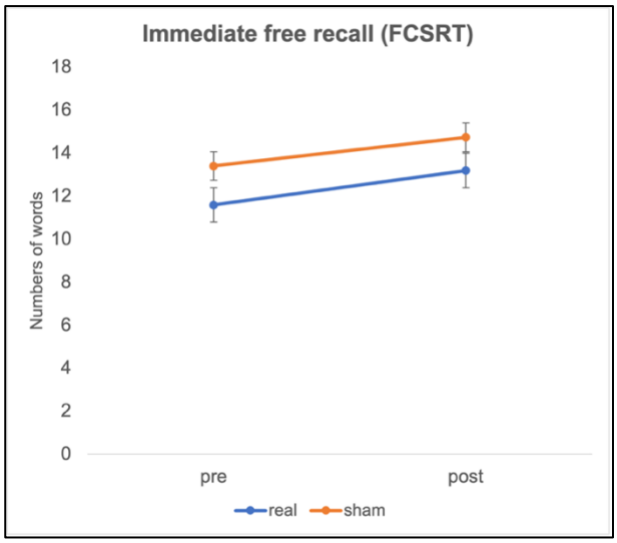

Figure 1. Comparison between Real and Sham groups in the Pre and Post treatment. Y axis = numbers of retrieved words in the Immediate Free Recall of the FCSRT. Bars are Standard Error.

Conversely, in the delayed recollection phase, there was a significant main effect of Time ($F(1,8) = 23.516$, $p = 0.001$, $\omega^2 = 0.061$) as well as a significant interaction Time*Group ($F(1,8) = 10.245$, $p = 0.013$, $\omega^2 = 0.026$), indicating that the Sham group recollected more words Post treatment (M = 7.72±3.03) than Pre treatment (M = 4.79±3.09), while the Real group did not significantly change between Pre (M = 3.68±3.65) and Post (M = 4.28±4.40). No main effect of Group was found ($F(1,8) = 1.031$, $p = 0.34$) (See Figure 2).

Post-hoc comparison confirmed that there was no difference between groups at baseline (Pre: M difference = -1.11, t = -0.49, $p = 1.00$), nor after treatment (Post: M difference = -3.44, t = -1.52, $p = 0.99$). No other significant differences emerged.

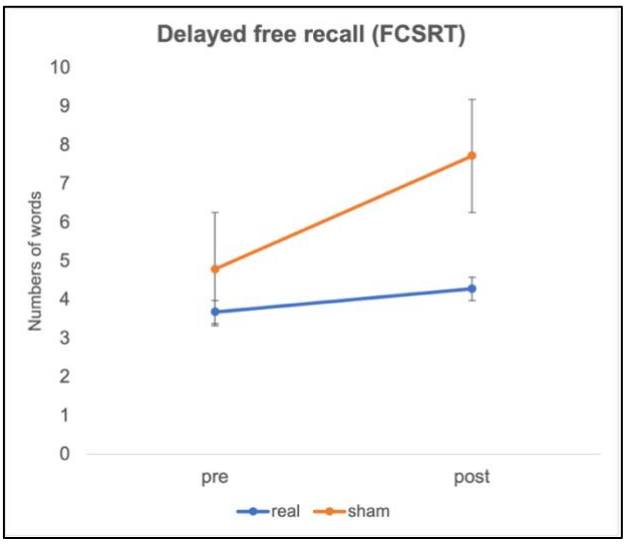

Figure 2. Comparison between Real and Sham groups in the Pre and Post treatment conditions. Y axis = numbers of retrieved words in the Delay Free Recall of the FCSRT. Bars are Standard Errors.

ANT. Reaction Times at the ANT were reduced significantly after the treatment in both groups (Time: $F(1,8) = 10.096$, $p = 0.013$, $\omega^2 = 0.285$). No effect of Group ($F(1,8) = 0.193$, $p = 0.672$) nor interaction between Group*Time ($F(1,8) = 0.220$, $p = 0.651$) were found, meaning that the reduction in RTs did not depend on Group and that the Real group (Pre: M = 908.58±103.63; Post: M = 772.168±72.40) did not improve significantly more than the Sham group (Pre: M = 959.58±196.80; Post: M = 775.91±97.36) (see Figure 3).

Also, we could observe a decrease in the number of errors from Pre (M Real = 28.8±40.15; M Sham = 29±33.64) to Post (M Real = 10.4±8.05; M Sham = 9.80±11.01) treatment in both groups, but such decrease didn't reach significance (Time, $F(1,8) = 2.82$, $p = 0.132$; Group, $F(1,8) = 2.39e^{-4}$ $p = 0.99$; Time*Group, $F(1,8) = 0.001$, $p = 0.97$) (see Figure 4).

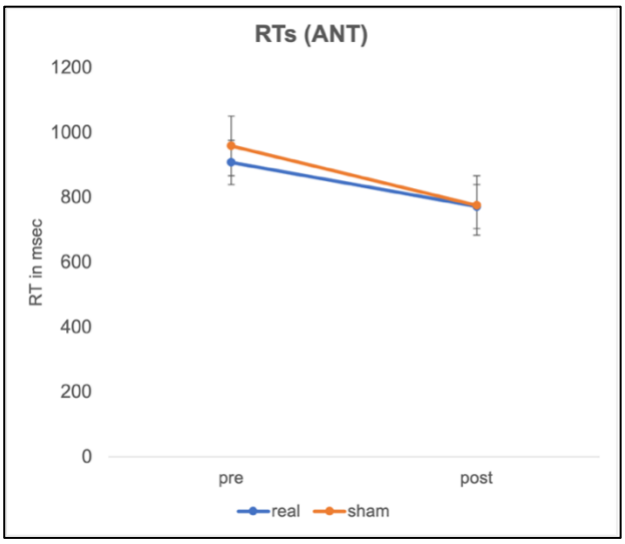

Figure 3. Comparison between RTs in msec for the Real and Sham groups, Pre and Post treatment. Bars are Standard Errors.

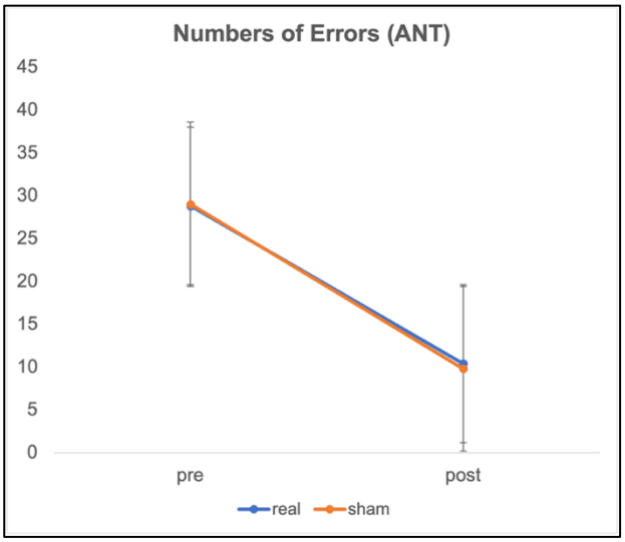

Figure 4. Comparison between numbers of errors for the Real and Sham groups, Pre and Post treatment. Bars are Standard Errors.

For what concerns the executive control index, neither the interaction between Group*Time ($F(1,8) = 0.67$, $p = 0.44$) nor the main effects (Time: $F(1,8) = 0.87$, $p = 0.38$; Group: $F(1,8) = 1.74$, $p = 0.22$) reached significance. However, it is worth noting a greater decreasing after the treatment in the Real group (Pre: M = 264.19±344.07, Post: M = 139.06±32.64 compared to the Sham group (Pre: M = 95.83±33.19; Post: M = 87.37±11.85), despite not statistically relevant (see Figure 5).

The alerting and orienting components did not yield significant results, either, with respectively *alerting*: Time, $F(1,8) = 0.44$, $p = 0.53$; Group, $F(1,8) = 0.50$ $p = 0.50$; Time*Group, $F(1,8) = 0.76$, $p = 0.41$; and *orienting*: Time, $F(1,8) = 0.41$, $p = 0.54$; Group, $F(1,8) = 8.88$ $p = 0.02$, $\omega^2 = 0.304$; Time*Group, $F(1,8) = 1.07$, $p = 0.33$. This last result

regarding the *orienting*, with the main effect of Group, is explained by Post-Hoc tests, that unfortunately show a difference at baseline which prevents from take the result into consideration (Pre: M Real = -18.09±35.70; M Sham = 38.16±7.12; Mean difference = -56.25, t = -2.87, p = 0.06).

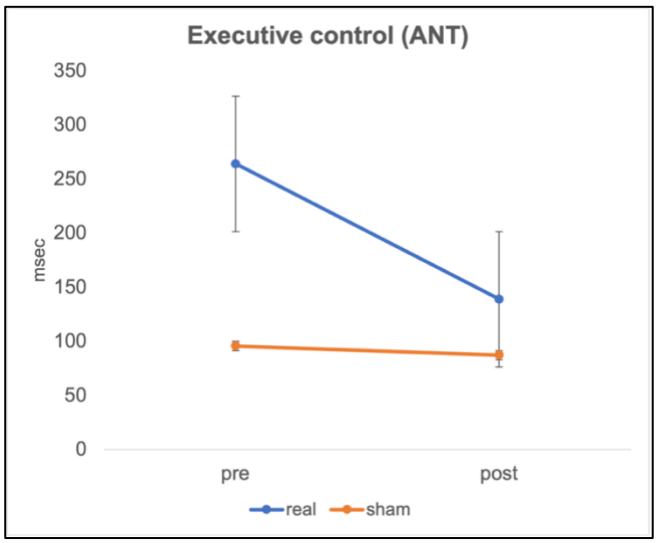

Figure 5. Comparison between the executive control index for the Real and Sham groups, Pre and Post treatment. Bars are Standard Errors.

MTCF and Verbal naming test. No significant results were found for either copy (Time: F(1,8) = 3.12, *p* = 0.12; Group: F(1,8) = 2.74, *p* = 0.14; Time*Group: F(1,8) = 0.42, *p* = 0.54) or delayed recall (Time: F(1,8) = 2.56, *p* = 0.15; Group: F(1) = 0.12, *p* = 0.74; Time*Group: F(1,8) = 0.84, *p* = 0.39) of the Modified Taylor Complex Figure. Moreover, the Verbal naming test did not change either after the treatment (Time: F(1,8) = 0.78, *p* = 0.40; Group: F(1,8) = 0.27, *p* = 0.62; Time*Group: F(1,8) = 0.44, *p* = 0.53). Descriptive statistics of the two tests are reported in Table 1.

Taylor – copy			Taylor – delayed recall			Verbal naming test		
Time	Condition	Mean	Time	Condition	Mean	time	Condition	Mean
post	real	35.340	post	real	9.340	post	real	58.600
	sham	33.480		sham	8.840		sham	60.800
pre	real	33.624	pre	real	6.040	pre	real	58.400
	sham	29.780		sham	7.940		sham	59.400

Table 1. Descriptive statistics of the results Pre and Post treatment, of the Real and Sham groups. Means refer to corrected score at the MTCF test and Verbal naming test.

Questionnaires. Geriatric Depression Scale (Time: F(1,8) = 0.34, *p* = 0.58; Group: F(1,8) = 0.91, *p* = 0.37; Time*Group: F(1,8) = 0.12, *p* = 0.74), Quality of Life in Alzheimer Disease

(Time: F(1,8) = 1.67, p = 0.23; Group: F(1,8) = 0.23, *p* = 0.64; Time*Group: F(1,8) = 1.67, *p* = 0.23), and Prospective and Retrospective Memory Questionnaire (Time: F(1,8) = 1.65, *p* = 0.23; Group: F(1,8) = 3.29e-4, *p* = 0.99; Time*Group: F(1,8) = 2.96, *p* = 0.12) remained stable across Group and Time (all *p* > 0.05). Descriptive statistics of the three questionnaires are reported in Table 2.

a) GDS

Time	Condition	Mean
post	real	2.800
	sham	4.400
pre	real	2.600
	sham	3.600

b) QoL - AD

Time	Condition	Mean
post	real	35.400
	sham	34.800
pre	real	37.400
	sham	34.800

c) PRMQ

Time	Condition	Mean
post	real	32.000
	sham	40.800
pre	real	47.200
	sham	38.600

Table 2. Descriptive statistics of the results Pre and Post treatment, of the Real and Sham groups. a) Geriatric Depression Scale; b) Quality of Life in Alzheimer's Disease; c) Prospective and Retrospective Memory Questionnaire.

Serious Games scores

Both groups significantly improved in all games apart from *Mind the bomb* (Sessions: F(1,8) = 3.32, *p* = 0.11; Group: F(1,8) = 1.08, *p* = 0.33; Sessions*Group: F(1,8) = 0.04, *p* = 0.85), which remained stable across sessions. Interactions between Sessions and Group did not reach significance in any of the games: *The Café* (Sessions: F(1,8) = 22.73, *p* = 0.001, ω^2 = 0.36; Group: F(1,8) =, *p* = 0.69; Sessions*Group: F(1,8)= 1.59, *p* = 0.24); *Find the outsider* (Sessions: F(1,8) = 12.13, *p* = 0.008, ω^2 = 0.272; Group: F(1,8) = 0.37, *p* = 0.56; Sessions*Group: F(1,8) =0.054, *p* = 0.82); *Semantic associations* (Sessions: F(1,8) = 9.24, *p* = 0.02, ω^2 = 0.19; Group: F(1,8) = 0.024, *p* = 0.88; Sessions*Group: F(1,8) = 0.48, *p* = 0.51); *Reverse order* (Sessions: F(1,8) = 11.51, *p* = 0.009, ω^2 = 0.23; Group: F(1,8) = 0.26, *p* = 0.62; Sessions*Group: F(1,8) = 2.53, *p* = 0.15); *Mathematical reasoning* (Sessions: F(1,8) = 9.06, *p* = 0.02, ω^2 = 0.182; Group: F(1) = 0.08, *p* = 0.79; Sessions*Group: F(1,8) = 0.662, *p* = 0.44).

