FACULTY OF MEDICINE AND PSYCHOLOGY
Psychology department

PhD in Behavioral Neuroscience:
Psychobiology and Psychopharmacology

"Verbal and visual dissociation in retrieval practice paradigm in neurodegenerative diseases."

Dottorando:
Di Domenico Carlotta

Tutor:
Prof. Bozzali Marco

“C’è in noi un bisogno radicale di
riconoscimento che non ha niente a
che fare con l’ammirazione, la stima, la fama.
È come un bisogno di benedizione,
di parentela o almeno di familiarità,
di iniziazione superata,
di passaggio a stirpe che ti sceglie
all’improvviso e ti dà il nome.”

Chandra Candiani

Index:

Bibliography

Other publications

Abstract

As is well known, prefrontal functions assert the control of inhibition for the retrieval of semantically related elements that lead to forgetfulness.

The aim of this study is to document any verbal and visual dissociation in the Retrieval-Induced Forgetting (RIF). We want to test the hypothesis that representations in long-term visual memory are sufficiently rooted to be immune to impairment based on recognition, unlike oblivion induced by the retrieval of verbal material. The aim of this project is also to investigate which brain areas are most involved in the processes of inhibition and facilitation in patients with different types of cognitive impairment.

To do this, 21 patients with Alzheimer's disease (AD), 21 mild cognitive impairment (MCI), 16 patients with subjective cognitive decline (SCD) and 23 healthy subjects (HS) were enrolled. All participants underwent an extensive neuropsychological evaluation by Addenbrooke's Cognitive Examination-Revised (ACE-R; Mioshi et al., 2006) and the Retrieval Practice Paradigm (RPP), with an experimental recognition task, where the same items were presented both in visual and verbal form to calculate, at a group level, the RIF and FAC (facilitation effect) effects.

Only subjects who did not have contraindications to perform MRI, (14 AD, 16 MCI, 14 SCD and 18 HS) underwent 3 T-MRI scanning including a T1-w volume. Voxel-based morphometry (VBM) was used to assess associations between grey matter (GM) volumetrics and RPP indices: items practiced by practiced categories (Rp+), items which were not practiced, but were members of the same category as the Rp+ items (Rp-), items which received no additional retrieval practice and were not members of a practiced category (Nrp) in each group separately.

ANOVA models were used to assess cross-sectional differences in all neuropsychological measures and experimental conditions and effects. In each of the 4 groups, separately, Pearson's correlations were used to assess potential association between each domain of ACE-R and the three RPP indices (Nrp, RP +, Rp-).

Regarding the results about the RPP indices (Nrp, RP +, Rp-), for the verbal task, we observed a significant between-group difference in Nrp items. Post-hoc showed that the proportion of items in the Nrp condition is statistically higher in HS group than AD group. Moreover, we found a significant effect of group in Rp+ items: post-hoc revealed a significant

difference between AD and SCD and between AD and HS. Interestingly, the tendency of significance was present on the comparison between AD and MCI. No significant differences were observed between MCI and SCD and between MCI and HS. Similarly, HS and SCD groups showed comparable performance on Rp+ items.

Regarding the RPP effects (RIF and FAC), we observed a significant main effect of group in the FAC effect. Post-hoc revealed significant a main effect of group since AD recognized less items than SCD and HS, respetively. We found also a significant main effect of Condition, because the proportion of items retrieved in the Rp+ condition is statistically higher than that retrieved in the Nrp condition in all groups. Finally, we found no significant Group by Condition interaction indicating that the FAC effect was present in all considered groups.

Finally, regarding the RIF effect, we observed a significant main effect of group, due to a significant difference exclusively between AD and HS groups; we revealed no significant effect of condition: indeed, in this case the means of item retrieved in two conditions Nrp and Rp- were almost the same. Finally, we found a significant Group by Condition interaction. The planned comparisons showed that the RIF effect was present in the SCD group only, but no RIF effect was observed in AD, in MCI and HS groups.

For the visual task, no significant differences were observed between groups in the accuracy of the Nrp items, RP+ items, RP- items.

As regards the FAC effect, we observed a significant main effect of group, due to a significant difference exclusively in the recognition of the global accuracy between AD and HS groups. We found also a significant main effect of Condition: in this case, the Rp+ items were better recalled than Nrp items in all groups. Finally, we observed no significant Group by Condition interaction, indicating that the FAC effect was present in all groups.

Furthermore, about the RIF effect, in the verbal task, we observed no significant main effect of group, but significant main effect of Condition, since the Nrp items were better remembered than Rp- items. Moreover, we found no significant Group by Condition interaction: in this case, the planned comparisons revealed that the RIF effect was present in the SCD only.

Comparing the groups individually, no significant dissociation emerged between two tasks, verbal and visual. There is only a tendency in SCD, due to greater accuracy of subjects who

performed the verbal task, compared to those who performed the visual task, in the Rp- condition.

For the MRI analysis results, in the Verbal task, VBM results showed in AD patients, revealed a positive association between Rp- items and GM volumes in the Right Putamen, Cingulus Gyrus and Left Putamen.

In the Visual task the VBM analyses, revealed in AD patients a positive association between Nrp items and GM volumes in the Middle Frontal Gyrus, Inferior Frontal Gyrus, pars triangularis and Insular Cortex.

Moreover, in SCD subjects, a significant positive association were found between Rp- items and GM volumes in the Postcentral Gyrus, Supramarginal Gyrus, Superior Frontal Gyrus, and Precuneous Cortex, bilaterally.

In conclusion, in our study, in line with other experiments (Hogge et al., 2008; Saunders and Summers., 2011; Traykov et al., 2011; Ortega et al., 2012; Serra et al., 2022), shows the presence of an inhibitory effect: the RIF is not evident in the pathological group of AD and MCI, but not even in healthy subjects, which generally show good inhibition capacity; this result could be because the recognition task was too simple for healthy subjects, who were able to recall multiple items without distinction. Although there is a trend, in both tasks, in favor of a RIF effect as the pathology increases.

We can also hypothesize that the worse performance observed in the RIF obtained from patients is not a direct expression of an inhibitory deficit but could depend on a general deficit of episodic long-term memory processes.

Chapter I
Introduction

1.1 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder, and it is the prevalent form of dementia. This disease is named after the German neurologist Alois Alzheimer who first described its characteristics in the early 1900s. As stated by Knopman and colleagues about this disorder: "ss characterized by β-amyloid (Aβ)-containing extracellular plaques and tau-containing intracellular neurofibrillary tangles" (Knopman et al., 2021). AD typically presents with prominent amnestic cognitive impairment as early clinical sign but can also less commonly manifest as non-amnestic cognitive impairment (Knopman et al., 2021). It may also occur impairment of language, executive functions, or visuospatial skills as clinical onset. During the clinical course accumulation of cognitive dysfunctions is unavoidable.

A study by Knopman et colleague's states that there is a complex relationship to genetics in many patients with AD, though most cases (*however most cases*) are not dominantly inherited (Knopman et al., 2021). In patients with AD, we have different severities of cognitive impairment; we may have as the initial manifestation of the condition, a subjective decline in cognitive function or in mental abilities, even in the absence of impaired performance on cognitive tests (Jessen et al., 2014).

The preclinical phase of AD is called mild cognitive impairment (MCI): the first symptomatic stage of cognitive impairment. MCI is a clinical condition in which one or more cognitive domains can be compromised at least to a slight extent, while the skills of daily functions are relatively preserved (Petersen et al., 2004), dementia, instead, is a cognitive deterioration that affects and compromises independence and daily life. McKhann (2011) says: "the prototype clinical phenotype of AD is dementia with gradual onset and continuous progression with prominent amnesic symptoms and signs" (McKhann et al., 2011).

1.1.2 AD Classification

McKhann and colleagues (2011) proposed the following terminology to classify patients with dementia caused by AD: (a) *Probable AD dementia*, (b) *Possible AD dementia*, and (c) P*robable or possible AD dementia with evidence of the AD pathophysiological process (*McKhann et al., 2011*)*.

According to these criteria of McKhann, probable AD dementia is diagnosed when the patient has the following characteristics:

A) Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days.
B) Clear-cut history of worsening of cognition by report or observation.
C) The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a) *Amnestic presentation*: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
b) *Nonamnestic presentations*:

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D) The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Patients recruited into our study (Amnestic AD) reflect the typical onset with memory impairment.

1.1.3 AD Epidemiology

Though AD is the most common cause of dementia (Schneider et al., 2009) is entwined (*is cross – is crossed*) with that that of all-cause dementia (Nelson et al., 2011; Boyle et al., 2018), there are different types of dementia, and they can be caused by different pathologies, especially in older individuals. The prevalence of overt cognitive impairment increases with advancing age the incidence of dementia extended after 65 years and continues to increase after that (*following that*), the incidence of all-cause dementia in individuals aged 65–70 years is approximately 1 per 100 per year and increases to 4 per 100 per year in those aged 80–90 years (Niu et al., 2017, Knopman et al., 2021).

Prince and colleagues (2016) conducted a review of twenty-one studies on incidence and trends in prevalence for individuals with dementia, data emerged from this review suggesting that the incidence of dementia may be higher in low-income countries, and decreasing in

high-income countries, although the evidence emerged was inconsistent among the reviewed studies and did not suggest a clear overall effect (Prince at al., 2016).

1.4 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a clinical condition that indicates a greater cognitive decline than expected for the reference age, but not severe enough to significantly affect the subject's daily life. This condition is not synonymous with Alzheimer's disease, it can remain stable over time and there is not necessarily a progression of the disease towards dementia. MCI is therefore a syndrome that can be defined by functional, clinical, and cognitive symptoms, and is considered a high-risk factor for the development of Alzheimer's disease; over the years, from a clinical point of view, changes may occur at the cognitive level and in memory, this condition is called "age-related cognitive decline" (Sanford, 2017), these changes are part of normal aging.

An important change from a clinical point of view took place in 2013, when the American Psychiatric Association published the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), where the category "dementia, amnesic delirium and other cognitive disorders" has undergone a revision, compared to previous editions. The category has been renamed “neurocognitive disorders” (NCD), and concerns: delirium, main NCD, mild NCD. Furthermore, the DSM-5 specifies that these symptoms must occur associated with a decline in one or more of the 6 cognitive domains involved in the pathology (memory, executive functions, attention, language, visuospatial skills). These symptoms should not interfere with normal activities of daily living, and present in the absence of delusions or other psychological disturbances (American Psychiatric Association, 2013).

The National Institute on Aging-Alzheimer's Association (NIA-AA) working group outlined the clinical criteria for identifying symptomatic individuals who do not conform to the pathophysiology of AD (Reiman et al., 2011); in these individuals, family members or themselves, identified cognitive disturbances with respect to previous normal functioning. These deficits can affect one or more cognitive domains: memory, attention, language, executive functions and / or visuospatial skills. Albert and colleagues (2011), about the subject with MCI, state that "The patient can maintain good independence in daily life, as these changes are minor and have a low impact on the patient's general functioning" (Albert et al., 2011).

1.2.1 MCI classification

Clinical diagnosis is made by integrating the anamnesis, neuroimaging techniques, and carrying out neuropsychological tests.

Peterson and colleagues (2014) divide MCI patients into two categories:

- *amnestic MCI* (amnestic MCI, a-MCI): this category of patients performs below the normality cut-off of episodic memory.
- *non-amnestic MCI* (non-amnesic MCI, na-MCI): i.e., patients who present pathological performances in cognitive domains other than memory, for example language, executive functions and visuospatial skills

There is a further distinction, regardless of the category to which they belong (a-MCI, na-MCI), which concerns the impairment of a single cognitive domain (single domain MCI), or more cognitive domains (multiple domain MCI). It is therefore possible to have four different subtypes of MCI: a-MCI single domain, a-MCI multiple domain, na-MCI single domain, na-MCI multiple domain (Petersen et al., 2014).

Among the criteria related to the research emerges the use of biomarkers of different classes for the diagnosis of "MCI due to AD" (Albert et al., 2011): some of these directly reflect AD, signaling the presence of abnormal proteins in the brain such as beta-amyloid protein or tau, and include cerebrospinal fluid analysis of beta-amyloid levels and traces of beta-amyloid detected by PET (Selkoe, 2005). In fact, the low level of beta-amyloid and the high presence of tau protein in CSF indicate a high probability of progression to Alzheimer's disease in MCI patients (Blennow et al., 2003; Shaw et al., 2009).

Another group of biomarkers reflects the biochemical changes related to the processes of cell death, synaptic damage, oxidative stress and inflammation, these may play a role in both the damage and the response to damage caused by AD pathology (Albert et al., 2011). Biomarkers can be classified among those that indicate a high probability that MCI syndrome is due to AD disease, others that indicate a medium-low probability that MCI syndrome is due to AD disease and biomarkers that almost completely exclude the possibility that MCI syndrome is due to AD disease. MCI syndrome is due to AD pathology (Albert et al., 2011).

Albert and colleagues classified MCI subjects according to the likelihood of developing Alzheimer's disease:

• MCI - *Core Clinical Criteria*: individuals who meet the basic clinical criteria for MCI diagnosis and who have a high risk of progression to AD; these patients perform poorly on episodic memory tasks.

• MCI due to AD - *Intermediate Likelihood*: these are patients who meet the basic criteria for diagnosis, but also have positive biomarkers for beta-amyloid deposits or for neuronal damage and have an average probability of developing AD.

• MCI due to AD - *High Likelihood*: these are patients who meet the basic criteria and have positive biomarkers for both beta-amyloid and neural damage, therefore they have a high probability of developing AD.

• MCI - *Unlikely due to AD*: individuals who have negative biomarkers for both indices and are therefore less likely to develop AD.

1.2.2 MCI epidemiology

There is a degree of variability in the results regarding the prevalence of MCI disease in the population. This variability may be caused by the population studied, the distribution by age and sample size, and the use of different criteria for MCI (Petersen et al., 2010). Ladavas and Berti (2014) say that: "the prevalence of patients with MCI varies according to age as a prevalence of 5-10% has been estimated in subjects aged up to 65 years" (Ladavas and Berti, 2014), a prevalence between 12% and 18% in subjects over 60 years of age (Larrieu et al, 2002; Di Carlo et al., 2007; Ganguli et al., 2010) 16% over 70 years (Petersen et al.,

2010) while it reaches 20-25% in the population over 80 years old (Ladavas & Berti, 2014). The progression rate of MCI patients in dementia varies from 8% to 15% per year, this implies that it is an important condition to identify and treat (Petersen et al., 2016).

In a retrospective study by Petersen and colleagues (2010), it was highlighted that MCI pathology manifests itself more in men than in women, these results are in line with previous studies on MCI (Koivisto et al., 1995; Ganguli et al., 2004); however, there are two studies (one Italian and one French) which demonstrate that MCI prevalence is in women compared to men (Larrieu et al, 2002; Di Carlo et al., 2007). The prevalence of gender therefore seems not yet to be a shared fact in the literature that deals with the demographic characteristics of subjects with Mild Cognitive Impairment.

In a longitudinal report by Roberts and colleagues (2012), MCI patients aged 70 or older were evaluated over 5 years; the outcomes showed that the illness movement rate is somewhere in the range of 5% and 6%, also the speed is straightforwardly relative to progress in years (Roberts et al., 2012). Besides, subjects with MCI progress rapidly throughout brief timeframes (Roberts and Knopman, 2013).

1.3 Subjective Cognitive Decline

1.3.1 Definition and characterisation of SCD

Nowadays, there is a greater awareness of Alzheimer's disease and an increasing attention to the well-being and health of the brain (Jessen et al., 2020).

This awareness is pushing more and more people (including the elderly and not), worried about having some disorder (mainly concerning memory or attention), to contact specialized medical facilities and centers to be examined and undergo clinical examinations and tests. neuropsychological. These tests can provide objective data on the possible presence and degree of functional and cognitive impairment.

From this condition, of more and more people who present themselves spontaneously, in 2014 the term "subjective cognitive decline" (SCD) was born. Most people with SCD do not show progressive cognitive decline, although epidemiological data provide evidence that there is an increased risk of cognitive impairment and dementia in SCD individuals (Jessen et al., 2020).

The interest in this recent and growing phenomenon has given rise to an increasing number of studies, which investigate the link between the earliest forms of AD and SCD (Jessen et al., 2020). As already mentioned, it may happen that some subjects report a (subjective) decreases in one or more cognitive functions, which are not however found in the test performance results, thus resulting in HS.

Regardless of the absence of evidence for objective cognitive impairment (as measured by tests), subjective malaise due to impaired cognitive function experienced by subjects may become increasingly important to physicians as the number of subjects with these concerns seeking medical help and advice is on the rise (Jessen et al., 2020, Slot et al., 2019).

Since the 1980s, various studies have been interested in the association between subjective decline in cognitive functioning and aging, objective test performance and future risk of cognitive decline. It is important to underline that SCD is not a diagnostic category of the Diagnostic and Statistical Manual of Mental Disorders-5., the International Statistical Classification of Diseases-10, or the International Classification of Diseases-11.

An international working group of researchers and clinicians, known as the SCD-initiative (SCD-I), in 2014, worked to create a framework of standardized criteria to identify SCD. These criteria are divided into two main characteristics:

a) A self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event. (That is, that the cognitive decline that the SCD complains of is only subjective. No observation of the deficit by others is required)

b) The individual's cognition is unimpaired from an objective standpoint; there must be a normal performance on standardised cognitive tests used to classify MCI, adjusted for age, sex, and education.

To date, being a relatively recent phenomenon, there are few tools to classify the severity of SCD, but they are increasing, being a phenomenon of growing interest. Some of these tools include: the Cognitive Function Index (Amariglio et al., 2015), the Cognitive Change Index (Rattanabannakit et al., 2016), the Everyday Cognition questionnaire (Tomaszewski et al., 2011) the Subjective Cognitive Decline questionnaire (Rami et al., 2014), the SCD interview (Miebach et al., 2019), or a simple two-question approach about their decline in memory and any associated concerns (Jessen et al., 2010).

Until now, there is no validated cut-off to differentiate individuals with SCD from those without SCD in the clinical setting, only indices; what distinguishes an MCI patient from an SCD subject (up to now) is the absence of objective cognitive impairment.

With aging, there are many physiological mechanisms related to various pathologies that could contribute to a slight decline in cognitive functions. Primarily, these "dips" in cognitive function involve memory, executive functions, processing speed and visuospatial abilities (Harada et al., 2013; Hoogendam et al., 2014).

Many people, as they age, notice some cognitive changes; Population studies (Jessen et al., 2010; van Harten et al., 2018) show that between 50% and 80% of older individuals (aged 70 and over), who perform cognitive tests by normal limits, signal a "lowering" of one or more cognitive functions (Jessen et al., 2020).

1.3.2 SCD and future risk of cognitive decline

Meta-analysis longitudinal epidemiological studies (Mitchell et al., 2014) on cognitively healthy subjects with SCD, with at least 4 years of data obtained from follow-up studies, they identified a future conversion to dementia in 14% of subjects and to MCI in 27% of subjects. Although SCD does not correlate directly with cognitive impairment in most cases, this condition may prove to be an early indicator of future cognitive decline for some individuals (Slot et al., 2019). Long-term prospective studies (Amieva et al., 2008; Verlinden et al., 2016)

in individuals who eventually developed dementia suggest that the subjective perception of cognitive decline occurs, on average, about 10 years before the diagnosis of dementia (Jessen et al., 2014).

As mentioned, Jessen and colleagues (2014) published an article in which they suggest criteria for identifying SCD, subsequently, they also have the "SCD plus" condition which is more related to dementia for certain characteristics (Jessen et al., 2014), the criteria for this condition are constantly subject to revision and may be subject to change in the future.

The first SCD plus feature concerns the subjective decline in a subject's memory, regardless of the decline of other domains. This feature, however, is because most SCD studies have focused on memory.14 Indeed, the association between the extent of subjective decline in other cognitive domains and future objective cognitive decline is uncertain (Jessen et al., 2020; Valech et al., 2018; La Joie et al., 2016)

The second characteristic described concerns the fact that the perception of cognitive decline is present in the 5 years prior to when the subject requires a diagnostic assessment.

This feature is based on longitudinal studies (Amieva et al., 2008; Verlinden et al., 2016) which show that the onset of SCD occurs approximately 10 years before a diagnosis of dementia. Taking into consideration that individuals with cognitive decline will switch to MCI before converting to severe dementia, a 5-year earlier onset of SCD is less likely to be related to future dementia than an onset of SCD within 5 years.