Plots depicting changes between initial and final sessions of each game are reported in Figure 6. Table 3 reports descriptive statistics.

GAME	**SESSIONS**	**First two**		**Last two**	
	CONDITION	Real	Sham	Real	Sham
Mind the bomb	***Mean***	28.20	29.90	33.40	36.40
	SD	7.96	6.57	6.43	2.49
The café	***Mean***	21	19.80	29.20	33.90
	SD	3.59	5.61	4.51	13.06

Find the outsider	***Mean***	14.40	15.90	19.20	20.10
	SD	3.65	3.21	4.13	3.83
Semantic associations	***Mean***	4.60	5.50	8.10	7.70
	SD	2.04	1.23	5.18	1.53
Reverse order	***Mean***	11.20	10	14.20	18.30
	SD	6.14	1.77	6.93	4.45
Mathematical reasoning	***Mean***	16.20	15.40	21.60	24.80
	SD	5.76	3.73	12.78	5.66

Table 3. Means and Standard Deviations (SD) of the scores in the first two sessions, and in the last two sessions, of the six Serious Games taken into consideration, divided for the Real and the Sham groups.

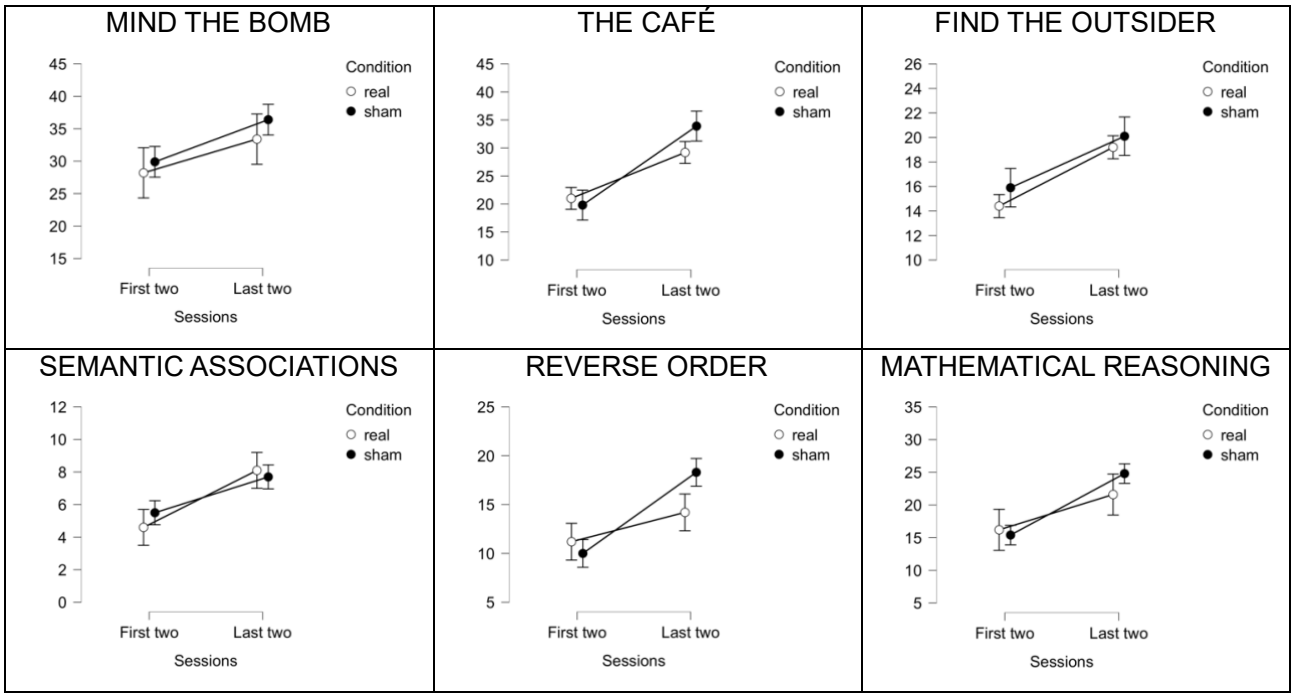

Figure 6. Plots of the scores in the first two sessions and in the last two sessions, divided for the Real and the Sham groups. Higher scores correspond to better performances.

To sum up, after 10-sessions treatment, we found an amelioration in both groups in the FCSRT-Delayed recall and in the ANT, in terms of reduction of RTs. These changes present a main effect of Time, meaning that there is no difference due to the experimental group, but a general improvement of both Real and Sham groups. Likewise, we can observe that during the treatment, both groups significantly improved in the SG across the sessions.

For what concerns memory tests, neither the FCSRT-Immediate recall, nor the MTCF improved after the treatment. Also, all other tests and questionnaires remained stable.

3.4.2 Neurofunctional results

We explored changes in resting-state connectivity between the two groups (Real > Sham) after the treatment (Post > Pre). Before doing so, we made sure that differences in brain

atrophy would not interfere with the results. Thus, we extrapolated, after segmentation, the grey-matter volume for each participant and ran an independent sample t-test between Real and Sham groups. Grey-matter did not differ between groups (t(8) = 0.36, *p* = 0.73), thus we proceeded with the planned analyses.

Based on CONN templates, we had selected 4 brain regions in the DMN and 4 in the DAN as ROIs. The DMN includes the left and right paracentral lobules (l-LP and r-LP), medial prefrontal cortex (MPFC), and posterior cingulate cortex (PCC); the DAN includes the left and right frontal eye fields (l-FEF and r-FEF) and left and right intraparietal sulcus (l-IPS and r-IPS) (see Figures 7 and 8). The ROI-to-ROI analysis identified a difference between groups (Real > Sham) after the treatment (Post > Pre), with uncorrected $p < 0.05$ at connection level and no *p*-FDR at cluster level thresholding. We found:

- one positive connection within DMN, specifically between r-LP (MNI coordinates: 47, -67, 29) and PCC (MNI coordinates: 1, -61, 38), with a larger increase in connectivity in the Real group compared to the Sham group after the treatment (T(8) = 2.55, *p*-unc = 0.034, *p*-FDR = 0.48);
- one negative connection between DMN and DAN, specifically between MPFC (MNI coordinates: 1, 55, -3) and r-IPS (MNI coordinates: 39, -42, 54), indicating greater anti-correlation in the Real group compared to the Sham group after the treatment (T(8) = -3.45, *p*-unc = 0.008, *p*-FDR = 0.48).

Connectogram to visualize resting-state functional connectivity between ROIs is shown in Figure 9. The above results, albeit preliminary, reflects the potential neurofunctional effects of PA.

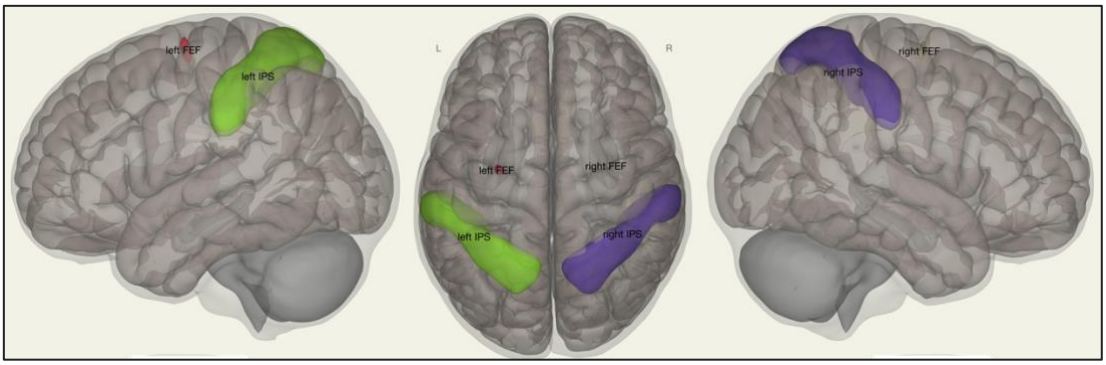

Figure 7. Dorsal Attention Network node location in resting Networks: four main nodes of the network are selected, and their locations are shown in the figure.

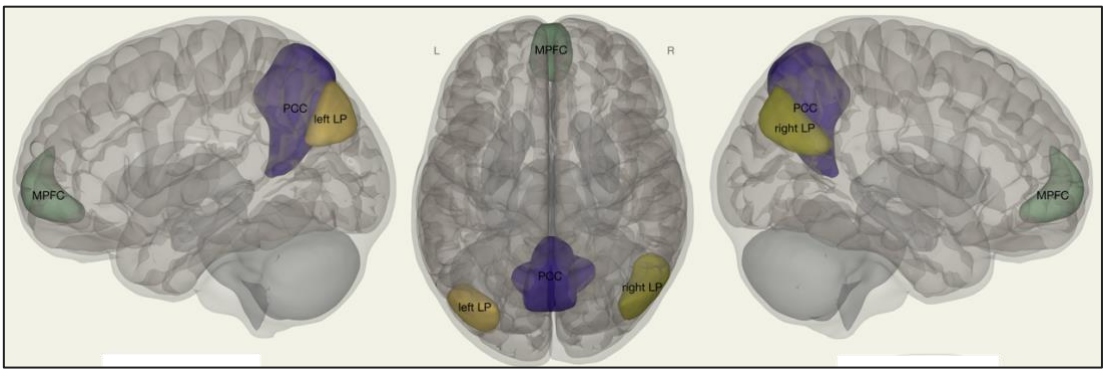

Figure 8. Default Mode Network node location in resting Networks: four main nodes of the network are selected, and their locations are shown in the figure.

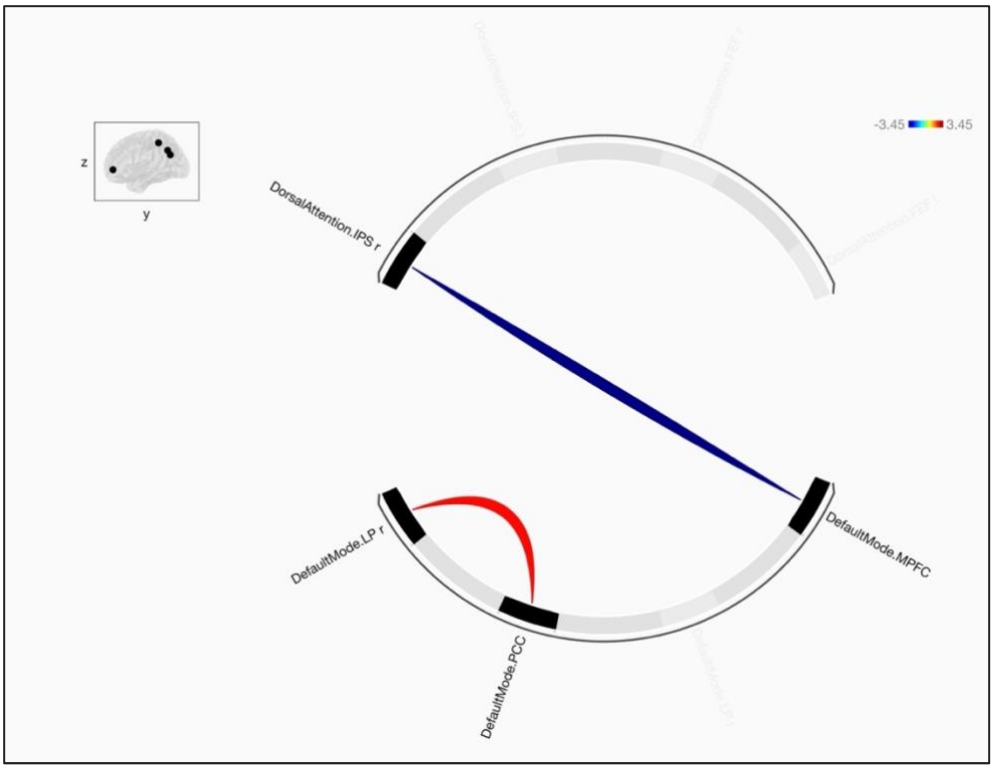

Figure 9. Connectome map of changes in resting state connectivity after the treatment, ROI-to-ROI analysis. IPS r = Intraparietal sulcus right; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; LP r = paracentral lobule right. Color scale represents t-values.

4. Discussion

The main goal of this Study was to explore whether PA associated with SG (MindLenses protocol) could positively impact cognitive functions in patients with single and multiple-domain aMCI, both behaviorally and functionally. Particularly, our research question was to investigate whether PA might have a neuromodulatory effect on cognitive stimulation, in terms of enhancing the effectiveness of SG alone.

Since the MindLenses protocol involves a digital transposition of PA, in the first place it was crucial to confirm that patients in the Real group adapted effectively to the prismatic lenses. The PA technique relies on the theoretical premise that, in situations where the interaction with an environment is consistently changing and the original parameters of reaching behavior are altered, individuals gradually develop compensatory adjustments in visuo-motor coordination. Thus, to ensure that the anticipated compensation and adaptation occurred, the mean accuracy of pointings during the baseline (pre-exposure phase), early exposure, and late exposure were compared. If patients in the Real group adapted to the prismatic lenses, an attention shift towards the right visual hemifield should be evident. Consequently, rightwards deviations in the initial pointings immediately after wearing the lenses (early exposure phase) should be observed. Moreover, as successive trials are performed, the rightwards shift error should gradually be compensated and reduced to pre-exposure levels. In contrast, rightwards deviations should not be observed in patients who wore neutral lenses (Sham group). Our results confirmed these theoretical premises, showing a statistically significant difference between the mean deviations at early and late exposures only in the Real group, namely the mean deviations during early-exposure were larger and rightwards deviated than those during late-exposure, which were accurate. No differences were detected between pre-exposure and late-exposure phases in both groups. Moreover, since we implemented a 10-session treatment, it was important to ensure that the progression in the number of sessions did not influence the prism's effectiveness; the results indicated that the mean deviations in pointings were consistent between the 10 adaptation sessions.

This initial result has important implications. First of all, since PA traditionally requires a non-easily transportable setup, proving that the effect of prismatic lenses can be observed and can be effective if administered via a tablet introduces opportunities for more accessible and ecologically valid rehabilitation procedures, even feasible at the patient's bedside. Second, considering the age of our patients, it's worth noting that a technology-based rehabilitation involving PA has been feasible with an old population.

After confirming adaptation to the real lenses, analyses of neuropsychological tests were run to determine the impact of the rehabilitation protocol on patients' cognitive performance. Focusing on the FCSRT, the cognitive stimulation intervention significantly improved episodic long-term memory in all patients, as evidenced by a significant main effect of Time in the Delayed Free Recall. Moreover, the significant interaction between Time and Condition suggests that the Sham group, but not the Real group, ameliorated after

treatment, suggesting that prismatic lenses might have had an interfering effect, in contrast with our hypotheses. Yet, considering the small sample size, these results need to be taken cautiously.

Analyzing the ANT, a significant main effect of Time was found for the RTs, suggesting that both groups significantly reduced their response time after the cognitive stimulation intervention. This hints to the fact that the treatment with SG facilitated their overall reactivity and concentration, independently from the use of real or sham lenses. No statistically significant effects were found for the numbers of errors, neither for the attention subcomponents, indicating that both group performances remained stable after stimulation concerning the percentage of wrong answers, the capacity to increase vigilance and response readiness, and the ability to monitor and resolve conflict between cognitive processing.

No significant effects were found for the direct and the delayed copy of the Modified Taylor Complex Figure, indicating that the stimulation program did not affect patients' visuo-spatial abilities nor visual memory. No significant effects were found for the Visual Naming Test, suggesting that the linguistic abilities of both groups did not change from Pre to Post intervention, nor for the questionnaires that investigated patients' affective states, Quality of Life, and subjective perception of memory processes.

Since the effectiveness of a rehabilitation program can be observed also by the progress patients achieve as the sessions advance, we opted to compare the scores obtained in SG during the first (two) sessions with those in the final two. Results showed an improvement obtained by all patients in those games involving divided attention, planning, visuo-spatial exploration, semantic associations, and working memory.

In summary, improvements due to the intervention were already observed during the treatment sessions and then confirmed by the outcome tests in long-term episodic memory, overall concentration, and attentive reactivity, in all patients.

Although the significant positive outcomes are a few, considering that our clinical population is susceptible to progressive cognitive decline, it is worth noting that no worsening in patients' cognitive performance occurred after the 5-week study. Yet, we are equally aware that 5 weeks might be a too short period to detect a decline in cognitive abilities; this limitation could be addressed in the future by recruiting a control population, i.e., other MCI patients tested after a 5-week interval without undergoing any kind of treatment. This would help establish whether the observed improvements and the stability of other cognitive variables taken into consideration in this Study are attributable to the relatively short time

elapsed or to the treatment itself. However, the ethical implications of an experimental paradigm that involves patients without administering available treatments should be taken into consideration. Furthermore, this type of paradigm would go beyond our current aims, addressing a different research question compared to the one of the present Study, which aimed at investigating whether PA can modulate cognitive stimulation.

The other variable that we focused on in our study was the modulation of digital PA at the neurofunctional level. We based our hypotheses on the evidence in the literature of a reduction in the anti-correlation between the DMN and DAN in MCI patients compared to healthy individuals, and of PA in strengthening this anti-correlation in healthy subjects. Thus, we expected to observe an increase in this anti-correlation only in the group of patients who underwent the treatment with Real lenses. In line with our hypotheses, we found a greater anti-correlation in the Real group compared to the Sham group, when comparing connectivity changes after the treatment between the two groups. Specifically, the anti-correlation emerged between the right IPS and the MPFC, one node of the DAN and one of the DMN, respectively. It's interesting that these very preliminary results are in line with our initial hypotheses on the neurofunctional effect of PA in patients with MCI, even though not mirrored at behavioral level.

The limited outcomes at both behavioral and neurofunctional level could be also due to the very small size of the sample recruited so far. Confirming the hypothesis that the combination PA+SG has a significant positive effect compared to SG alone will, thus, require waiting until the entire group of 40 patients has undergone the program.

The discussed results underscore the efficacy of non-specific domain training, with significant improvements observed in some of the tests assessing both memory and attention. Following the literature analyzed in the previous chapters, the use of SG that stimulate various cognitive functions should lead concurrently to overall cognitive improvements and, consequently, enhanced mood and quality of life. The assumption is that, by the end of the project and with the recruitment of the planned sample size, these primary and secondary objectives should be reached.

CHAPTER FOUR - Experimental Study 2

In this chapter I will present an experimental project that has been carried out at University of Pavia, in which we tested healthy older participants (N = 20), to investigate whether a single session of Prismatic Adaptation (PA) could modulate attention as measured through ANT (Study 2.1).

Furthermore, we selected 12 participants of this sample, who were matched with the 12 patients of the previous study (see Chapter Three), in order to compare their performance at ANT at baseline (i.e., Pre treatment) (Study 2.2).

The study's procedures are in accordance with the 1975 Helsinki Declaration and the project was approved by the Ethical Committee of the University of Pavia.

4.1 Introduction and Rationale

Recent neuropsychological models concerning attention predict its parcellation into three main subcomponents: alerting, orienting, and executive control (Fan et al., 2002a; McDonough et al., 2019; Posner & Petersen, 1990). As argued in the previous chapters (see paragraph 1.3 and 1.4), the ANT, through the assessment of the efficiency of these subcomponents, could be useful in detecting early stage of cognitive deterioration (Van Dam et al., 2013). However, it has been shown that these attentional subcomponents can decline independently over the lifespan. For example, in healthy elder individuals, some studies have shown changes only in the alerting and executive control components, as compared with younger participants (Mahoney et al., 2010). Nevertheless, the direction of these changes remains unclear, as some studies demonstrate larger alerting in the elderly (Fernandez-Duque et al., 2006), while others find reduced alerting in the same population (Gamboz et al., 2010; Jennings et al., 2007). At the same time, selective alteration of executive control has been observed in patients with aMCI (see chapter 1.3). Thus, as previously discussed, it is crucial to investigate and explore the evolution and the alterations in these attentional components among both healthy and pathological elderly, in order to both prevent cognitive decline and implement cognitive rehabilitation or stimulation interventions.

Among intervention for neuromodulation, there is evidence that PA modulates visuo-spatial attention and resting-state functional connectivity of DAN and DMN (see chapter 2.3), central nodes for attentive functions, in young healthy subjects. Some studies highlight a difference between groups of elderly and young subjects during PA procedure: indeed, the

elderly seem to adapt more slowly during PA, and they also exhibit more persistent after-effects (Fernández-Ruiz et al., 2000). However, the influence of PA on the three attentional subcomponents has not been systematically investigated. To the best of our knowledge, the only study that combined the examination of orienting and alerting in healthy elderly individuals with the study of PA is that of Kintzel and colleagues (2015). Their study attempts to understand whether auditory alerts can have a facilitatory effect during PA itself, guiding orienting, and what implications there may be in terms of improvement in visuo-motor abilities (Kintzel et al., 2015). However, Kintzel's study uses an auditory version of the ANT, and it does not assess the direct effect of PA on the modulation of attentional subcomponents.

Thus, in light of inconsistent results regarding the evolution of the three attentional networks with aging, along with the proven utility of PA in rehabilitating visuo-attentional and visuo-spatial disorders with a potentially different effects on young and elderly individuals, this study aims at investigating the effects of PA on the three attentional subcomponents in healthy elderly subjects. The hypothesis is that PA may be beneficial in supporting attention even in healthy elderly individuals.

STUDY 2.1

4.2 Procedures and methods

4.2.1 Participants

Twenty volunteers were recruited through informative flyer distribution about the study at "UNITRE" (University of the Third Age) in Pavia and gave their consent to participate. Exclusion criteria were (i) age < 60 or > 90, (ii) the presence of a diagnosed psychiatric or neurological disorder, (iii) untreated primary sensory disorders or worsening sensory disturbances (i.e., not-corrected vision and hearing impairments), and (iv) a deficit score at MoCA test (MOntreal Cognitive Assessment, Nasreddine et al., 2005; italian version: Conti et al., 2015) or FCSRT - Picture version (Grober & Buschke, 1987; italian version: Frasson et al., 2011). Since a participant declared after the testing to have a developmental dyslexia, evidenced by an extremely elevated number of errors at the task, that one participant was excluded from the analyses. Thus, the final sample included 19 participants (9 females, 10 males, Mean age = 71.63±6.64 (min. 62, max. 90); Mean education level = 14.05±4.48 (min. 5, max. 21)). Participants were randomly assigned to the experimental (N = 10, 5 females) or the control group (N = 9, 4 females) (see Table 4.2.1 for descriptives).

	Condition	Mean	SD	Min.	Max.
Age	experimental	71.30	5.74	64	83
	control	72	7.86	62	90
Education level	experimental	14.60	5.48	5	21
	control	13.44	3.25	8	19
MoCA	experimental	23.71	2.59	17.48	26.84
	control	23.07	1.97	19.67	25.20
FCSRT IFR	experimental	28.94	4.09	20.93	34.63
	control	29.42	4.45	23.27	36
FCSRT DFR	experimental	10.24	1.48	8.18	12
	control	10.92	1.07	9.29	12

Table 4.2.1. **Demographics and cognitive tests used to include the participants.** The table reported the corrected mean scores obtained by the experimental and the control groups. MoCA: MOntreal Cognitive Assessment (Conti et al., 2015); FCSRT IFR: Free and Cue Selective Reminding Test – Immediate Free Recall (Frasson et al., 2011); FCSRT DFR – Free and Cue Selective Reminding Test – Delayed Free Recall (Frasson et al., 2011).

4.2.2 Experimental procedure

The study involved two experimental sessions lasting one hour each. The first one was dedicated to global cognitive functioning and memory screening, through the administration of MoCA and FCSRT – Picture version. Right afterwards cognitive screening, ANT (baseline) was administered to those participants who did not obtain deficient score.

Then, participants were randomly assigned to the experimental (PA with real rightwards lenses) or control (PA with sham lenses) group. PA procedure was administered in the second experimental session, the day after the first encounter, followed by a second ANT administration.

The ANT (see chapter one and figure 3.2.3) was performed on a MacBook Pro using the software “Psychology Experiment Building Language” (PEBL) battery, version 2.1 (website: https://pebl.sourceforge.net), with the same methodology as in Study 1 (see chapter 3.2.4).

During PA procedure, participants were comfortably seated in front of a table on which a rectangular wooden support was placed, open on both sides. They were asked to point as

quickly as possible with their index finger, from the center of the trunk towards a transparent barrier in correspondence of target wooden sticks located either at the center, right or left of the participant's midline. Targets were 15 cm distant from each other, and the examiner verbally indicated, in a randomized order, which target the patient had to point to. Spatial accuracy of the participant's pointings were recorded through a ruler fixed to the transparent barrier, in terms of distance in cm between the target's position and the final position of the participant's index finger. The pointing movements were executed below the wooden support, whose upper part can be moved forward or backward to make the final part of the pointing movement visible or not visible to the subject (see Figure 4.1). The pointing task was performed in four conditions: (i) before wearing prisms (pre-exposure, 15 visible and 15 invisible pointings), (ii) while the subject wore prisms (exposure, 90 visible pointings), (iii) immediately after prism removal (post-exposure, 15 invisible pointings), and (iv) 20 minutes after prism removal (15 delayed-pointings).