The third characteristic of SCD plus concerns the age of onset of the subjective perception of cognitive decline. Subjects must be over 60 years old. In people younger than 60, the likelihood of a medical condition causing future cognitive decline and dementia is low, suggesting that the likelihood of SCD in people younger than 60 is related to other potentially reversible causes (e.g., depression)

The fourth SCD plus feature concerns "worry", or the extent of concern about the perceived presence of changes in cognitive abilities. There is evidence that individuals who express high levels of concern about the perception of their cognitive decline have a higher risk of developing objective cognitive decline or dementia in the future (Jessen et al., 2010; Verfaillie et al., 2019).

The final SCD plus feature concerns the confirmation (or denial) of cognitive decline by an outside observer. A subject with SCD who receives confirmation of cognitive decline also perceived by an observer is more likely to have a future cognitive decline (Valech et al., 2015). However, recent evidence suggests that only the individual with SCD will experience early cognitive decline, which will only be noticed by observers at a slightly more advanced stage. Several studies show that this sequence also occurs before subjects reach the MCI stage (Caselli et al., 2014; Nicholas et al., 2017).

Jessen and colleagues, in a second study (2020) added two additional criteria to those previously proposed for the characterization of SCD-plus (Jessen et al., 2014).

The first concerns the continuity over time of concerns about perceived cognitive decline (rather than sporadic complaints about some difficulties sometimes experienced). In fact,

some evidence reports that subjects who are constantly and repeatedly concerned about their cognitive abilities over time run a greater risk of future objective cognitive decline than those who report a subjective decline in cognitive function only occasionally. (van Harten et al., 2018; Roehr et al., 2016; Wolfsgruber et al., 2016).

The second added criterion concerns the search for medical assistance due to the difficulties experienced. This feature is associated with a higher risk of future objective cognitive decline in individuals with SCD than in those with SCD not seeking medical care (Slot et al., 2019; Snitz et al., 2018).

Unfortunately, there are still very few studies on these people, considered “borderline” between the patient and the HS.

1.4 Memory disorders in AD and MCI

We can define memory as a process of encoding, storing and retrieving information concerning stimuli that can be outer or inner; memory has been classified into several categories, with different neuroanatomical and neurophysiological correlates: short-term memory, long-term memory, implicit and declarative memory.

Mainly, the first clinical manifestations of AD, as we have already said, begin with episodic memory, language disorders like speech production, with naming or semantic problems [this one loss in AD may occur several years prior to diagnosis (Verma et al., 2012)] or with orientation deficits. The cognitive profile of AD, with deficits in multiple cognitive domains, develops over time and patients often begin to show a progressive decline in working memory, for example they become more easily distracted in memory tasks, even if in other tasks, in the initial phase of the disease, they can be fine, as for example in the digit span.

In patients with AD, damage to the frontal subcortical circuits associated with attention and working memory deficits also affect executive functions, this involves the impairment of skills such as planning and problem solving, so test scores in the Stroop test, the Tower of London Test, or the Wisconsin Card Sorting Test, are below (*under*) the norm. As Jahn Statein 2013: "The manifestation of impairment in such tests of executive functioning corresponds to the onset of difficulty in carrying out daily activities in these patients and marks the progression to the state of total dementia" (Jahn, 2013).
As mentioned, changes in multiple cognitive domains are known in MCI patients including memory, executive functions, attention, language, and visuospatial skills. Impaired episodic memory is most regularly found in MCI patients who subsequently develop AD dementia (Albert et al., 2011). Recent research supports the hypothesis that a-MCI have the highest conversion rate to AD due to early episodic memory deficits, language / semantic memory, attention, and even short-term memory deficits are considered strong predictors of progression from MCI to AD (Saunders et al., 2014).
Murphy and colleagues (2008) claim that (*assert that*): “Amnesic cognitive impairment (a-MCI) is characterized by the decline in antegrade memory as measured by the ability to learn and remember new information”. A-MCI patients show a specific volume loss of the hippocampus and the entorhinal cortex of the medial temporal lobes. The atrophy of these

regions can be considered a factor of progression from a-MCI to AD (Murphy et al., 2008; Serra at al., 2010).

In a 2004 study conducted by Gonzalez and colleagues, semantic memory deficits were investigated: a group of healthy subjects, MCI patients who had not developed dementia and MCI patients who had subsequently developed dementia were considered. MCI patients achieved intermediate results between healthy subjects and MCI patients who had developed AD, the study confirmed that semantic memory is also reduced in MCI patients. These studies indicate that episodic memory and semantic memory are affected by mild cognitive impairment and may be related to early degenerative changes in a network extending from the medial temporal lobe to related neocortical regions (Estevez-Gonzalez, 2004).
In another study, conducted by Perri and colleagues (2005) the different aspects of episodic, short-term and long-term memory in a-MCI patients were investigated; it was possible to observe a maintenance of short-term memory in the a-MCI patients in contrast to the tests conducted to measure the episodic memory indices since the results obtained were lower in the a-MCI patients compared to the control group. (Perri et al., 2005)

1.5 Structural brain changes in AD and MCI

To date, thanks to quantitative magnetic resonance techniques, it is possible to non-invasively detect tissue parameters that are believed to reflect some pathophysiological aspects of brain damage, which play different roles in the various stages of the disease (Bozzali et al., 2016).

By being able to quantify these parameters, we obtain data that can be useful for longitudinal analyzes and statistical comparisons, allowing the study of associations between brain tissue alterations and various factors, including genetic and environmental data, clinical, neuropsychological and behavioral (Bozzali et al., 2016).

Quantitative magnetic resonance imaging is used for example in studies on dementia, for example we can measure, with high anatomical resolution, various pathophysiological aspects of pathologies, including focal cerebral atrophy, loss of regional gray matter, structural disconnection of the brain (or microscopic damage of the white matter), functional disconnection and metabolic abnormalities (Bozzali et al., 2016).

Brain volume also highlighted some critical aspects of Alzheimer's disease in vivo (Bozzali et al., 2016). Data extrapolated from volumetric measurements, which are based on high-resolution T1-weighted volumes, are used for different types of image analysis, which can be manual or semi-automatic approaches for measuring volumes of specific brain structures (e.g., volumetry hippocampus), or even voxelwise methods, which analyze the entire brain.

The healthy human brain, like all organs, undergoes normal "aging", in patients with Alzheimer's disease, however, the damage is widespread: many neurons stop functioning properly and lose connections with other neurons. In the first phase of the disease, the first deteriorated areas usually involve memory, such as the hippocampus and the entorhinal cortex, this brain atrophy gradually spreads causing significant loss of brain volume. Thanks

to neuroimaging techniques it is possible, for example, to obtain an objective measurement of the loss of gray matter in the areas affected by atrophy, and therefore to try to identify the structures most affected by the development of Alzheimer's disease.

Chètelat and colleagues (2005) conducted a Voxel Based Morphometry (VBM) study on AD patients in different phases of the disease; this study showed a loss of gray matter located mainly in the hippocampus and cingulate gyrus (Chètelat et al., 2005). In a previous study, using again the VBM, Karas and colleagues (2004) showed that in MCI patients there is also a significant reduction of gray matter in the insula and thalamus (Karas et al., 2004). MCI patients, compared to Alzheimer's, show greater conservation of gray matter in the parietal associative areas and in the anterior and posterior cingulate (Bozzali et al., 2016). These studies suggest that medial temporal lobe atrophy is already present in the prodromal condition of MCI, while a more widespread condition of cortical atrophy is typical of Alzheimer's disease (Karas et al., 2004). Thanks to the VBM studies it is also possible to detect the volumetric differences between MCI with different clinical manifestations (Bozzali et al., 2016): the a-MCIs show patterns of gray matter atrophy like those observed in Alzheimer's patients, while patients with MCIs are characterized by atrophic patterns indicative of other forms of dementia (Whitwell et al., 2008; Serra et al., 2013).

From a study by Serra and colleagues (Serra et al., 2010) it emerged that AD patients are characterized by diffuse patterns of brain atrophy compared to HS, particularly in the temporal, parietal and frontal lobes, and that a-MCI, compared to AD, have larger volumes of gray matter in the precuneus, in the supramarginal gyrus (bilaterally), in the left insular cortex and in the temporo-occipital area of the frontomedial gyrus, indicating a relative conservation of these areas. Of great importance are the data derived from the comparison between a-MCI patients and control subjects within the same study (Serra et al., 2010): a-MCI patients have a reduced volume of the hippocampus and amygdala bilaterally, bilaterally parahippocampal gyrus, left fusiform temporal gyrus, right insular cortex and precuneus.

Since MCI is a disorder characterized by a clinical course, it is important to characterize its neuropathological changes. As previously described, the clinical definition of MCI is distinguished in a-MCI and na-MCI. In a longitudinal study carried out on MCI patients conducted by Serra and colleagues (2010) it was observed that the a-MCI and na-MCI patients can be distinguished both from a neuropsychological point of view and from a cerebral point of view, confirming the hypothesis that specific patterns of brain atrophy can predict the progression of this condition in different forms of dementia. A-MCI patients present with gray matter atrophy mainly in the hippocampus, entorhinal cortex and orbitofrontal cortex, bilaterally: BA11 and 47 (Serra et al., 2010). A-MCI subjects are at high risk of conversion to AD, as the entorhinal cortex, involved in the processing of memories, is affected in the early stages of the disease. On the other hand, na-MCI patients show more dysfunction of executive functions due to the impairment of the orbitofrontal cortex (BA25) and of the basal ganglia.

It also emerged that a-MCI patients have larger volumes of gray matter in the precuneus, in the supramarginal gyrus, in the left cortex, in the temporal-occipital area of the fronto-medial gyrus, compared to AD (Serra et al., 2010).

Although Alzheimer's is considered a disorder that mainly involves GM (Bozzali et al., 2016), it is also important to consider the changes affecting the WM white matter. The presence and extent of atrophy in terms of WM in the patient with Alzheimer's disease is assessed through appropriate neuroimaging techniques. As mentioned, these techniques allow to quantify the damage to microscopic tissue (Serra et al., 2010).

MRI diffusion tensor imaging (DT26 MRI) reflects tissue size, orientation, and organization, in a non-invasive way, enabling measurement of the random movement of water molecules (Basser et al., 1994). Voxel-based methods can also be used on DT-MRI to reflect specific anatomical distributions of microscopic white matter abnormalities in patients with different forms of dementia (Rose et al., 2008; Matsuo et al., 2008). Thanks to a DT-MRI analysis method, called SSD, it is possible to perform voxel-wise statistical analyzes of fractional anisotropy (FA) and other indices derived from DT-MRI images. The FA is a measure of the intravoxel coherence of the direction of the white matter fiber, therefore it reflects the structure and organization of the tissue (Pierpaoli & Basser, 1996). Another measure of tissue microstructure provided by DTMRI is the mean diffusivity (MD), an unchanged directional estimate of the mean magnitude of the diffusion shift in a voxel (Basser & Pierpaoli, 1996). A consistent pattern of damage in all main sections, with a relative saving of the motor pathways and occipital lobes. These studies pointed out that the extent of the damage correlated significantly with the patients' overall level of cognition.

Through the first DTI studies carried out on patients with Alzheimer's disease (Hanyu et al., 1998; Bozzali et al., 2002), where the integrity of WM was assessed, measured by MD and FA, a consistent pattern of damage was found in all the main tracts, with a relative saving of the motor pathways and occipital lobes. These studies pointed out that the extent of the damage correlated significantly with the patients' overall level of cognition.

In 2011 a study conducted on AD and healthy subjects (HS), Canu and colleagues studied the independent contribution of macrostructural atrophy and microstructural alterations on AD pathology (Canu et al., 2011). All participants underwent MRI, the microstructural damage was assessed by processing the images, obtaining volumes of gray and white matter, and for the evaluation of macrostructural atrophy with FA and MD.

The authors found microstructural differences between patients and controls in temporal and retrosplenial regions, thalamus, corticopontine tracts, striatum and precentral gyrus, which were independent of macrostructural atrophy (Canu et al., 2011). Moreover, they also revealed volumetric differences especially in the entorhinal cortex, posterior cingulate and splenium (Canu et al., 2011).

Serra and colleagues (2017) studied the frontal aslant tract (FAT), studying its microstructural integrity and its potential relationship with cognitive functioning, in patients with AD. 23 AD and 25 HS patients were recruiter, all subjects underwent cognitive examination and MRI, to study probabilistic tractography analysis.

We reconstructed the individual FAT bilaterally and evaluated their microstructural integrity using the FA, calculated both as the mean tract value of the stretch and in terms of voxel (Serra et al., 2017). The study found that mean tract FA and voxel-wise analyzes revealed that patients with AD, compared to HS, had a decrease in FA in both FAT, revealing bilateral damage of FAT in patients. Mean FA values were correlated with cognitive measures obtained from tests and, in patients, positive associations were found between FA in FATs and test performance for constructional praxis and visuospatial logical reasoning (Serra et al., 2017).

In a postmortem study conducted by Mufson (2012) in a-MCI, AD and HS observed a widening of the sulci such as the ventral portion of the lateral fissure and a thinning of the anterior part of the temporal lobe, in a-MCI patients and with mild AD, compared to HS. These morphological changes are magnified and extended to other cortical regions in the advanced stage of AD.

Karas and colleagues (2004) observed that MCI patients also have a reduction of gray matter in the insula and thalamus; it can be said that in the MCI condition there is an atrophy of the medial temporal lobes, while a more widespread cortical atrophy is typical of Alzheimer's disease. In the same study, a comparison was also conducted between the a-MCI and HS patients: MCIs had a reduced volume of the hippocampus and amygdala bilaterally, of the hippocampal gyrus bilaterally, of the left fusiform temporal gyrus, of the right insular cortex and of the precuneo (Karas et al., 2004).

Chapter II
Retrieval Practice Paradigm

2.1 Executive functions

In neuropsychology, the term “executive functions” refers to higher functions responsible for controlling and planning behavior, which allow us to plan, pursue and arrive at a goal. Miyake (2000) defines executive functions as: "general purpose control mechanisms that modulate the functioning of various cognitive sub-processes and thus regulate the dynamics of human cognition" (Miyake et al., 2000), processes such as: attention, control of impulses, self-regulation, initiative, working memory, problem solving, cognitive flexibility and inhibition (Cantagallo et al., 2010). We know that a high-risk factor for developing dementia can be a decline in executive function. According with Albert and colleagues (2001), only when an MCI patient exhibit impaired executive functioning, can be considered prodromal AD patient (Albert et al., 2001).

In 1986 Baddeley and colleagues studied how the impairment of the executive components of working memory is a feature present in Alzheimer's disease (Baddeley et al., 1986), it was also seen that in the AD patient, after the impairment of episodic memory often there is the onset of executive dysfunction (Bondi et al., 2002).

For inhibition, we can define it as the ability to “block” (*inhibit*) interfering responses, to maintain attention selectively. Inhibition therefore allows you to focus only on relevant information, suppressing attention to distracting stimuli (Diamond A., 2013).

In a study, Hasher and Zacks theorized a model according to which inhibition suppresses the activation of irrelevant information, decreasing the likelihood of accessing working memory and removing that relevant information in a previous situation (Radvansky, Zacks, & Hasher, 1996; Hasher and Zacks, 1988). Carlson also saw (1995) that older adults are more capable of inhibiting irrelevant information (Carlson et al., 1995).

Wylie and colleagues administered the Flanker Test to study in MCI and healthy controls the deficits of response inhibition (Wylie et al., 2007). In this test, the subject is presented with a target stimulus to which he must pay attention, ignoring a series of incongruent surroundings with respect to the target stimulus (Eriksen et al., 1974). Comparing the two samples it was seen that the response times were greater for MCI patients, moreover the reaction time to stimuli increased when an incongruent stimulus was presented. A second experiment was conducted by administering a cholinesterase inhibitor to a group of MCI patients; in subjects who had taken the drug, reaction times and interference effects decreased contrasted with patients who didn't take the drug.

These inhibition deficits observed in MCI and AD patients are associated with memory impairment, especially in memory retrieval (Collette et al., 2009; El Haj et al., 2015), recovery of irrelevant autobiographical memories (Haj et al., 2011).

2.2 Retrieval-Induced Forgetting

Retrieving information from episodic memory (for example the memory of a certain information or of a specific event) can have the paradoxical effect of hindering the subsequent memory of information associated with it, which, however, are not relevant to the needs. the context or activity we are carrying out. It may happen, later, that precisely these irrelevant memory traces are recovered with more effort. This phenomenon is called Retrieval-Induced Forgetting and has been mainly investigated through the paradigm of the practice of recovery (*Retrieval Practice Paradigm*). Retrieval-Induced Forgetting (RIF) is a form of accidental forgetting which consists in the temporary inaccessibility of material associated with previously recovered information (Anderson, Björk and Björk, 1994).

With advancing age, older people, experience an increasing difficulty in suppressing or reducing the activation of distracting thoughts or stimuli. Consequently, their minds are filled with insignificant information, leaving fewer resources for processing relevant information (Aslan et al., 2012). In an inhibition study, conducted by Alp Aslan and Karl-Heinz T. Bauml, the goal was to clarify whether or not the elderly showed a decline in retrieval-induced inhibition by dividing the sample into "young-old" (aged up to 75 years) and "old-old" (over 75 years of age) (Aslan et al., 2012).

RIF was observed using mainly pairs of verbal stimuli. Although it has not been studied with taxonomic categories alone, in most cases, the stimuli used concerned semantic associations pre-existing at the study stage (Anderson, 2003). Based on the inhibition-aging deficit hypothesis, RIF should be reduced or absent in the elderly, however, the results of previous studies suggest the opposite. In older adults, in fact, a reliable RIF has been demonstrated; it has been studied through several tasks (Gómez-Ariza et al.,2009), such as using categorized word lists (Hogge, Adam, & Collette, 2008), or phrases (Gómez-Ariza, Pelegrina, Lechuga, Suárez, & Bajo, 2009), photographs (Koutstaal, Schacter, Johnson, & Galluccio, 1999), and personality traits (Lechuga, Gómez-Ariza, Iglesias-Parro, & Pelegrina, in press). In addition, reliable RIF has been shown in a variety of memory tests, like category-guided recall (Moulin et al., 2002), item recognition (Ortega, Gómez-Ariza, Román, & Bajo, 2012, Experiment 1), and independent probe tests (Aslan, Bäuml, & Pastötter, 2007).

Ciranni and Shimamura (1999) were the first to investigate relationships of a more selectively episodic nature, using material of a visuo-spatial type. In this study, the participants learned the spatial position occupied by geometric figures (Ciranni and Shimamura, 1999). Since the relationship between retrieval cues (geometric figures) and spatial location was entirely arbitrary, participants learned episodic associations that were not based on pre-existing knowledge (Ciranni and Shimamura, 1999).

In a study by Maxcey and Woodman (2014) wanted to investigate whether memory for simultaneously learned visual stimuli was prone to a similar type of verbal memory impairment. Participants were shown real-world objects, then practiced recognizing only a subset of these objects, and finally their memory was tested for all learned objects (repeated and not). The researchers found that the practice of recognizing a subset of elements resulted in the forgetting of other objects in the group. However, compromised recognition did not spread to new objects belonging to the same category (Maxcey & Woodman, 2014).

This paradigm was studied only on healthy subjects; with the aim of evaluating whether the ability to recover a learned visual information is influenced by the inhibitory effect exerted from retrieving related visual information in these patients.

In only one study, a reduction in RIF was reported in older adults. In this study, conducted by Ortega and colleagues (2012), the RIF was studying by administering the Retrieval Practice Paradigm, presenting to the two groups (one composed of young people and one of elderly) a list of words, divided into six categories and subsequently to the task were also added a list of numbers. It happened that, while a relatively demanding task (during which five digits were added) was needed to eliminate the RIF in young adults, a less demanding task (during which three digits were added) was sufficient to eliminate the RIF in the elderly (Ortega et al., 2012).

The term RIF was coined by Anderson et al. (1994), although observations attributable to forms of retrieval-induced oblivion have been reported in previous studies (e.g., Roediger and Schmidt, 1980). Anderson et al. (1994) devised a specific experimental paradigm to study the RIF phenomenon: this procedure is known as "*retrieval practice paradigm*".

In the standard variant of this study, the participants study several semantic categories and subsequently perform a task during which the patient is asked to recall only twelve of the categories read during the first phase of the test. The last phase involves a recall test of the categories, for all words read in the first phase of the test, after a latency period of about 20 minutes where the participants perform a distracting task (Anderson et al., 1994).

Usually, the recall of practiced (hence “repeated”) objects improves, while the recall of non-practiced objects is compromised compared to the control objects of the non-practiced categories. Saunders et colleagues (2006) claim that, RIF is attributed generally to inhibitory control processes (Saunders et al., 2006).