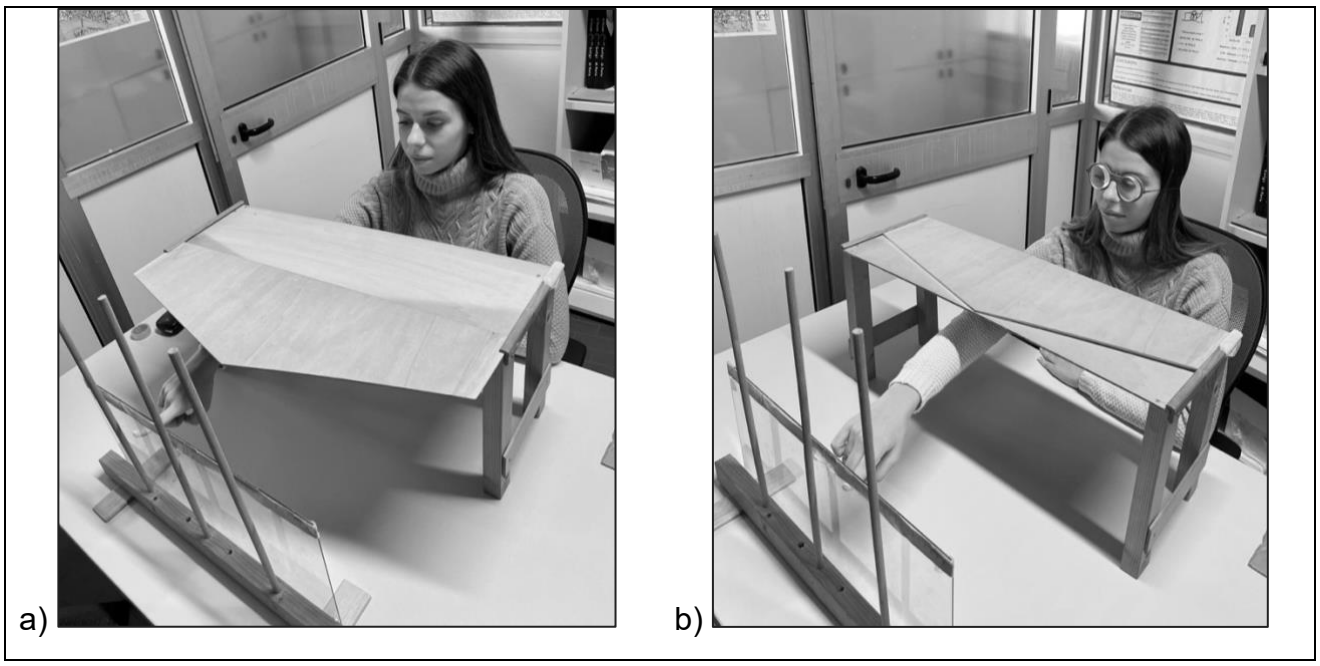

Figure 4.1. Experimental set up for PA procedure; a) invisible pointings, b) visible pointings while wearing real prisms.

4.3 Statistical analysis

This study presents a 2x2 research design with Time (Pre *vs.* Post PA; within-subjects) and Group (Real *vs.* Sham, between-subjects) as factors.

JASP Statistical Software (Version 0.18.1 intel, available online at: https://jasp-stats.org/) was used for statistical analysis.

PA data were analyzed using a 2x2 repeated measures analysis of variance (ANOVA). The deviations means (in cm) from the target were considered and compared in the following conditions: visible pre-exposure (mean of the 15 visible trials of the pre-adaptation phase), early-exposure (mean of the first 3 visible trials of the adaptation phase), late-exposure (mean of the last 3 visible trials of the adaptation phase), post-exposure (mean of the 15 invisible pointings after prism removal), and delayed-pointings (15 invisible pointings) (Calzolari et al., 2016; Frassinetti et al., 2002). Visible pointings pre-exposure were compared to the visible pointings of the exposure phase, while invisible pointings pre-exposure were compared to the invisible pointings post-exposure. Delayed invisible pointings were compared to both the pre-exposure invisible trials and the post-exposure immediate invisible trials.

Additionally, ANT data were analyzed using a 2x2 repeated measures analysis of variance (ANOVA). In particular, we analyzed RTs, numbers of errors, and alerting, orienting, and executive control scores of the corrected items.

4.4 Results

Prismatic Adaptation.

As expected, PA was effective in the Real group as compared to the Sham group (see Figure 4.2). In particular, a significant difference emerged between visible pre-exposure trials and early-exposure trials (Group*Exposure: $F(1,17) = 19.09$, $p < .001$, $\omega^2 = 0.33$; Exposure: $F(1,17) = 18.58$, $p < 0.001$, $\omega^2 = 0.33$; Group: $F(1,17) = 18.62$, $p < 0.001$, $\omega^2 = 0.33$), indicating that participants in the Real group deviated rightwards in the early-exposure trials (M = 5.017±3.419) more than the Sham group in both phases (pre: 0.07±0.103; early: 0.037±0.261) and more than in the pre-exposure of the Real group itself (M = 0.059±0.099). Likewise, comparison between early- and late- Exposure were significantly different between the groups (Group*Exposure: $F(1,17) = 19.10$, $p < .001$, $\omega^2 = 0.33$; Exposure: $F(1,17) = 19.38$, $p < 0.001$, $\omega^2 = 0.34$; Group: $F(1,17) = 18.64$, $p < 0.001$, $\omega^2 = 0.33$). Also, invisible pre-Exposure trials were different from invisible post-Exposure trials with a significant main effect of Exposure ($F(1,17) = 20.40$, $p < 0.001$, $\omega^2 = 0.17$) and a significant Group*Exposure interaction ($F(1,17) = 18.79$, $p < .001$, $\omega^2 = 0.16$), with no effect of Group ($F(1,17) = 1.80$, $p = 0.20$): only the Real group showed a difference between pre- (M = 0.053±0.761) and post-exposure (M = -1.838±1.645). Descriptive statistics are reported in Table 4.4.

Exposure	*Group*	*Mean*	*SD*	*N*
Visible Pre	Real	0.059	0.099	10
	Sham	0.070	0.103	9
Invisible Pre	Real	0.053	0.761	10
	Sham	-0.285	0.787	9
Early	Real	5.017	3.419	10
	Sham	0.037	0.261	9
Late	Real	0.017	0.053	10
	Sham	0.019	0.100	9
Invisible Post	Real	-1.838	1.645	10
	Sham	-0.324	0.691	9

Table 4.4. Deviations means (in cm) in the Exposure phases of PA procedure, of the Real and Sham groups.

Lastly, the comparison between Immediate post-exposure pointings and delayed post-exposure pointings showed a reduction of the shifting in the Real group (post M = -2.92±2.73; delayed M = -0.76±0.79) and a stable outcome in the Sham group (post M = -0.22±0.79; delayed M = -0.22±0.64), with a main effect of Exposure ($F(1,17) = 9.05$, $p = 0.007$, $\omega^2 = 0.11$) and Group ($F(1,17) = 9.07$, $p = 0.007$, $\omega^2 = 0.17$), as well as a significant interaction between Exposure*Group ($F(1,17) = 8.99$, $p = 0.007$, $\omega^2 = 0.11$).

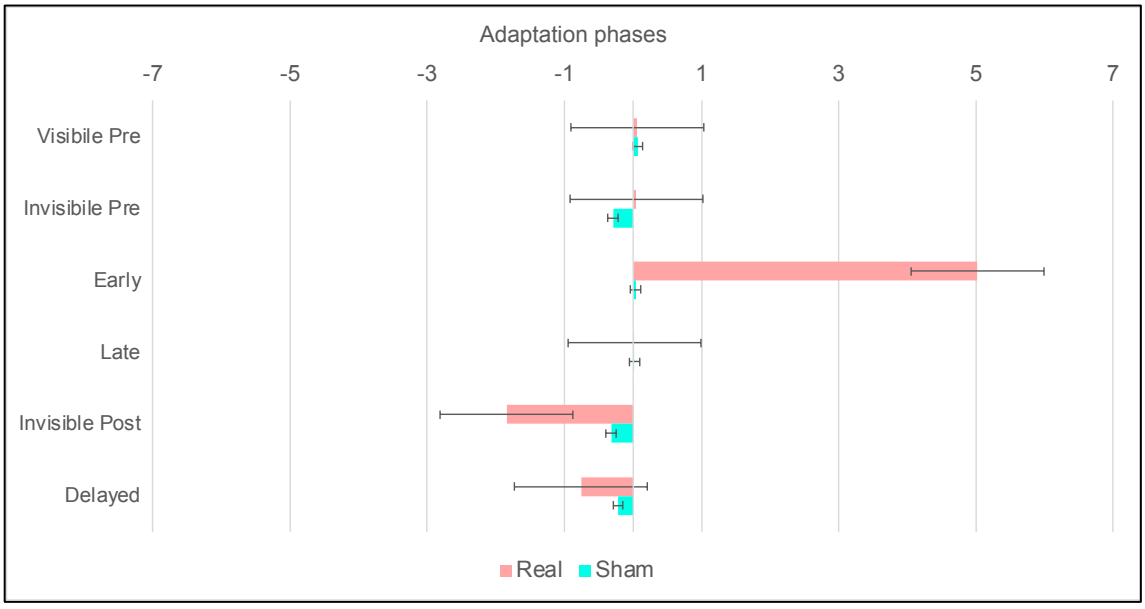

Figure 4.2. X axis: Deviation means from 0 (accuracy) in cm, across the exposure phases of prismatic adaptation procedure.

ANT.

Reaction Times at the ANT were reduced significantly after PA in both groups (Time: $F(1,17) = 8.46$, $p = 0.01$, $\omega^2 = 0.03$). No effect of Group ($F(1,17) = 0.36$, $p = 0.56$) nor interaction between Group*Time ($F(1,17) = 0.61$, $p = 0.44$) were found. Comparison between Real (Pre: M = 700.30±120.63; Post: M = 654.81±88.49) and Sham (Pre: M = 719.01±103.05; Post: M = 692.83±110.54) groups are plotted in Figure 4.3.

Numbers of errors remained stable across Pre (M Real = 7.6±16.32; M Sham = 5.11±4.46) and Post PA procedure (M Real = 4.2±9.81; M Sham = 5.44±9.66) in both groups (Time: $F(1,17) = 0.95$, $p = 0.34$; Group: $F(1,17) = 0.02$, $p = 0.90$; Time*Group: $F(1,17) = 1.41$, $p = 0.25$).

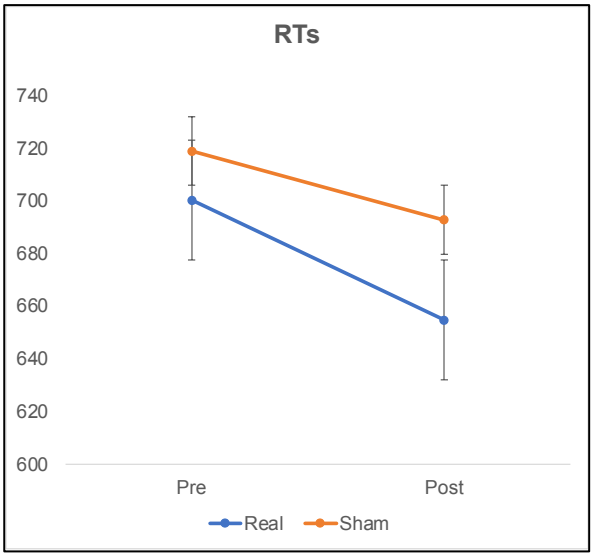

Figure 4.3. Comparison between RTs in msec for the Real and Sham groups, Pre and Post PA. Bars are Standard Errors.

For what concerns the ANT subcomponents, only *alerting* was significantly different in the Post PA session, with a main effect of Time ($F(1,17) = 4.63$, $p = 0.046$, $\omega^2 = 0.03$), but no effect of Group ($F(1,17) = 0.02$, $p = 0.91$), nor interaction between Time*Group ($F(1,17) = 3.31$, $p = 0.09$) (see Figure 4.4), indicating that both the Real (Pre M = 36.28±55.78, Post M = 62.63±38.94) and the Sham (M = 50.42±16.22, Post M = 52.62±36.24) groups changed after PA.

Figure 4.4. Comparison between the alerting component for the Real and Sham groups, Pre and Post PA. Y axis = RTs in msec. Bars are Standard Errors.

In order to deeply understand the meaning of the alerting component change, since *alerting* represents the difference between the RTs at no-cue and at double-cue trials, we analyzed how the RTs at no-cue trials and at double-cue trials changed after PA session, separately, by means of an ANOVA (factors: Time (Pre *vs.* Post PA) and Group (Real *vs.* Sham)). The RTs at no-cue trials did not change between Pre (M Real = 719.16±109.45; M Sham = 750.35±101.99) and Post (M Real = 696.96±97.02; M Sham = 725.42±104.90) PA sessions, in none of the groups (Time, $F(1,17) = 3.87$, $p = 0.07$; Group, $F(1,17) = 0.42$, $p = 0.53$; Time*Group, $F(1,17) = 0.013$, $p = 0.91$). On the contrary, there was a significant main effect of Time ($F(1,17) = 9.926$, $p = 0.006$, $\omega^2 = 0.037$) for the double-cue trials, with no significant effect of Group ($F(1,17) = 0.408$, $p = 0.53$) nor interaction Time*Group ($F(1,17) = 1.97$, $p = 0.178$), meaning that RTs at double-cue significantly decreased in both groups between Pre (M Real = 682.88±85.39; M Sham = 691.42±85.46) and Post (M Real = 634.31±73.64; M Sham = 672.80±94.42). An explorative analysis comparing the changes in RTs at double-cue separately for the two groups, showed a significant difference only for the Real group between Pre and Post PA session (Mean difference = 48.57, $t = 3.31$, $p = 0.025$) while the Sham group did not present the same significant reduction of RTs (Mean difference = 18.62, $t = 1.20$, $p = 1.00$).