2.3 Retrieval Practice Paradigm

As mentioned, the RIF was studied by Anderson and colleagues through the Retrieval Practice Paradigm (1994). This procedure requires the participants to undergo three temporally distinct experimental phases. The first phase (called *study phase*) consists in the study of a list, formed by pairs of verbal stimuli, where the first word represents a category and the second word represents an example of the same category (e.g., FRUIT-pear, ANIMALS-turkey). The set of stimulus pairs is constructed from 8 categories, each consisting of an equal number of items (for example, in the FRUIT category, the items could be apple, strawberry, kiwi, etc).

The second phase (the *retrieval-practice phase*) consists, through a memory recovery task, in the repetition of a subset of words (e.g., three of the six studied in the first phase) belonging to certain categories (e.g., four categories out of eight), not all the words read in the first phase are recalled. In this phase, the subjects repeat the same word list three times. For example, it is required to recover specimens of the FRUIT category but not those of the TRANSPORTATION category and, within the FRUIT category, to recover pear, peach and pineapple, but not kiwi, pear and banana.

The typology of the retrieval task can vary a lot, but in the classic version by Anderson et al. (1994), reproduced in **Figure 1**, it is a guided re-enactment task that involves the presentation of the category together with the first letters of the specimen to be recovered. (eg, FRUIT-*pe* ___ for the item “pear”).

This second phase allows to divide the specimens into three types:

- items subjected to practice (hereinafter "practiced", indicated with the initials: *Rp+*)
- items not subjected to practice of categories subjected to practice (from now on "not practiced": *Rp-*)
- non practiced items of non-practiced categories (none of which receive any retrieval practice: *Nrp*).

A final *test phase*, is performed after a lapse of time of about 20 minutes, during which a distracting task is administered; in this phase the subjects are asked to recall all the words studied during the first phase of the paradigm (Anderson et al., 2000).

As a rule, the percentage of items correctly recalled is higher for *Rp+* items than for *Nrp* items (the "control" items that act as a baseline). This effect, called *retrieval-induced enhancement* (RIE), shows the effective benefits of the practice on the ability to remember. (**Figure 2**)

Figure 1

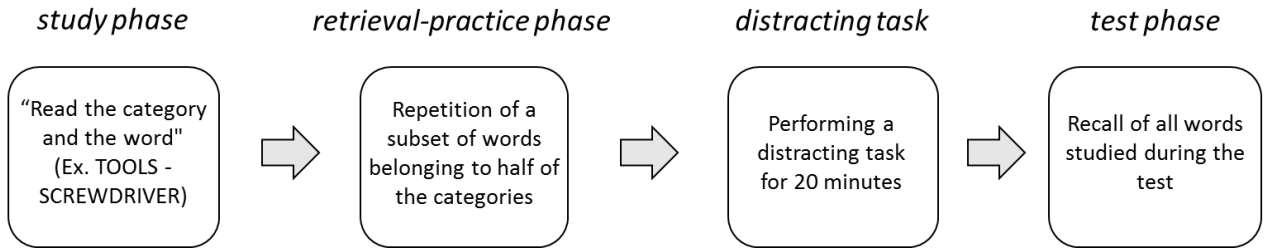
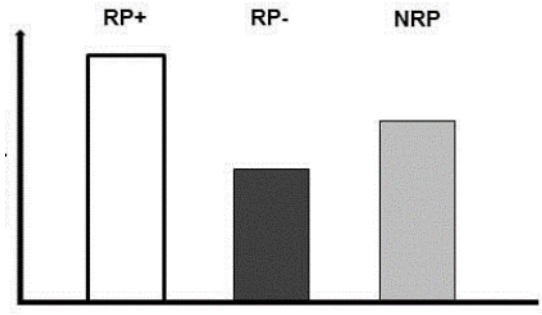


Figure 2



2.4 Neural correlates of the inhibition process

The main theories advanced to explain the RIF are inhibitory theories and interference theories.

The theories of interference (Camp, et al., 2007) are based on more general models that have identified interference as the main cause of oblivion in various contexts: they argue

that the reiteration (repetition) of Rp+ strengthens their mnestic representations. This would have as a side effect the "associative block" or the weakening of access to non-repeated semantically associated stimuli (Rp-) in the subsequent test phase. This would determine a disadvantage in the recovery of these items compared to the Nrp items.

Therefore, according to these theories, the RIF would not necessarily be the product of a mechanism in its own right, but rather an indirect consequence of the facilitation (FAC).

Inhibitory theories, on the other hand, interpret oblivion as an active process: when you try to retrieve information from memory, other memory traces associated with it interfere with its recovery; such competition would determine the need to recruit inhibitory mechanisms to suppress the mnestic representations that interfere with the repeated stimuli, to favor the recovery of the latter. In the experimental paradigm called the Recovery Practice Paradigm (RPP) this would happen during the practice phase, when the request to recover the target stimuli Rp + would trigger inhibitory processes aimed at suppressing the target stimuli associated with them (Rp-), which would subsequently be recalled with greater difficulty in the final phase of testing (Anderson, 2003).

On the contrary, the inhibitory theories maintain that the RIF is due to the inhibition of the memory trace of the Rp-, and therefore foresee that the RIF emerges although the suggestion for recovery used in the test phase is the same one used in the phase of practice. In the original model, in the test phase there is an easier retrieval that shows the first two letters of the item to be recalled: eg. “FRUIT ME___”, in our experiment this last phase was modified in favor of a recognition study and not a recall study. To test this hypothesis, Anderson and Spellman (1995) modified the test phase into a retrieval practice paradigm (with taxonomic categories), so that specimens were tested with recovery suggestions other than those shown in the practice phase, and entirely new to the attendees. For example, the 'VEGETABLE' category was used in the test phase to evaluate the recovery of 'lettuce' and 'mushrooms', respectively Rp- specimens of the 'GREEN' and 'SOUP' categories used in the practice phase.

The use of this procedure, called re-enactment guided by independent suggestions, was able to directly test the activation of the memory traces rather than the associative links between the suggestion and the target stimulus, and generated results largely congruent with the forecasts. of inhibitory theories (Anderson and Bell, 2001).

Numerous research identify the inhibitory mechanisms as the main responsible for RIF, and the core of these mechanisms in the executive functions (Anderson, 2003; Levy and Anderson, 2002); many authors have investigated the relationship between executive control and RIF.

According to some research, FAC and RIF are functionally related mechanisms, as Penolazzi and colleagues claim (2014). Neuroimaging studies have suggested that a large prefrontal neural network is involved during the recovery practice, such as anterior cingulate cortex, anterior ventromedial prefrontal cortex, and dorsolateral prefrontal cortex (Penolazzi et al., 2014).

In a study by Penolazzi and colleagues, the aim was to establish a causal relationship between the prefrontal areas and the cognitive mechanisms underlying the RIF, through transcranial direct current stimulation (tDCS). Stimulation was delivered during the recovery practice phase of the RPP test. Studies by fRMI have suggested that the dorsolateral prefrontal cortex (DLPFC) may play an active role in determining the RIF, as its recruitment during the practice phase caused forgetfulness in the later stages of the test. However, this does not necessarily mean that this is the only area causally involved in the phenomenon (Penolazzi et al., 2014).

Importantly, a growing literature focusing on coding, retrieval and reconsolidation mechanisms has shown that the right lateral prefrontal cortex also plays a key role in episodic memory (Manenti et al, 2012).

Chapter III

"Are the inhibitory and faciliatory effects during retrieval of semantically related items present in amnestic mild cognitive impairment?"

Serra L., Bechi Gabrielli G., Di Domenico C., Del Bono C., Marra C., Lopiano L., Caltagirone C., Bozzali M.
J Neuropsychol. 2022 Aug 15. doi: 10.1111/jnp.12286.

3.1 Introduction to studies

The idea of the study expounded in the thesis is subsequent to this study one: "*Are the inhibitory and facilitatory effects during retrieval of semantically related items present in amnestic mild cognitive impairment?*". The objective of the previous study, recently published (Serra et al., 2022), was to investigate in patients with a-MCI, the RIF and FAC effects using RPP, in a recall task, only on verbal stimuli. We aimed, additionally, at investigating potential associations between patient's regional GM volumetrics and their accuracy in the Rp−, Rp+, Nrp, RIF and FAC effect (Serra et al., 2022). Subsequently to this study, I wanted to study in a recognition study task (and not in a recall task, how this one exposed), investigated how and if there were dissociations in verbal and visual tasks in the RPP, and also in the processes of brain areas are more involved inhibition and facilitation in patients with different types of cognitive impairment.

3.2 Abstract

Prefrontal functions subserve inhibition control for retrieval of semantically related items inducing forgetting 19 a-MCI patients and 29 controls underwent neuropsychological evaluation and retrieval-practice paradigm (RPP) to estimate baseline remember (BR), retrieval-induced facilitation (FAC) and retrieval-induced forgetting (RIF). A-MCI patients underwent also 3 T-MRI to assess relationship between regional grey matter (rGM) volumes and RPP indexes Behaviourally, RIF and FAC were both observed controls, while RIF only was observed in a-MCI patients. In patients but not in controls, RIF was associated with cognitive efficiency and FAC with memory performance. Patients showed also associations between BR and rGM volumes in the precuneus, no association was found between rGM volumes and RIF and FAC. A-MCI patients did not benefit from repeated practice during retrieval of studied items, which is likely due to their memory disorder. In contrast, patient cognitive efficiency would drive retrieval suppression of interfering stimuli.

3.3 Introduction

Long-term memory implies a dynamic process by which remembering an item produces forgetting for other related items (Anderson et al., 1994). It is due to competition exerted by the strength of newly acquired items that increase the risk to forget related items. Anderson et al. (1994) hypothesized three different mechanisms to explain this interferential phenomenon: (a) the competition-assumption: items associated to a common cue compete for accessing to recall when that cue is provided; (b) the strength-dependence assumption: the cued-recall of an item decreases as a function of increases in the strength of its

competitors' associations to the cue; (c) the retrieval-based learning assumption: retrieval implies a learning act that enhances the following recall of retrieved items. All these assumptions postulate that repeated retrieval of an item reinforces the item itself causing loss of access to retrieving other related items (Anderson et al., 1994). This phenomenon is known as the retrieval-induced forgetting (RIF; Anderson et al., 1994).

To test this phenomenon the retrieval-practice paradigm (RPP) has been proposed (Anderson et al., 1994), which consists of three different phases. In the first one, called Study phase (SP), the examiner provides participants with a series of category-stimulus pairs. Stimuli of a given category share the category labels as retrieval-cue, which compete for accessing to recall on a subsequently presented category cue. In the second phase of the RPP (named retrieval-practice RP) the examiner provides again the participants with half of the stimuli from half categories previously studied, as retrieval practice. In this phase each selected category label is presented together with the related stimulus stem for three times. The final Test phase (TP) implies a cued-recall test to be performed after a 20 min delay. In this phase participants are cued with each category label and requested to perform a free recall of previously seen stimuli for each category (Anderson et al., 1994). The retrieval-practice phase is supposed to produce enhancement of memory traces; then, the practiced stimuli in a given category should induce competition with the unpractised stimuli from that category during the delayed cued-recall test (Anderson et al., 1994). The recall of unpractised stimuli derived from practised categories contrasts against the recall of unpractised items derived from unpractised categories and provides a measure of the RIF effect (Anderson et al., 1994). The RIF effect is generally attributed to inhibitory control processes (Anderson et al., 1994; Aslan & Bäuml, 2012). Indeed, during retrieval practice, the ‘not to be retrieved items’ interfere producing forgetting. Conversely, practising a certain item induces facilitation for its subsequent retrieval. This effect is called facilitation effect (FAC), which is frequently observed in healthy subjects (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009). For a better comprehension of these effects we highlight here that RIF and FAC effects are computed at group level (not at individual level) as follows: RIF is the statistical difference between unpractised items from practised categories against baseline memory level; FAC is the statistical difference between practised items from practised categories against baseline memory level.

Studies on healthy subjects revealed the presence of intact RIF effect in both young and elderly individuals (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009). Additionally, Gómez-Ariza et al. (2009) showed a facilitation effect due to retrieval practice, again in young as well as in elderly healthy subjects. The RIF effect was observed in healthy individuals regardless of their age and interpreted as due to a facilitation mechanism for selection of memories' targets (Gómez-Ariza et al., 2009). Another study in healthy subjects demonstrated the presence of RIF effect in elderly (mean age: 70 years) but not in older elderly individuals (mean age > 75 years), hypothesising an inhibitory deficit in the latter group (Aslan & Bäuml, 2012). In contrast, the FAC effect was equally present in both groups of elderly individuals (Aslan & Bäuml, 2012). The Authors hypothesized the presence of inhibitory deficit in older subjects and concluded that inhibitory abilities decline rather late in the life span.

From a neurobiological viewpoint, by using non-invasive brain stimulation (Penolazzi et al., 2014) or functional MRI (fMRI) techniques (Kuhl et al., 2007; Wimber et al., 2008, 2009) on healthy subjects, the efficiency of RIF effect has been associated to integrity of the dorsolateral prefrontal cortex (Kuhl et al., 2007; Penolazzi et al., 2014), the anterior cingulate (BA32; Wimber et al., 2009), the ventrolateral prefrontal cortex (BA47) and the posterior temporal cortex (BA22; Wimber et al., 2008). Moreover, integrity of the precuneus (BA7) and the inferior parietal lobule (BA40) were associated to the FAC effect (Wimber et al., 2008). These data in healthy individuals highlight the key role played by the prefrontal regions in mediating the inhibitory memory control (Wimber et al., 2009) and postulate the occurrence of deficits in inhibitory mechanisms in patients suffering from frontal dysfunction. Principal aim of all these studies was to assess brain-behaviour correlations at individual level. To obtain, an individual proxy measure of RIF the Authors subtracted (for each participant) the unpractised items from practiced categories, from the baseline memory level (Penolazzi et al., 2014; Wimber et al., 2008, 2009). Conversely, as a proxy measure of FAC, they subtracted the practiced items from practiced categories, from the baseline memory level (Penolazzi et al., 2014; Wimber et al., 2008).

Unexpectedly, contrasting results have been derived from clinical studies. Some studies indicate an intact RIF effect in patients with frontal lobe lesions (Conway & Fthenaki, 2003), schizophrenia (Nestor et al., 2005) and Alzheimer's Disease (AD; Moulin et al., 2002). Conway and Fthenaki (2003) investigated the RIF, but not the FAC effect, and the direct forgetting (whenever each stimulus was followed by an explicit instruction to remember or forget and was regarded as a measure of intentional forgetting) in patients with frontal lobe lesions and in patients with amnesia due to temporal lobe lesions (including a selective hippocampal or medial temporal damage). They reported a normal RIF effect and impaired direct forgetting in patients with frontal lobe lesions. Conversely, abnormal RIF effect and impaired direct forgetting were observed in patients with temporal lobe lesions (Conway & Fthenaki, 2003). These results were interpreted by the Authors as an evidence that patients with frontal lesions are impaired in the intentionally inhibitory memory processes only (as shown by their performance on the direct forgetting task), while patients with temporal lobe lesions are impaired in all episodic memory tasks (Conway & Fthenaki, 2003). Taken together, these models of focal lesion indicate a phenomenon, which is paradoxical with respect to the predictions based on data from healthy subjects. An interesting model to challenge these inconsistencies is that offered by a progressive condition, such as AD, which begins with a focal damage of the temporal lobes followed by spreading to other regions of the association cortex including the frontal lobes. To the best of our knowledge, there are only two published studies that investigated the RIF effect in patients with AD. Moulin et al. (2002) focused on this effect as a potential explanation for the intrusion errors that are typically observed in AD patients during recall tasks (Moulin et al., 2002). Intrusion errors are considered characteristic of the memory impairment observed in AD pathology (Amieva et al., 1998; Bandera et al., 1991; Le Moal et al., 1997), and their presence was investigated also in patients with prodromal AD in association with measures of amyloid load (Cid et al., 2020; Loewenstein et al., 2018). In particular, Loewenstein et al. (2018) developed a new cognitive task to measure semantic intrusion errors that distinguish patients with a-MCI and high amyloid load from those with a-MCI due to a non-AD condition.

Moulin et al., using the retrieval-practice paradigm (RPP) in patients with AD, focussed on their inhibitory mechanism (as measured by reduced performance on the unpracticed items from practiced categories, defined as Rp−) without measuring their performance on the practiced items from practiced categories (defined as Rp+), which is a measure of faciliatory mechanisms. This study showed that AD patients do not suffer from a lack of inhibition during retrieval of episodic memories as demonstrated by their intact RIF (Moulin et al., 2002). Unfortunately, Moulin et al. (2002) did not investigate quantitatively the FAC effect that would have further clarified the mechanisms underlying recall. Their conclusion was that AD patients perform normally with regard to inhibition of competitor items in retrieval tasks. This means that the propensity of AD patients to make intrusions in recalling items is unlikely to be due to any deficient inhibitory process that automatically suppresses competitor items on retrieval. Conversely, intrusions may be due to intentional mechanisms to reject items brought to mind during retrieval (Moulin et al., 2002).

This result is consistent with previous literature on AD and inhibitory processes, indicating that the inhibitory ability is not a unique process, but different inhibitory systems might be selectively affected (Bjorklund & Harnishfeger, 1995; Kramer et al., 1994; Nigg, 2000). Coherently, several studies showed that there is not a general inhibitory deficit in AD. In particular, tasks requiring controlled conscious inhibition (such as the Stroop test) appear to be deficient in AD, while automatic processes of inhibition operating below the level of conscious control seem to be preserved (for a review see Amieva et al., 2004).

In a later study, Tempel et al. (2021) modified the paradigm used in Moulin's work to investigate the influence of other processes besides memory inhibition, resolving the interference that occurs during retrieval. The Authors did not find any RIF effect in their AD patients and hypothesized the presence of a blocking mechanism resolving the interference of related items during recall.

Results obtained by Moulin et al. (2002) are in clear contrast to those observed in patients with temporal lobe lesions (Conway & Fthenaki, 2003). Indeed, Conway and Fthenaki showed an abnormal RIF in amnestic patients with temporal lobe lesions and argued that these patients suffer from a widespread memory deficit. In a more general perspective, the evidence coming from clinical studies allows to suppose that automatic mechanisms, independent from the prefrontal control and not requiring any attentional resources, drive the resolution of interference during episodic memory tasks (Wimber et al., 2009).

However, it remains largely unclear the contribution of either, the prefrontal or temporal cortex to the inhibitory and faciliatory effects observed when using the RPP. No previous studies have investigated in the model of AD the association between neuronal substrates and the presence of RIF and FAC effects. Admittedly, patients with AD suffer from a severe memory deficit together with poor general cognitive efficiency and diffuse brain atrophy, which make it difficult to disentangle the role of the prefrontal and temporal structures in retrieval of studied items. For this reason, we focused on patients with amnestic mild cognitive impairment (a-MCI), a clinical condition recognized to be associated with a higher risk for developing dementia, mainly of AD-type (Falini et al., 2005; Giulietti et al., 2012). A-MCI patients show an episodic memory disorder that mimics that observed in patients with

organic amnesia due to hippocampal/temporal lobe damage (Perri et al., 2005) with preservation of general cognitive efficiency. In addition, neuroimaging studies (Giulietti et al., 2012; Serra et al., 2010) on a-MCI patients report grey matter atrophy mainly localized in the hippocampus and medial temporal lobe structures. In our opinion, this population, which is considered as belonging to a transitional stage between normal ageing and dementia, allows us to investigate the mechanisms underlying the RIF and FAC effects distinguishing the role played by the prefrontal and temporal structures. Based on the prevalent damage to the temporal lobes in a-MCI, two hypotheses may be advanced on the neurobiological substrate of RIF and FAC: (a) a prominent role of the dorsolateral prefrontal cortex (Kuhl et al., 2007; Penolazzi et al., 2014), the anterior cingulate (Wimber et al., 2009), ventrolateral prefrontal cortex and posterior temporal cortex in support of RIF (Wimber et al., 2008), and a prominent role of the precuneus and inferior parietal lobule in support of FAC (Wimber et al., 2008); in this case, from a behavioural point of view, MCI patients are expect to show intact RIF and FAC effects; (b) a prominent role of the temporal lobe structures in support of RIF and FAC in the absence of any relevant frontal lobe contribution; in this case, we expect, behaviourally, that RIF and FAC are both altered in MCI patients (Conway & Fthenaki, 2003).

Against this background, we designed the present study to investigate, in patients with a-MCI, their RIF and FAC effects using RPP. Additionally, we aimed at investigating potential associations between patients' regional GM volumetrics and their accuracy in the Rp− (unpractised items from practised categories), Rp+ (practised items from practised categories), baseline memory conditions (Nrp), RIF and FAC effect.