The *orienting* component did not change Post PA (Time, $F(1,17) = 0.62$, $p = 0.44$; Group, $F(1,17) = 3.52$, $p = 0.08$; Time*Group, $F(1,17) = 0.23$, $p = 0.64$) and neither did the *executive control* (Time, $F(1,17) = 1.58$, $p = 0.23$; Group, $F(1,17) = 0.16$, $p = 0.70$; Time*Group, $F(1,17) = 0.01$, $p = 0.93$).

4.5 Interim discussion

The main aim of this study was to investigate the effect of PA in supporting attention and its subcomponents, in healthy elderly. To do so, we recruited healthy old participants and assessed their attention capabilities through ANT before and after PA.

Our results proved that both the experimental group and the control group significantly reduced their RTs in the Post session test, whereas the accuracy rate did not change after (real or sham) PA.

This, in contrast with our hypothesis, may be explained in two different ways: (i) the attention, in terms of RTs, has been modulated by the visuo-motor exercise of pointings *per se*, independently from the visual shifting and correlated neuromodulatory effects; (ii) the attention has been modulated by the fact that participants in the control group were undergoing a treatment session (i.e. pointings with sham lenses), as a "placebo effect". There is also an alternative possibility, related to the test-retest effect, as if in the second test administration a learning effect had come into play. However, we initially selected the ANT because it has been demonstrated that it remains reliable in test-retest scenarios up to the tenth consecutive repetition (Ishigami & Klein, 2010). Thus, we could exclude that the reduction of RTs was simply due to a learning effect in the second ANT administration.

In order to better clarify this result, it is worth discussing the changing in the *alerting* component of attention, the only component among the three which exhibited a significant difference after PA. Even though also in the case of alerting we observe only a time effect, i.e., a Pre-Post change in both groups, the interaction Time*Group showed a trend, albeit not yet significant, towards an increase of alerting only in the experimental group. When dissecting this change, analyzing the RTs at no-cue and at double-cue condition separately, we also see a trend where only the experimental group reduced RTs in response to double-cue. Nevertheless, in the no-cue condition RTs did not change Post PA in either group, but they did in the double-cue condition, as if the PA had modulated the reactivity to double-cue and not to no-cue, causing better alertness in general. We could hypothesize that with a larger sample size, the effect of PA on the alerting component may become significant, mirroring higher readiness towards the double-cue condition. If so, it could be argued that PA has a role in sustain attention in the elderly, but we need to increase our sample to verify this hypothesis. Yet, our finding regarding the alerting remains interesting, since this is the attentional component most frequently reported and discussed as undergoing changes in healthy older individuals compared to the young.

Although in the Study 2.1 we only found a significance for the alerting component, we have decided to proceed with an investigation concerning the executive control component, given its primary role in aging. Along these lines, Study 2.2 took further the comparison between healthy elderly participants and MCI patients.

STUDY 2.2

In order to investigate whether Zhang and colleagues' observation (2015) on executive control network in aMCI patients is consistent (see chapter 1.3) and can be replicated, we devised a second investigation comparing the baseline results at ANT of the 12 aMCI patients of Study 1, matched with 12 healthy participants of Study 2.1.

4.6 Procedures and methods

Twelve participants among the 19 collected in the Study 2.1 were selected (6 females, 6 males, Mean age = 74.92±5.99 (min. 70, max. 90); Education level = 13.09±4.36 (min. 5, max. 19)) to match the aMCI patients of the Study 1 (see chapter 3) on age, gender, and education level (6 females, 6 males, Mean age = 78.83±5.98m (min. 71, max. 85); Education level = 13.33±3.75 (min. 8, max. 19)).

Both groups performed the ANT in the first encounter, before embarking in the treatment (Study 1) or the PA session (Study 2.1), with the same procedure, as previously described.

4.7 Statistical analysis

This study presents Group: Patients *vs.* Healthy Controls (HC) as main independent variable. ANT scores (numbers of errors, accuracy, RTs, alerting, orienting, and executive control indexes) are the dependent variables.

We used an independent sample t-tests (for variables not normally distributed we used the Mann U Whitney) to compare ANT scores in the two groups.

4.8 Results

Independent sample t-tests confirmed that the groups were equally matched on age ($t(22) = -1.60$, $p = 0.12$) and education level ($t(22) = 0.35$, $p = 0.73$).

Shapiro-wilk test showed that numbers of errors ($W = 0.62$, $p < .001$), accuracy ($W = 0.63$, $p < .001$), orienting index ($W = 0.89$, $p = 0.01$) and executive control index ($W = 0.46$, $p < .001$) were not normally distributed, whereas all remaining variables did.

Numbers of errors at ANT (Figure 4.5), accuracy (Figure 4.6), and RTs (Figure 4.7), were significantly different between patients (M errors = 25.42±32.66, M accuracy = 0.91±0.11, M RTs = 919.36±151.40) and HC (M errors = 7.92±14.98, M accuracy = 0.97±0.05, M RTs = 758.77±95.42) (errors: U = 26.5, p = 0.009, Cohen's d = -0.63; accuracy: U = 113.5, p = 0.02, Cohen's d = 0.58; RTs: t(22) = -3.11, p = 0.005, Cohen's d = -1.27).

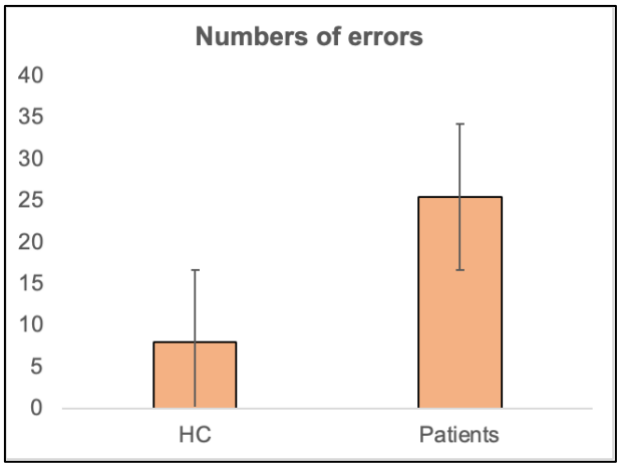

Figure 4.5. Numbers of errors at ANT of patients and Healthy Control (HC). Bars are Standard Errors.

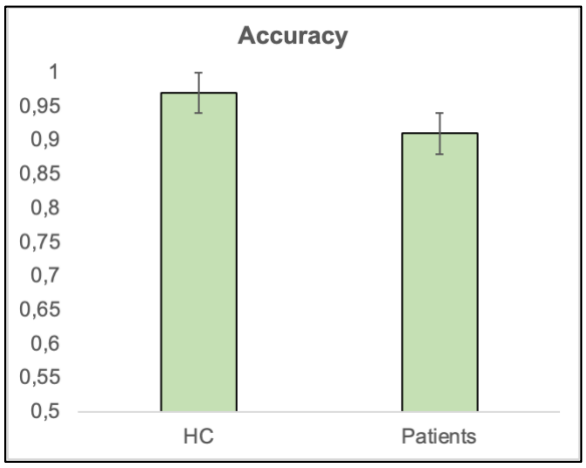

Figure 4.6. Means accuracy at ANT of patients and Healthy Control (HC). Bars are Standard Errors.

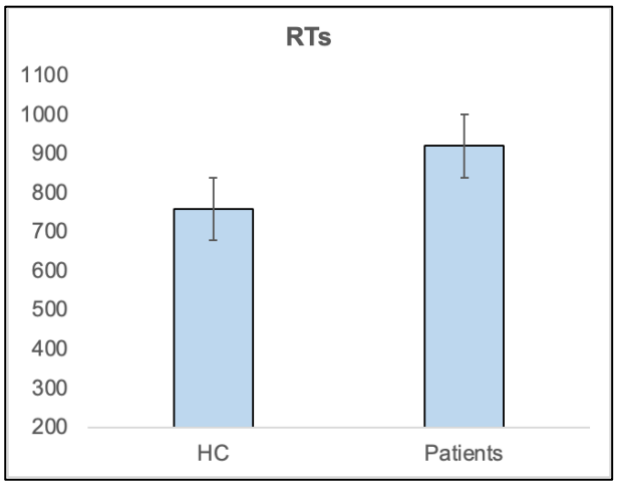

Figure 4.7. Comparison of RTs (in msec) at ANT between patients and Healthy Control (HC). Bars are Standard Errors.

For what concerns the attention subcomponents, neither alerting (M patients = 47.32±39.19; M HC = 48.28±48.48 ; t(22) = 0.05, *p* = 0.96), nor orienting (M patients = 11.51±35.01; M HC = 35.79±19.95U = 98, *p* = 0.14) were different between the groups. Also, executive control (U = 42, *p* = 0.08) did not yield a significant result, even though it is possible to qualitatively observe a greater executive control index for patients (M = 176.41±223.61) compared to HC (M = 85.32±41.35).

4.9 Discussion

In contrast with the literature previously presented, our Study 2.2 did not confirm the alteration of the executive control network in aMCI patients compared to healthy controls. Indeed, although we found a significant difference between patients and healthy elderlies in accuracy and RTs, with the patients being more slowly and less accurate, none of the attention subcomponents differed between the groups. However, considering the very small sample size, from a qualitative point of view and looking at the statistical trend, continuing to explore executive control in relation to pathological aging could lead to significant results in line with what other authors had found, and a better understanding of the cognitive dynamics involved in aging.

Expanding the sample size of both Study 2.1 and 2.2 may lead to insights regarding the development of more precise intervention or assessment strategies, most of all considering that the alerting component, the only one modulated in the Study 2.1, is far from being different between aMCI patients and healthy elderly in Study 2.2. Although being mere speculations, this result, if confirmed, would imply that modulating alerting in MCI patients might not prove beneficial, as this component is already similar to that of healthy controls.

On the other hand, enhancing alerting could be useful in healthy elderly individuals as a cognitive stimulation. Future studies, in addition to expanding samples sizes, might focus on understanding whether modulating alerting in healthy elderly individuals can lead to benefits in daily life activities, and how the efficiency of this component is related to the one of the executive control.

CHAPTER FIVE - Experimental Study 3

In the first two chapters of this dissertation, I discussed the importance of prevention and early diagnosis of age-related diseases. Although AD is the most prevalent form of dementia, other degenerative conditions deserve particular attention. To date, such conditions are more challenging to diagnose since they do not fall within the classification of MCI, nor do they have in-vivo biomarkers available. Indeed, Cerebrospinal Fluid (CSF) markers that directly reflect the disease molecular pathology have become available for AD, Creutzfeldt-Jakob disease (CJD), and Levy-Body Dementia (LBD) spectrum, while they are missing for rarer degenerative conditions (Mattsson, 2011; McKhann et al., 2011). In particular, there is a growing interest in Cortical Basal Syndrome (CBS). This condition presents heterogeneous cognitive and/or motor disturbances that may have different neurobiological underlying causes, which can be definitively confirmed only post-mortem (Armstrong et al., 2013; Svenningsson, 2019; D. Wilson et al., 2021).

In the following chapter, I will present a single case of a patient I've been following longitudinally for three years. This is a clinical case highly relevant for the study of a rare degenerative condition, namely Cortical Basal Degeneration (CBD), which represents one of the possible underlying pathologies of CBS. At the same time, because of the initial clinical manifestations of the pathology in our patient, the case also offers an occasion to shed light on the neuropsychological mechanisms of tactile object recognition and tactile agnosia (the first symptom that the patient presented at onset).

The patient came to the Center of Neuropsychology of ASST G.O.M. Niguarda, and she has been followed by neuropsychologists in collaboration with neurologists and neuroradiologists of the same hospital. The Ethical Committee of the ASST G.O.M. Niguarda (Milano, Area 3) approved the diagnostic investigation through experimental instruments, and the patient signed the informed consent. The collection of healthy control data was carried out at the University of Pavia, and it was approved by the Ethical Committee of the same University.

5.1 Introduction

Tactile objects recognition (TOR) is a very complex ability that requires the identification of elementary sensory elements, the integration of sensory–cutaneous, proprioceptive, kinesthetic, and thermal–information in a coherent representation, and the association of this representation to semantic knowledge (C. Reed & Ziat, 2018; Veronelli et al., 2014). Historically, the process of object recognition has been divided into two stages, (1) the

perception of physical features of objects, or “perceptive level”, and (2) the association of the perceptive representation with semantic memory, or “associative” level (Lissauer, 1890; Wernicke, 1895). Although these processes have been extensively investigated for the visual modality and, to some extent, for the acoustic one, haptic recognition processes are still poorly understood (Bottini et al.,1995; Grossi e Trojano, 2011). Existing cognitive models are mainly derived from the clinical observation of patients with difficulties in recognizing objects via haptic exploration. An impairment in TOR, in the absence of sensorimotor impairment and higher-level cognitive deficits, is referred to as tactile agnosia (Claparède, 1899; Déjérine, 1907; Endo et al., 1992).