3.4 Methods

3.4.1 Participants

Fifty-two participants were screened for the study by a neurologist and a neuropsychologist operating in a specialist dementia clinic, both expert in neurodegenerative cognitive declines. Four patients were excluded due to claustrophobia (three participants) and severe anxiety (one participant). Nineteen patients (12 females, age M = 74.4, SD = 6.8, education M = 12.7, SD = 5.2) fulfilled the criteria for MCI-due to AD at intermediate likelihood (Albert et al., 2011) according to a clinical evaluation and were enrolled in the study. From a neuropsychological viewpoint, all patients showed a long-term memory deficit (amnestic MCI [a-MCI] single or multiple domain); they all reported a subjective memory impairment as clinical onset, corroborated by an assistant and confirmed by performances below the cut-off scores of normality on at least one of the administered tests (i.e. immediate and delayed recall of 15-Word List [Carlesimo et al., 1996], immediate and delayed recall of the Short Story test [Carlesimo et al., 2002], immediate and delayed recall of the Rey's Complex Figure [Carlesimo et al., 2002]) for episodic memory included in the cognitive screening battery used to patients' selection. Details of the screening battery used for patients' selection is reported below.

A-MCI patients had not to fulfil the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for the diagnosis of major neurocognitive disorders (APA, 2013). Their MMSE score (Folstein et al., 1975; Measso et al., 1993) had to fall within the cut-off of

normality (≥23.8) and their Clinical Dementia Rating score (CDR; Hughes et al., 1982) had to be equal to 0.5. In order to respond to the criteria of aMCI-due to AD at intermediated likelihood, all patients had to report scores at the medial temporal lobe atrophy scale (MTA; Scheltens et al., 1995) equal or higher than 1. Twenty-nine healthy individuals (healthy subjects; HS; 22 females, age M = 76.7, SD = 6.5, education M = 9.5, SD = 3.9) were also enrolled to undergo cognitive tests and serve as controls. To be eligible their MMSE score had to range from 25 to 30, and their CDR score had to be equal to 0. To exclude the contribution of cerebrovascular disease, all subjects (patients and healthy controls) with a Hachinski score (Hachinski et al., 1975) higher than 4 were excluded. Major systemic, psychiatric and other neurological illnesses (with a special attention to Parkinson disease and Parkinsonism) were also carefully investigated and excluded in all participants. Finally, participants had to be right-handed, as assessed by the Edinburgh Handedness Inventory (Büsch et al., 2010).

The study was approved by the Local Ethical Committee and written informed consent was obtained from all participants before study initiation. All procedures performed in this study are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3.5 Neuropsychological assessment

3.5.1 Screening battery

An extensive screening battery was used to assess cognitive functions in patients and healthy subjects (HS), which included the following tests: (a) verbal episodic long-term memory: 15-Word List (Immediate, 15-min Delayed recall and recognition; Carlesimo et al., 1996); Short Story Test (Immediate and 20-min Delayed recall; Carlesimo et al., 2002); (b) visuo-spatial long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall; Carlesimo et al., 2002); (c) short-term and working memory: Digit span (forward and backward) and the Corsi Block Tapping task (forward and backward) (Monaco et al., 2013); (d) executive functions: Phonological Word Fluency (Carlesimo et al., 1996) and Modified Card Sorting Test (Nocentini et al., 2002); (e) language: Naming objects subtest of the BADA (‘Batteria per l'Analisi dei Deficit Afasici’, Italian for ‘Battery for the analysis of aphasic deficits’) (Miceli et al., 1991); Trail Making Test (TMT-A and B parts) (Giovagnoli et al., 1996) (f) Reasoning: Raven's Coloured Progressive Matrices (Carlesimo et al., 1996); (g) constructional praxis: copy of simple drawings with and without landmarks (Carlesimo et al., 1996) and copy of Complex Rey's Figure (Carlesimo et al., 2002). For all of the tests, Italian normative data were available for both score adjustment (sex, age and education) and for defining normality cut-off scores, which were determined as the lower limit of the 95% tolerance interval for a confidence level of 95% (normative data for each test are reported in the corresponding references).

3.5.2 Addenbrooke's cognitive Examination-Revised battery

After recruitment, all 19 patients and 29 controls (HS) underwent the Italian version of the Addenbrooke's Cognitive Examination-Revised (ACE-R; Mioshi et al., 2006). This is a validated brief screening test developed to detect different forms of dementia (Mioshi et al.,

2006). It assesses attention, memory, fluency, language and visuo-spatial cognitive functions providing a score ranging from 0 to 100. The Italian normality cut-off score is ≥66.92.

Additionally, ACE-R allows the MMSE score to be derived. Individual MMSE raw scores and total ACE-R scores were adjusted for age and years of formal education according to the Italian normative data (please see for MMSE Measso et al., 1993; for ACE-R Pigliautile et al., 2011).

3.6 Experimental procedure

3.6.1 Retrieval-Practice Paradigm (RPP)

All patients and HS underwent the retrieval-practice paradigm (RPP). The RPP was set-up as follows: we selected 144 concrete nouns as stimuli, chosen from the standard norms for production in Italian language (CoLFIS database, Bertinetto et al., 2005) belonging to eight different semantic categories. Each category included 18 stimuli, and all categories were semantically unrelated with each other. By definition, each item belonging to a specific category was semantically related with all items of that category. The stimuli had to be at least five letter long and, within each category, they had to present with a unique first letter. The stimuli were divided in three different lists: every list contained eight categories with six stimuli each, for a total of 48 items in each list. The lists were matched for word length and frequency. Each participant received one list only, which was randomly selected. The list of items was presented on a PC screen; each stimulus being positioned into the centre to replace a fixation point. Stimuli presentation was self-paced by each participant pressing a keyboard button but not exceeding a maximum presentation-time (see below).

According to Anderson et al. (1994), the retrieval-practice paradigm (RPP) included 3 steps:

a) Study phase (SP): participants studied a list of category-stimulus pairs (e.g. Fruit-Apple, Fruit-Strawberry, Drink-Whisky) by reading them aloud. Each category-exemplar pair remained on the screen for 5 s maximum.
b) Retrieval-practice phase (RP): participants performed a cued-recall test on half stimuli derived from half categories; category label and stem of each stimulus were presented on the screen for 10 second maximum (e.g. Fruit-Ap__). The instruction for the participants was to retrieve an item that they had seen in the previous experimental phase, in that category corresponding to that stem.
c) Test phase (TP): 20 min after RP completion (during which participants were engaged in visuo-spatial tasks from ACE-R), participants were requested to perform a category cued-recall test from all studied items; as for the RP phase, category label and stem of each stimulus were presented (e.g. Fruit-Ap__). The instruction was to retrieve, from any part of the experiment, the exemplar belonging to that category, which corresponded to that stem. Subjects were given 10 s maximum to recall each item.

Subjects' performance was examined for three typologies of items contained in each list:

- 12 practiced items from practiced categories (identified as: Rp+, Fruit – Apple).
- 12 unpractised items from practiced categories (identified as: Rp−, Fruit – Strawberry).
- 24 unpractised items from unpractised categories (identified as: Nrp, Drink – Whisky).

At group level, the retrieval-induced facilitatory (FAC) effect was calculated contrasting statistically Rp+ items against Nrp items. The retrieval-induced inhibitory (RIF) was obtained contrasting statistically Rp− items against the Nrp items. Nrp items reflect the individual baseline for memory retrieval (baseline remember). To obtain, at individual level, an estimation of RIF and FAC effects differential scores were computed as proxy measures (see below). These proxies of RIF and FAC were used to assess both correlations with neuropsychological scores and potential associations with brain correlates.

3.7 MRI acquisition

A-MCI patients (N = 19) underwent a 3 T-MRI examination (Magnetom Allegra, Siemens, Erlangen, Germany), including the following acquisitions: (a) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); (b) fast-fluid attenuated inversion recovery (FLAIR; TR = 8170 ms, TE = 96 ms, TI = 2100 ms); (c) 3D-Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR = 1338 ms, TE = 2.4 ms, Matrix = 256 × 224, n. slices = 176, thickness = 1 mm). TSE and FLAIR scans were reviewed to exclude the presence of remarkable macroscopic brain abnormalities, as previously described (Serra et al., 2010).

3.8 Whole brain VBM analysis

None of the T1-weighted (MDEFT) volumes were affected by macroscopic artefacts, as assessed by visual examination.

T1-weighted volumes were pre-processed using the VBM protocol (Ashburner & Friston, 2001, 2005) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), which consists of an iterative combination of segmentations and normalisations to produce a GM probability map (Ashburner & Friston, 2001, 2005) in standard space (Montreal Neurological Institute, or MNI coordinates) for every subject. In order to compensate for compression or expansion, which might occur during warping of images to match the template, GM maps were ‘modulated’ by multiplying the intensity of each voxel in the final images by the Jacobian determinant of the transformation, corresponding to its relative volume before and after warping (Ashburner & Friston, 2001). GM, white matter and cerebrospinal fluid volumes were computed from these probabilistic images for every subject. All data were then smoothed using a 12-mm FWHM Gaussian kernel.

3.9 Statistical analyses

Statistical analyses on demographic and cognitive data, the latter obtained through the screening neuropsychological battery and the ACE-R, were performed using SPSS-20.0. (https://www.ibm.com/it-it/analytics/spss-statistics-software). One-way ANOVA models

were used to compare age and years of formal education between a-MCI patients and HS. Chi-square was used to assess their sex distribution. For the screening neuropsychological battery, a-MCI patients and HS were compared using a series of one-way ANCOVAs. To avoid the type-I error, Bonferroni's correction was applied (p value threshold $\alpha = 0.05/20 = 0.002$).

A-MCI patients and HS were compared in each ACE-R domain using one-way ANCOVAs models with age and years of formal education as covariates of no interest. To avoid the type-I error, Bonferroni's correction was applied (p value threshold $\alpha = 0.05/5 = 0.01$). Adjusted MMSE and total ACE-R scores were compared between groups using a one-way ANOVA model (p value threshold $\alpha = 0.05/2 = 0.025$ survived after Bonferroni's correction).

According to Anderson et al. (1994), behavioural analyses were performed to calculate, at a group level, the RIF and FAC effects. RIF was obtained contrasting Rp− items (unpractised items from practised categories) against Nrp items (unpractised items from unpractised categories – baseline condition), while FAC was obtained contrasting Rp+ (practised items from practised categories) against Nrp items. RIF and FAC effects in a-MCI patients were evaluated by comparing their performances with those from HS using a two-way ANCOVA for repeated measures (MANCOVA) with Group as between factor (a-MCI vs. HS) and Conditions (Nrp, Rp−, Rp+) as within factor. Participants were entered as random variable, while age and education were used as covariates of no interest. Post-hoc planned comparisons were used when appropriate.