In the most influential models of tactile agnosia, in addition to the classic distinction made by Lissauer (1890) between difficulties either at the perceptive level (apperceptive agnosia) or at the associative level (associative agnosia), a further classification into hyloagnosia and morphoagnosia has been proposed (Delay, 1935). Hyloagnosia is defined as a difficulty in discriminating the qualities of objects (weight, texture, etc.), while morphoagnosia is the inability to discriminate the shape and size of objects; these two aspects are accounted for the level of intermediate perception, such as Lissauer’s apperceptive level, dissociating both from each other and from higher-level processing (Delay, 1935; Endo et al., 1992; Kubota et al., 2017; Saetti et al., 1999). However, double dissociation between hyloagnosia and morphoagnosia has never been reported since, to the best of our knowledge, there are no cases of hyloagnosia without morphoagnosia described in the literature, and the presence of morphoagnosia without hyloagnosia has been reported only in two cases (Kubota et al., 2017; Saetti et al., 1999). Moreover, a double dissociation between tactile apperceptive and associative levels has been described only once (Kubota et al., 2017), while most of the reported cases state that in the presence of apperceptive agnosia there is also associative agnosia (C. L. Reed et al., 1996; Bohlhalter et al., 2002; Crutch et al., 2005; Estañol et al., 2008). However, it is worth noting that the recognition of real objects varies among the reported apperceptive agnosia cases: for example, the correct recognition rate of Reed’s case was 13/28 objects, while Saetti’s case, who showed selective morphoagnosia, recognized 7/10 objects (Kubota et al., 2017). The question as to whether an accuracy of more than 50% and less than 100% in real objects recognition, as in Saetti’s case, could represent double dissociation is still open.

De facto, tactile agnosia is rare to detect as an isolated disorder, and it is difficult to observe clinically, as somatosensory disturbances caused by brain lesions often overlap with the gnosis disorder, making its identification complex (Platz, 1996). Indeed, in the literature,

reported cases of tactile agnosia are usually caused by brain events of vascular origin, either ischemic or hemorrhagic, and in only one case, by a meningioma (Platz, 1996). An open question is whether other types of brain damages, including degenerative conditions, can lead to similar TOR impairments. For example, Cortico Basal Syndrome (CBS) is a condition characterized by insidious onset of motor and sensory disturbances, unresponsive to Levodopa treatment (Mathew et al., 2012). Diagnostic criteria include the presence of "cortical sensory loss", which falls within the realm of somatosensory disorders, but its definition is vague. Some authors describe it as the co-occurrence of astereognosis, agraphesthesia, and loss of position sense (Bassetti, Bogousslavsky, and Regli 1993), while others include the extinction of double stimuli among the symptoms (Belfor et al. 2006). Additionally, some authors define it as “tactile inattention” and impairment in the two-point discrimination task (Misra et al. 1997), while others incorporate also pain and temperature discrimination in the assessment of cortical sensory loss (Kim 2007). Actually, to the best of our knowledge, only one study tried to provide a more precise characterization of these deficits (Matsuda et al. 2020), interpreting cortical sensory loss as a “somatosensory dysfunction”, and investigating tactile localization, weight and texture perception, letter, and object recognition. In Matsuda and colleagues’ study, authors found difficulties in patients with CBS in the two-points discrimination task and in object naming. Their study, although attempting to characterize somatosensory dysfunction and TOR disorders in patients with CBS through a comprehensive assessment, did not include the evaluation of geometrical and meaningless shapes (i.e., the evaluation of morphoagnosia).

Thus, only a few cases of pure tactile agnosia have been described (Endo et al., 1992; Veronelli et al., 2014; Kubota et al., 2017), also due to the absence of standardized diagnostic tests for investigating the phenomenon.

Case report

Here we present the case of C.P., a right-handed 55-year-old woman with 18 years of education, who came to our attention for a referred chronic progressive worsening in right hand sensitivity and in objects recognition during activities of daily life. Eight months before our first encounter, which took place in March 2021, she underwent a CT scan because of the right hand and arm dysesthesia that she referred to starting 6 months before. Images showed an oligodendroglioma in the right posterior parietal parasagittal area, then surgically removed (in 2020). Her symptoms did not disappear after the surgery; an MRI exam documented a stabilized outcome of surgery with a liquor-filled cavity in the posterior

parasagittal right parietal region, along with a diffuse hyperintensity of signal in the left fronto-parietal cortico-subcortical area, associated with left focal atrophy of the convolutions, particularly in the pre and postcentral gyri, and a marked enlargement of corresponding cortical sulci. Subsequently, C.P. underwent a DaTSCAN and an 18-FDG SPECT, that were both negative. The standard neuropsychological assessment, executed 6 months after the oligodendroglioma removal, showed a melokinetic ideomotor apraxia (Tessari et al., 2013) only for the right hand, along with a difficulty in real objects haptic recognition (Nottingham Sensory Assessment, Lincoln et al., 1998), still only for the right hand. On the other hand, the patient's general cognitive status (Mini Mental State Examination (MMSE) (Measso et al., 1993), memory, language, attention, visuo-spatial abilities, and executive functions were all intact (See Table 5.1). Additionally, it is worth noting that the patient was collaborative, and her spontaneous speech was fluent.

TEST	**C.P.'S SCORE**
MMSE (Measso et al. 1993)	30/30
Activities of Daily Living (Katz 1983)	6/6
Instrumental Activities of Daily Living (Katz 1983)	8/8
Verbal fluency (Novelli et al. 1986)	42.54
Semantic fluency (Novelli et al. 1986)	43.71
Denomination (Catricalà et al. 2013)	48/48
Short Story Recall (Novelli et al. 1986)	13.5
- Immediate Recall	10
- Delay Recall	17
Rey AVLT (G. A. Carlesimo et al. 2014)	
- Immediate Recall	37.2/60
- Delay Recall	6/15
Digit Span (Monaco et al. 2013)	6,66
Digit Span Backward (Monaco et al. 2013)	5.65
Rey-Osterrieth complex figure (Carlesimo et al. 2002)	
- Immediate recollection	36/36
- Delayed recollection	14.5
Corsi Span (Monaco et al. 2013)	6.62
Corsi Span Backward (Monaco et al. 2013)	3.82
Trail Making Test (Giovagnoli et al. 1996)	
- A	45.90''
- B	88.25''
Stroop Test (Caffarra et al. 2002)	
- Time	15.84''
- Errors	0
Symbol Digit Modality Test (Nocentini et al. 2006)	66
Cancellation test (Uttl and Pilkenton-Taylor 2001)	53/53
Right arm apraxia (Tessari et al., 2013)	**55/72***
Left arm apraxia (Tessari et al., 2013)	65/72

Stereognosis subtest of NSA (right hand)	**13/20***
Stereognosis subtest of NSA (left hand)	19/20

Table 5.1. Neuropsychological assessment executed six months after the oligodendroglioma removal. Scores are adjusted based on Italian normative data. MMSE = Mini Mental State Examination. Rey AVLT = Rey Auditory Verbal Learning Test. NSA = Nottingham Sensory Assessment. * impaired

However, because of the absence of a standardized battery for tactile agnosia and considering that the patient showed a complex neuroanatomical correlate, we devised an experimental investigation to better characterize her symptoms.

The patient was also followed longitudinally via both neuropsychological and neuroimaging clinical exams, to clarify the diagnosis.

5.2 Methods and procedures

We devised an investigation of elementary sensorimotor abilities and higher gnosis functions based on Endo's and Kubota's models and procedures (Endo et al., 1992; Kubota et al., 2017) (See Figure 5.1). Details of every investigated level of tactile perception and cognition are described hereafter.

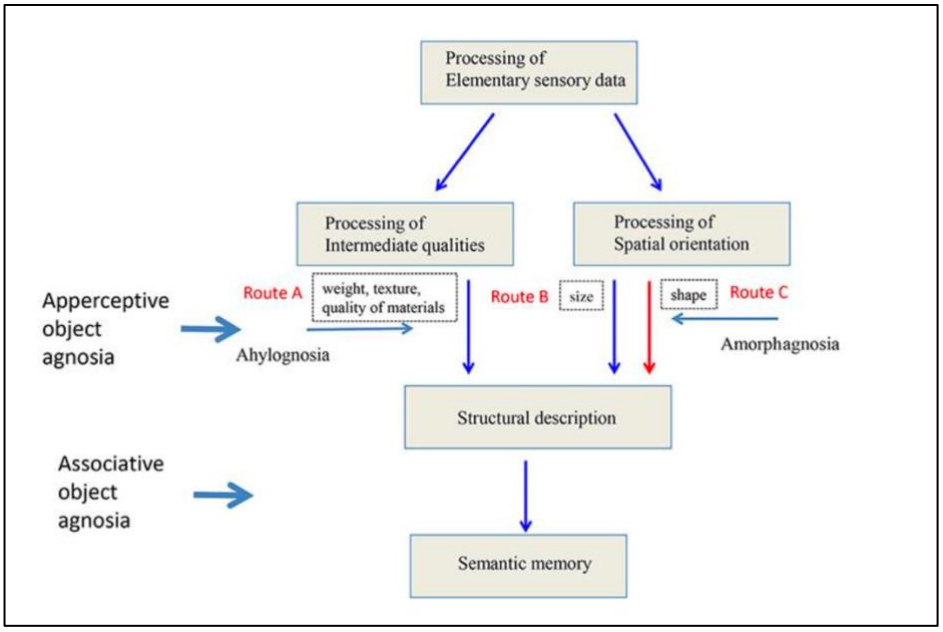

Figure 5.1. Cognitive model of tactile agnosia by Kubota et al., 2017, modified from Saetti et al., 1999.

The patient was blindfolded, and the right hand was tested before the left hand, to prevent a learning effect.

Furthermore, although in the literature morphoagnosia is reported to be usually tested using geometrical shapes, we argue that geometry already comprises a semantic aspect that could represent a confound in morphognosis's analysis. Thus, we additionally included meaningless-shapes in the assessment (Bottini et al., 1991).

Lastly, since a standard neuropsychological battery for tactile agnosia is missing, we recruited 18 healthy participants as a matched control sample (see below).

5.2.1 Control participants

The 18 healthy control participants (Mean age = 54.5± 5.33; Mean years of education = 16.22±3.34) were all right-handed females with normal tactile capabilities and no self-reported neurological or psychiatric pathologies. They all gave written informed consent before starting the experiment, according to procedures approved by the local Ethical Committee.

The participants made the same procedure as the patient while blindfolded. They did the primary and intermediate tasks, including the meaningless-shapes task, with both hands and the associative agnosia test with one hand only. The experimental session lasted about 2 hours.

For the tests' specifics, see the next paragraph.

5.2.2. Tests

5.2.2.1 Processing of elementary sensory data

Tactile detection

The experimenter administered single tactile stimuli by lightly resting the fingertips on the back of the patient's left or right hand. C.P. was asked to indicate on which hand she perceived the stimulus while keeping her eyes closed. Fifteen stimuli for the left hand and 15 for the right hand were randomized and alternated with 10 control trials with no stimulation (catch trials). The same task was proposed with double stimulation, in which 15 stimuli for the right hand and 15 for the left hand were mixed with 15 double touches administered simultaneously on both hands.

Two-points discrimination

The test was performed using a digital caliper (*Metrica 10745*), applying the two tips of the device on the index finger and on the palm of the hand and asking the patient to judge whether she felt one or two points. Stimulation started with two points 25 mm apart and continued with decreasing distance intervals of 5 mm from 25 to 15 mm and of 1 mm intervals from 14 mm down to a minimum of 1 mm.

This test was not administered to control participants since a standardized correction scale already exists.

Semmes-Weinstein test

A clinical sensory evaluation was administered using four Semmes-Weinstein monofilaments (2.83 mm, 3.61 mm, 4.31 mm, 6.45 mm) over the right and the left hands (*Touch Test® Sensory Evaluators Hand Kit, North Coast Medical, Inc*). Two touches over every finger (upper fingertip and lower finger) and one touch on the palm were administered asking the patient whether she could feel the stimulation.

This test was not administered to control participants since a standardized correction scale already exists.

Diadochokinesis

The patient was asked to rapidly move the fingers of the hands in progression, tapping on the table, first from thumb to little finger and then in the opposite direction, twice. The sequence of finger movements was shown in advance by the experimenter.

Perception of pain

The patient was stimulated on the back of the hand with a non-harmful painful stimulus (toothpick) or a neutral stimulus (cotton pad) for approximately one second, and she had to indicate whether the perceived stimulus was painful or neutral. Ten trials for each hand were administered.

Temperature discrimination

A test tube containing warm or cold water was placed on the back of the hand for about 2 seconds, 10 trials for each hand. The patient had to indicate whether the perceived stimulus was warm (about 60°) or cold (about 10°).

Perception of vibration

A neurological tuning fork was used by placing it on the back of the patient's hand and asking her to specify whether she felt the vibration. Ten trials (5 vibration, 5 no-vibration) were administered.

Proprioception

The examiner moved the middle finger of the patient's hand up or down in relation to the other fingers, and the subject was asked to report, while keeping the eyes closed, whether the finger was moved up or down. Ten trials for each hand were administered.

5.2.2.2 Assessment of Hyloagnosia

Weight

The patient was asked to compare four identical plastic balls, which differed only in weight, with a target-ball. Two heavier and two lighter balls than the target were presented twice, placing them one at a time on the same hand immediately after the target. The target was

re-presented before every comparison-stimulus in order to prevent the response to be biased by working memory overload.

Texture

Same task as for weight processing, made with 4 grades of sandpapers instead of different-weights plastic balls.

Dimension

Same task as for weight and texture processing, made with four polyester balls with same weights and texture but different in size.

Materials

The patient was presented with 10 squared pieces made of different materials: plastic, metal, wood, glass, foam rubber, paper, rubber, cotton, polystyrene, fabric. She was asked to explore the material as long as she preferred and to name it.

In the controls' sample, materials discrimination was made with one hand only, to prevent the learning effect. Half of the sample (N = 9) made the material discrimination with the left hand, and the other half with the right hand.

5.2.2.3 Assessment of Morphoagnosia

Two-dimensional figures

Eight wooden-made geometrical shapes (rectangle, square, pentagon, circle, cross, star, triangle, rhombus) were placed on the plasticine in such a way as to hold them still and only the edges emerged by a few millimeters, to favor exploration in 2-dimensions. The patient was presented with eight pairs of these shapes (four identical pairs and four different pairs) and asked to discriminate whether the second stimulus in the pair was the same or different from the first one.

Geometrical shapes

The same eight geometrical figures as in the previous task were given to the patient, without plasticine, asking her to explore them in 3 dimensions with her whole hand, for eight-pairs comparisons.

Meaningless-shapes

The patient was asked to compare 12 couples of the same or different shapes. The first stimulus was placed in the patient's hand, and she was allowed to manipulate it as long as she wanted. Then, the first stimulus was removed and, immediately after, the same identical object or a different one was placed in her hand, asking whether it was the same or different. Three reference targets were presented as the first stimulus to be compared with 9 different

meaningless-shapes objects or with itself. The meaningless-shapes had the same texture, weight, and size and differed only in the shape (see an example in Figure 5.2).

Figure 5.2. Examples of meaningless-shapes objects used to identify morphoagnosia (Bottini et al., 1995).

5.2.2.4 Assessment of Real Objects Recognition

Nottingham Sensory Assessment – Object Recognition

This test involves the use of 10 real objects: a 2€ coin, a 50-cent coin, a pen, a pencil, a comb, a sponge, a scissor, a flannel, a cup, and a glass. The object was placed in the patient's hand (max. 15 seconds), and she was asked to name or describe it. Two points were given if the object was correctly named; one point if the patient was unable to identify but still managed to describe some features; zero score if the identification was completely absent.

This test was not administered to control participants, since it is a standardized clinical procedure.

Naming of objects

The patient was asked to manipulate 12 real objects (lighter, brush, screwdriver, comb, fork, thimble, clothespin, teaspoon, sharpener, watch, key) and to name them.

Haptic exploration – drawing

In order to qualitatively explore morphoagnosia, we asked the patient to manipulate a funnel and then to draw what she perceived (Valenza et al., 2001).

Comparison of real objects

Since the real objects exploration with the left hand was intact, we decided to further explore associative tactile agnosia of the right hand only, devising a comparison task that does not include the naming of the objects.

Specifically, we asked the patient to compare with the right hand 64 pairs of real objects. The examiner explained in advance to the patient that she would be presented with pairs of

commonly used objects in which the second stimulus would have been: *(i)* an object with the same name, function and shape as the first stimulus; *(ii)* an object with the same name and function as the first stimulus but with a different shape (e.g. two kinds of comb); *(iii)* an object semantically related to the first stimulus (e.g. a pencil as first stimulus and an eraser as second one); *(iv)* a different object not related in name, function, or shape to the first stimulus. In the first two cases, when manipulating two identical objects (identity) or two objects with same name and function but different shapes (same category), the patient had to respond “same”; in the latter two cases, when manipulating two semantic related objects or not-related objects, she had to respond “different”. We presented 16 pairs of objects for each of the four categories ((*a)*identity, *(b)* same category, *(c)* semantic relation, *(d)* no-relation). The presented objects were: earring, corkscrew, screwdriver, socket, balloon, walnut, pebble, hourglass, pencil, locker, nail polish, thimble, clothespin, matchstick, tweezer, battery, tube of tempera, medal, sponge, hair clip, glue, locker, tea bag, zip, paperclip, string, fork, as well as two types of: button, watch, lighter, bottle cup, comb, power plug, brush, key, spoon, candle, nail file, scotch tape, screw, eraser, spool, ring.

5.2.3 Follow-up

The patient underwent a neuropsychological assessment and an MRI once a year, for 3 years (in 2021, 2022, 2023). At the same time, in 2023 she repeated both the experimental evaluation of tactile processing and the DaTSCAN, two years after the first ones (2021) and three years from symptoms onset (2020).

5.3 Results

Patient’s results were compared with the control sample using the Crawford-Howell t-test (1998) implemented in R Studio software (vers. 2023.03.0-524, https://posit.co/download/rstudio-desktop/).

5.3.1 First assessment

Elementary sensory data

C.P.’s response at the *Two-points discrimination task* fell within the normal range (based on Shimokata and Kuzuya, 1995) for both the index finger (two-point threshold distance: right finger = 1 mm; left = 4 mm) and the palm (two-point threshold distance: right palm = 13 mm; left palm = 9 mm). It is worth noting that the discrimination ability with the right palm (13 mm) was lower than with the left palm (9 mm), although remaining within the normal range. From a qualitative point of view, the patient’s response was unusual since she reported to feel two

points in the right finger even when they were 1 mm apart, describing the sensation as one normal touch accompanied by a lighter one.

The patient also correctly completed the *Semmes-Weinstein* test: fingertips sensibility fell within the normal range (2.83 mm perceived) for the upper left fingers and diminished for light touch in the left lower fingers (3.61 mm perceived); a diminished light touch sensibility was also found in the right hand for both upper and lower fingers. Normal sensibility emerged for right and left palms (2.83 mm perceived). Those results could be considered between the normal range based on the thresholds proposed by Bell-Krotoski and colleagues (1995). During the assessment of diadochokinesis, C.P. was able to complete the movements with both hands, as from a qualitative point of view, the movement of the right-hand fingers was clumsy compared to the left-hand fingers.

For what concerns the other primary sensory tests, all control participants and the patient correctly completed with both hands the single and the double tactile detection (both: 40/40), the pain, proprioception, and vibration assessments (all: 10/10). The only elementary sensory task slightly below 100% accuracy in the control sample was the temperature discrimination with the right hand (M = 9.92±2.28, *vs.* patient: 10/10)).

Since processing of elementary sensory information were intact, we proceeded in investigating the intermediate level of elaboration.

Hyloagnosia and morphoagnosia

C.P. correctly responded to every weight-comparison (8/8 in each hand, controls: M right = 7.83±0.38, M left = 7.89±0.32), every texture-comparison (8/8 in each hand, as controls), and every size-comparison (8/8 in each hand, as controls). Regarding the materials, she identified 6 materials out of 10 with the right hand (plastic, foam rubber, rubber, paper, cotton, fabric), and 8 materials out of 10 (plastic, wood, foam rubber, paper, rubber, cotton, polystyrene, fabric) with the left hand. These scores were significantly different from controls (M right hand = 9.33±0.87, M left hand = 9.33±1.32) for the right hand ($t(8) = -3.65$, $p = 0.006$), but not for the left hand ($t(8) = -0.96$, $p = 0.367$).

Concerning shapes recognition, C.P. was selectively impaired only with the right hand in exploring bi-dimensional (score: 5/8; $t(17) = -8.70$, $p < .001$) and 3-dimensional (score: 7/8; , $t(17) = -Inf$, $p < .001$) geometrical shapes, and she was significantly less accurate than controls (M right = 11.50±0.51; M left = 11.33±0.84) on the meaningless-shapes test with the right hand (score: 7/12, $t(17) = -8.51$, $p < .001$) but not with the left hand (score: 11/12, $t(17) = -0.39$, $p = 0.704$).

Associative agnosia

In the Nottingham Sensory Test, the patient scored 13/20 with the right hand and 19/20 with the left hand; with the left hand she only mistook the flannel for a cloth, but she properly described the material. In the naming test, with the right hand, C.P. correctly named 3 objects out of 12 (fork, teaspoon, watch), whereas she referred not to be sure about the answers; with the left hand, she correctly named all 12 objects. Exploration time was longer for the right hand (M = 44.7±13.52 seconds) than for the left hand (M = 5.30±2.71 seconds).

Figure 5.3 displays the drawings that C.P. did after haptic exploration of a funnel. It's worth noting that she couldn't understand what the object was with the right hand, as reflected by the drawing, while through left-hand manipulation she immediately named the object and drew it.

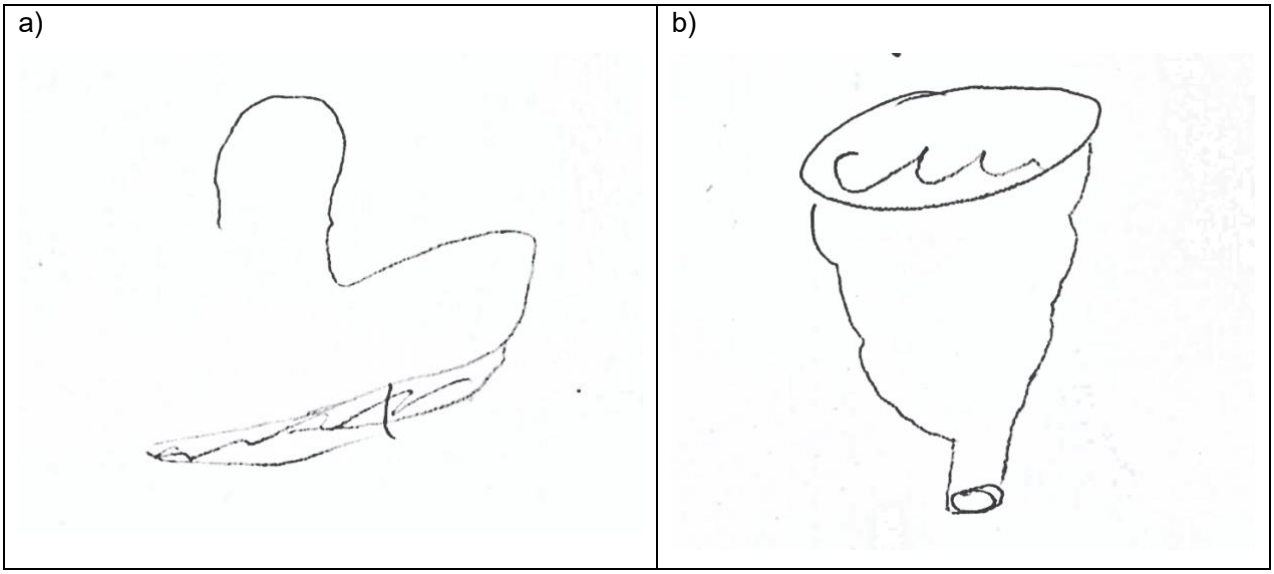

Figure 5.3. Drawing of a funnel after right hand exploration (a) and after left hand exploration (b).

For what concerns the experimental real objects comparison task, we preprocessed exploration time for the first and the second stimuli independently for each participant by excluding data points over and below 2.5 standard deviations from each participant's mean. Then, exploration time, overall accuracy, and accuracy of the four types of pairs (identity, same-category, semantic correlation, no-relation) were analyzed. The patient was both slower (first stimulus: 43.65±14.48; $t(17) = 27.96$, $p < .001$; second stimulus: 26.49±16.84, $t(17) = 28.25$, $p < .001$) and less accurate (score: 50/64, $t(17) = -11.96$, $p < .001$) than controls (stimulus: M = 3.32±1.1; second stimulus: 2.61±0.6; accuracy: M = 63±1.1) in exploring stimuli. Analysis of errors shows that the objects in the same category, with the same name and function but different shapes, were the most problematic for C.P.; indeed, she responded correctly in 7 out of 16 of these comparisons (controls: M = 15.44±1.10),

while she scored 14/16 for not-related (controls: M = 16.00) and sematic-related objects (M controls = 15.94±0.24) and she scored 15/16 for identical objects (controls: M = 15.94±0.24). However, each type of pairs showed a significant difference from the control group (all comparisons $p < .001$).

Noteworthy, during this task, even if the naming of the object was not requested, the patient commented every manipulation trying to figure it out. She correctly identified the objects (in particular: the fork, the thimble, the sponge, the zip, one of the two watches, one lighter, one key, one spool, one comb, one brush, both the screws, and the spoons) in 24 out of 128 presentation and most of the time she guessed the object or the answers using hylognosis information, as evinced by her comments (See Table 5.2).

OBJECTS	COMMENT
Screw	*"It is cold, and I feel a knurling, so it could be a screw."*
Two identical bottle cups	*"I don't know what these objects are, but they are both hollowed out in the center, so they could be the same."*
Tea bag	*"It feels like a fabric from the texture, but it doesn't make that sound."*
Two different types of erasers	*"This could be the same texture and material than the previous one, but it is smaller. I don't know what it is, but I think they could be the same object."*

Table 5.2. C.P.'s comments while manipulating real objects.

5.3.2 Follow-up

Two years after the first assessment (almost 3 years from symptoms onset), the apraxia for the right hand and associated motor difficulties had worsened to the extent that it hindered the patient from manipulating objects, making the administration of tests impractical. Therefore, the Nottingham Sensory Test, bi-dimensional geometrical shapes, 3-dimensional geometrical shapes, and meaningless-shapes were not administered to the right hand. Nevertheless, we tested the elementary sensory perception through: tactile detection of single and double touch, which were normal (both 40/40); pain discrimination (score: 6/10, significantly different from the controls, t(17) = -Inf, $p < .001$), temperature discrimination (score: 10/10), vibration (score: 9/10, significantly different from the controls, t(17) = -Inf, $p < .001$), proprioception (score: 5/10, significantly different from the controls, t(17) = -Inf, $p < .001$), weight (score: 8/8), texture (score: 7/8, significantly different from the controls, t(17) = -Inf, $p < .001$), and dimension (7/8, significantly different from the controls, t(17) = -Inf, $p < .001$). It can be evinced that, apart from simple tactile detection, temperature, and weight, 3

years from symptoms onset, C.P. did not have anymore the most basic sensory tactile abilities in the right hand.

We also tested the left hand, which did not have any deficit at the first assessment, even though for this hand the patient had not yet expressed any concern or difficulty.

All elementary sensory tests of the left hand were correct (simple tactile detection: 40/40, pain 10/10, temperature 10/10, vibration 10/10, proprioception 10/10), as the performance at the hyloagnosia tests (weight 8/8, texture 8/8, dimension 8/8). At bi-dimensional geometrical shapes discrimination, C.P. scored 7/8, which was not significantly different from the controls (M = 7.61±0.50, t(17) = -1.19, p = 0.252), while the score 7/8 of 3-dimensional geometrical shapes discrimination was different (M controls = 7.89±0.32, t(17) = -2.68, p = 0.016). Also, she lost two points in the meaningless-shapes test, scoring 9/12, which was significantly different from controls (M = 11.33±0.84, t(17) = -2.70, p = 0.015), determining the onset of morphoagnosia in the left hand.

From a cognitive point of view, C.P. remained stable across all the three years, in all cognitive domains, even though at the last neuropsychological assessment the MMSE score was lower than the first one (26.15 *vs.* 30), but still within the normal range. Also, apraxia for the right hand deteriorated (score 20/72 *vs.* 55/72 at first assessment), and it extended to the left hand (score 49/72 *vs.* 65/72 at first assessment; cut off = 62; Tessari et al., 2013). The Nottingham Sensory test for the left hand diminished only of one point, resulting 18/20 (*vs.* 19/20 at first assessment).

Neuroimaging exams

The MRI executed three years from symptoms onset showed a progression of the left frontoparietal atrophy (Figure 5.4), in the absence of a tumoral relapse. The DaTSCAN, previously negative, became positive, showing reduced integrity of the presynaptic dopaminergic system in the left putamen. From a neurological point of view, one year after the first assessment, the neurologist decided to introduce levodopa as a pharmacological treatment, suspended after about 6 months due to ineffectiveness.

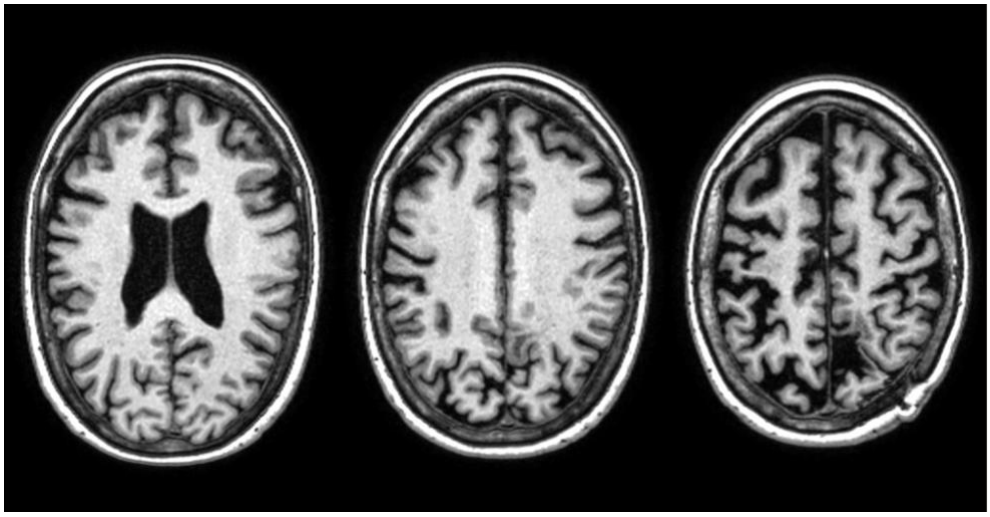

Figure 5.4. T1-weighted images of the CP's brain lesions three years after symptoms onset. Left hemisphere is on the left.

5.4 Discussion

At the very beginning of this study, we aimed to investigate clinically and experimentally a rare case of unilateral tactile agnosia. With the progression of time, while the diagnosis better delineated, we also became aware of the importance of this single case, for its implications in the study of both the manifestation and evolution of CBS, as well as tactile processing and object recognition.

Starting from the first assessment, it was possible to deduce the presence of tactile agnosia in the right hand, as the patient couldn't recognize objects, and her sensorimotor abilities, evaluated through elementary sensory tests, were intact, along with her cognitive capabilities. Thus, her difficulties could not be ascribed to basic tactile deficit nor to language difficulties in the access to semantics. When assessing the intermediate level of tactile processing, C.P. showed intact abilities in distinguishing texture, weight, and size with both hands, but she was different from control participants in naming materials and discriminating geometrical and meaningless-shapes only with the right hand. This result implied the presence of a unilateral right morphoagnosia, and the absence of hyloagnosia in most tasks, but with a difficulty in naming materials. In this regard, C.P. showed the ability to discriminate the texture, and she also correctly commented on the qualities of materials (e.g., "This is warm and soft" while manipulating the cotton), whereas she could not name them with the same level of accuracy as control participants. This opens up two possibilities: *(i)* the patient could have had an initial hyloagnosia for some specific materials only; or *(ii)* the patient did not have hyloagnosia, but rather a difficulty in accessing materials' names. Having correctly described the characteristics of the materials, we assume that if we had asked C.P. for a

comparison same/different of the materials, without naming them, she would have succeeded in the task. Thus, we consider the second to be the most likely hypothesis, so that the patient had intact hylognosis abilities but a reduced access to materials' names.

Although the complete absence of hyloagnosia remains the most likely but unconfirmed possibility, it is worth noting that this is the third case described in the literature with a dissociation between hyloagnosia and morphoagnosia (Kubota et al., 2017; Saetti et al., 1999). Furthermore, Kubota's model predicts that the processing of size is an intermediate function not entirely ascribed to hyloagnosia and neither to morphoagnosia (see Figure 5.1: Route A: processing of weight, texture, qualities of materials; Route B: processing of size; Route C: processing of shape). In our case, we could observe that perception of size was dissociated from shape discrimination, since C.P. correctly compared all sizes, but not the shapes, confirming the existence of a dissociation between the two (size *vs.* shape processing).

With regard to associative agnosia, as in the cases previously described in the literature, the patient managed to identify real objects with an accuracy of about 20%, as evinced by the 3 out of 12 objects correctly identify in the naming task, and the 24 out of 128 in the real object comparison. Although this accuracy rate is not sufficient to recognize object in daily life, nor to claim that the patient was capable of doing so, especially considering the long exploration time she needed before being able to identify them, it gives rise to interesting insights about the cognitive model of TOR. Indeed, it is possible to infer with a certain degree of certainty that the correct real object identifications were allowed by the intact hylognosis abilities. Having established that this was the only uncompromised pathway, dissociated from that of morphognosis, it is possible to confirm that the model proposed by Saetti (1999) and modified by Kubota (2017) is correct in predicting a non-serial processing of TOR. However, unlike other non-serial cognitive models, where the integrity of a pathway necessarily implies the absence of deficits in subsequent levels, in this case, we see that the integrity of the hylognosis pathway does not imply a complete integrity of the ability of recognize real objects (the highest, associative, level). Future studies need to clarify this aspect, and the pure possibility of accessing objects' identity and names from their qualities alone should be tested.

Finally, it is important to point out that, given the presence of apraxia in the right hand, the observed deficits may have been due to a difficulty in tactile exploration (Valenza et al., 2001). However, to exclude this possibility, at the end of the previously described assessment we tried to guide patient's exploration of both bi- and 3-dimensional geometric

figures, and the patient's response did not change. This confirmed the presence of a pure morphoagnosia.

The longitudinal follow-up of our patient allows to collect new evidence also concerning CBS. There are a few studies that systematically investigated the symptoms of CBS and related pathologies, and only in recent years there is a growing interest in better describing sensorimotor deficits of this condition, despite findings are inconsistent (Matsuda et al., 2020; Hu et al., 2009; Belfor et al., 2006; Rinne et al., 1994). Indeed, as discussed in the introduction (See paragraph 5.1), although “cortical sensory loss” is one of the diagnostic criteria for CBS (Armstrong et al., 2013), only one study provided a clear definition of it and clinically analyzed its characteristics in 14 patients with CBS (Matsuda et al., 2020). It is worth noting that in Matsuda and collogues’ study, texture perception was investigated using different materials (sandpaper, plastic, paper, vinyl, and paper towel), and they used Japanese characters or numbers for shape perception. Moreover, their study was a comparative study between patients with CBS and patients with Parkinson’s Disease (PD), not involving healthy controls. Thus, their results are not completely comparable to ours. However, they reported that none of CBS patients had impairments in shape or texture discrimination, nor in tactile object discrimination, whereas the 85% had difficulties in object naming. Our patient showed the opposite pattern: she showed morphoagnosia, without hyloagnosia in the majority of the task and a deficit in real object recognition, being the first case of CBS with morphoagnosia as disease onset described in the literature (Facci et al., in prep.).

For what concern other clinical characteristics, following Armstrong criteria (2013), we could conclude for the diagnosis of CBD with *Probable CBS* (i.e., Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus, plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)).

Finally, our case is in line with cognitive characteristics described by Jütten and colleagues (2014) in patients with right-side onset CBS. Indeed, as their cases, C.P. remained stable throughout the cognitive domains, while getting worse in apraxia, and she showed brain atrophy in frontoparietal area contralateral to the affected side.

The presented case highlights the need for further research on CBS and emphasizes the necessity to clarify its diagnostic criteria. As introduced by previous authors, given CBS asymmetric onset and predominant involvement of sensorimotor aspects, it could be crucial to begin studying CBS cases separately, based on the side of the body firstly involved.

Additionally, the assessment of sensorimotor deficits is essential, and it needs to be standardized across studies. Our study demonstrated that, if thoroughly investigated, morphoagnosia can emerge as one of the early symptoms to monitor for CBS diagnosis.

GENERAL CONCLUSIONS

This dissertation focused on the delicate phase of aging, which, while not manifesting as cognitive deterioration, may serve as its precursor. Given that the population is increasingly aging, it is crucial to prevent the onset of cognitive symptoms and the decline in daily life autonomy in the elderlies. Additionally, there is need to refine early diagnosis and develop novel intervention strategies.

In Study 1, we tested the efficacy of a technology-based intervention for single and multiple-domains aMCI patients, consisting in PA plus SG (MindLenses protocol), with the question as to whether PA may enhance the effectiveness of the games alone. Although there were no differences between the experimental (real lenses plus SG) and the control groups (sham lenses plus SG), we can conclude that, overall, the 5-weeks treatment with SG has been beneficial in preventing the cognitive deterioration in that amount of time, and in sustaining long-term memory and attention. Moreover, from a neurofunctional point of view, we observed an increased anti-correlation between the DMN and the DAN during resting-state in the experimental group, as compared with the control group, after the treatment. This result is in line with our hypotheses, and it reflects the potential neurofunctional modulation of PA. These findings are encouraging, although they are based on a small sample size: as initially determined, we are going to recruit more MCI patients to validate the outcomes. Yet, our Study 1 demonstrated the feasibility of a technology-based intervention with MCI patients and that PA can be transposed to a tech-device support with the same effect of the traditional set-up, together with its practical advantages.

Furthermore, since it has been argued that the attentional subcomponents, especially the executive control, might be useful in distinguishing between healthy and pathological aging, we explored whether these differences were also true for our MCI sample of Study 1, comparing our patients to a healthy matched-control sample (Study 2.2). We also decided to investigate the role of PA in sustaining attention in healthy aging (Study 2.1). In contrast with previous studies in the literature, we did not find a difference between MCI patients and healthy elderly in the executive control, whereas a significant difference emerged in the total RTs, comprising together alerting, orienting, and executive control. For what concerns attention modulation in healthy elderly, we only found an effect of PA on the alerting component. Future studies should focus on understanding the relationship between alerting and executive control in both healthy and pathological aging, in order to clarify which is the best rehabilitation target to sustain attention capabilities in the elderlies.

Finally, in the last part of this dissertation, I presented a single case of CBS (Study 3), a neurodegenerative disease firstly described in the 1960s and still poorly known. The initial symptoms of our patient were difficulties in haptically recognizing objects in daily life and a reported altered sensitivity. We analyzed her sensorimotor abilities and tactile processing from the lowest to the highest level of perception, and we followed her progression for three years. In the first assessment, we discovered a unilateral right morphoagnosia without hyloagnosia in most tasks. Her symptoms extended to the left limb after three years from onset and, neurologically, there was evidence of a progression of fronto-parietal atrophy. The patient represents the third described case with such a dissociation between morpho- and hyloagnosia at the intermediate level of tactile processing, and the first described CBS case with tactile agnosia as onset.

Altogether, the presented studies demonstrate that in-depth cognitive assessments can measure cognitive changes in prodromic stages of neurodegenerative diseases, not commonly detected through standardized neuropsychological tests, even in the absence of cognitive decline. For example, changes might occur in the realm of attention in MCI patients and in tactile recognition in patients with early-stage CBS. At the same time, the use of targeted cognitive stimulations to support such changes, with the use of serious games, can yield benefits to the patients.

Since computerized interventions with serious games are becoming easily accessible nowadays, our findings suggest that early diagnoses and non-specific domain cognitive stimulations can and should become a priority in the care of the elderlies.

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