In patients and HS separately, Pearson's correlations were used to assess potential association between each domain of ACE-R and Nrp, Rp− and Rp+ items (p value threshold $\alpha = 0.05/6 = 0.008$, after Bonferroni's correction). Moreover, to assess more directly the potential relationship between ACE-R measures and the RIF and FAC effects, correlations were tested between ACE-R measures and proxy measures of RIF and FAC, which were computed as differential scores between Nrp and Rp− items (proxy measure for RIF, pRIF) and Nrp and Rp+ items (proxy measure for FAC, pFAC), respectively. Moreover, the pRIF and pFAC were used in the discriminant analyses to verify the ability of inhibitory and faciliatory effects to correctly classify patients and healthy controls.

In the patient group only, statistical analyses of regional GM volumes were performed on smoothed GM maps within the framework of the general linear model in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) We investigated the potential association between patient GM volumes and RPP indexes, with the aim of identifying possible neural correlates for Rp−, Rp+ and Nrp. We were also interested to assess possible neural associations with RIF and FAC effect. Unfortunately, the investigation of RIF (calculated as a statistical contrast between Nrp and Rp−) and FAC (calculated as statistical contrast between Nrp and Rp+) effects on GM volumes implies the setting up of complex models that are not directly supported by classical VBM analyses. To overcome this important limitation we used here a different approach that included the following VBM design matrixes: (a) relationships between scores obtained by Nrp, Rp− and Rp+ items and regional GM volumes using multiple regression models to show the association between brain correlates and effects of practicing items when retrieved; (b) to assess the relationship between GM volumes and

RIF and FAC effects, the differential scores between Nrp and Rp− items (proxy measure for RIF, pRIF) and Nrp and Rp+ items (proxy measure for FAC, pFAC) were entered in separate multiple regression analyses. Intracranial Volume (obtained by adding up white matter volume + GM volume + cerebrospinal fluid volume) was entered in all analyses as covariate of no interest. Results were accepted as significant at p values FWE cluster level corrected <0.05.

3.10 Results

3.10.1 Demographic characteristics

There were no significant differences between a-MCI patients and HS in age ($F_{1,46} = 1.29$, $p = 0.260$) and sex distribution (a-MCI vs. HS = Yates Chi-square = 0.39, d.f. = 1, $p = 0.533$). Conversely, there was a significant between-group difference in years of formal education ($F_{1,46} = 5.54$, $p = 0.023$).

Results are reported in *Table 1*.

TABLE 1. Demographic and clinical characteristics of studied subjects

	a-MCI, *N* = 19	HS, *N* = 29
Mean (SD) age [years] [a] [range]	74.4 (6.8) [67–83]	76.7 (6.5) [65–85]
Gender (F/M) [b]	12/7	22/7
Mean (SD) years of formal education [a] [range]	12.7 (5.2) [5–18] *	9.5 (3.9) [5–18]

- *Note*: Mean and standard deviation are reported. See text for further details.
- Abbreviations: a-MCI, amnestic Mild Cognitive Impairment; HS, healthy subjects.
- [a] One-way ANOVA.
- [b] Yates Chi-square corrected.
- * a-MCI patients vs. HS $p < 0.05$.

3.10.2 Neuropsychological results

Seventeen out of 19 patients were classified as single domain a-MCI, showing on the screening battery an isolated verbal episodic memory disorder. The remaining two patients were classified as multiple domain a-MCI, reporting also anomias in one case, and low performances in the copy of the Rey's Complex Figure in the other case.

Table 2 summarizes the performances obtained by a-MCI patients and HS on the neuropsychological screening battery. As expected, a-MCI patients reported significantly worse scores than HS on episodic memory tests (15 Word-List Immediate recall: $F_{1,46} = 47.7$, $p < 0.001$; 15 Word-List Delayed recall: $F_{1,46} = 45.6$, $p < 0.001$; Short Story test Immediate recall: $F_{1,46} = 45.6$, $p = 0.001$; Short Story test Delayed recall: $F_{1,46} = 45.6$, $p < 0.001$, all surviving after Bonferroni's correction).

TABLE 2. Performance scores obtained by patients with a-MCI compared with HS on the tests of the screening neuropsychological battery

Domain	Test	a-MCI	HS	*F*	*p*-Level
Verbal episodic long-term memory					
	Rey's 15-word list:				
	Immediate recall (cut-off ≥ 28.5)	30.6 (7.3)*	47.5 (8.5)	47.7	<0.001
	Delayed recall (cut-off ≥ 4.6)	4.4 (3.3)*	10.0 (2.3)	45.6	<0.001
	Recognition: hit rates	10.7 (3.9)	13.9 (1.3)	9.1	=0.005
	Recognition: false	5.8 (5.2)	1.4 (1.9)	9.5	=0.004
	Short story test:				
	Immediate recall (cut-off ≥ 3.1)	4.2 (1.9)*	6.6 (1.4)	13.90	=0.001
	Delayed recall (cut-off ≥ 2.6)	3.9 (1.9)*	6.4 (1.2)	16.29	<0.001
Visuo-spatial episodic long-term memory					
	Rey's Complex figure:				
	Immediate recall (cut-off ≥ 6.4)	11.8 (7.1)	16.6 (6.9)	2.9	=0.098
	Delayed recall (cut-off ≥ 6.3)	10.7 (6.9)	14.8 (6.9)	1.8	=0.185

Domain	Test	a-MCI	HS	*F*	*p*-Level
Verbal working memory					
	Digit span backward	3.7 (0.9)	4.5 (0.9)	7.7	=0.008
Visuo-spatial working memory					
	Corsi span backward	4.1 (0.8)	4.5 (0.9)	2.7	=0.115
Executive functions					
	Phonological word fluency (cut-off ≥ 17.3)	32.3 (10.5)	37.2 (7.7)	3.4	=0.072
	Modified Card Sorting Test				
	Criteria achieved (cut-off ≥4.2)	5.9 (0.3)	5.7 (0.8)	0.4	=0.539
	Perseverative errors	3.0 (3.7)	1.4 (3.1)	0.1	=0.790
Language	**Naming of objects** (cut-off ≥ 22)	28.4 (3.7)	29.2 (0.8)	0.17	=0.237
Reasoning	**Raven's Coloured Progressive matrices** (cut-off ≥ 18.9)	27.9 (4.6)	29.2 (1.1)	1.4	=0.252
Constructional praxis	**Copy of drawings** (cut-off ≥ 7.1)	9.4 (1.7)	10.4 (1.2)	2.5	=0.115
	Copy of drawings with landmarks (cut-off ≥ 61.8)	67.3 (1.9)	65.1 (0.7)	0.5	=0.470
	Copy of Rey's Complex figure (cut-off ≥ 23.7)	32.6 (4.8)	31.1 (4.8)	0.7	=0.392

Post-Hoc comparison: *a-MCI vs. HS $p < 0.002$ Bonferroni-corrected.

As reported in *Table 3*, there were expected differences between patients and controls in their MMSE ($F_{1,46} = 28.7$, $p < 0.001$) and total ACE-R scores ($F_{1,46} = 15.5$, $p < 0.001$).

TABLE 3. Performance scores obtained by a-MCI patients and healthy subjects at neuropsychological tests

	a-MCI, *N* = 19	HS, *N* = 29
General cognitive efficacy		
MMSE score Mean (SD)[a]	25.3 (3.1)*	28.9 (1.5)
ACE-T Total score Mean (SD)[a]	74.7 (17.3)*	82.3 (8.6)
ACE-R domains		
Orientation/Attention score Mean (SD)[b]	15.8 (2.2)*	17.8 (0.5)
Memory score Mean (SD)[b]	14.7 (6.4)*	18.2 (3.1)
Executive Functions score Mean (SD)[b]	9.53 (2.8)	9.52 (2.0)
Language score Mean (SD)[b]	22.3 (3.6)*	25.0 (1.2)
Visuo-spatial abilities score Mean (SD)[b]	13.6 (2.2)	13.0 (2.9)

- *Note*: Mean and standard deviation are reported. See text for further details.
- Abbreviations: ACE-R, Addenbrooke's Cognitive Examination-Revised; a-MCI, amnestic Mild Cognitive Impairment; HS, healthy subjects; MMSE, mini- mental state examination.
- [a] One-way ANOVA.
- [b] One-way ANCOVA.
- * a-MCI patients vs. HS $p < 0.01$ after Bonferroni's correction.

Moreover, a-MCI patients showed significant lower scores than HS in the following domains of ACE-R: Orientation /Attention ($F1,44 = 19.5$, $p < 0.001$); Memory ($F1,44 = 12.5$, $p = 0.001$); Language. ($F1,44 = 14.5$, $p < 0.001$). No significant differences were observed between patients and controls in the Verbal fluency ($F1,44 = 2.09$, $p = 0.155$) and in the visuo-spatial abilities ($F1,44 = 0.07$, $p = 0.785$).

The retrieval-practice paradigm

Table 4 illustrates the proportions of the retrieved items in a-MCI patients and controls.

TABLE 4. Proportions of the retrieved items in the RPP in patients and controls

	a-MCI	HS
Nrp mean (SD) [range]	0.71 (0.1) [0.42–0.88]	0.78 (0.1) [0.42–0.92]
Rp+ mean (SD) [range]	0.73 (0.1) [0.33–1]	0.89 (0.1) [0.75–1]
Rp− mean (SD) [range]	0.57 (0.2) [0.25–1]	0.65 (0.1) [0.33–0.92]

We observed a significant main effect of Group ($F_{1,44} = 11.3$, $p = 0.001$) due to a lower accuracy of a-MCI patients in the overall recall (mean of a-MCI = 0.68; mean of HS = 0.79); we observed also a significant main effect of Conditions ($F_{2,92} = 17.9$, $p < 0.05$): Tukey's post-hoc showed that Rp+ items (mean = 0.83) were better recalled than Nrp (mean = 0.74) and Rp− (mean = 0.61), with no difference in the recall of Nrp and Rp−. Finally, we found a significant Group by Condition interaction ($F_{2,92} = 3.17$, $p = 0.046$) due to the fact that both groups showed same trends in the RIF effect ($F_{1,46} = 0.02$, $p = 0.88$), while a significant difference was present in the FAC effect ($F_{1,46} = 6.82$, $p = 0.012$). Planned comparisons revealed that the RIF was present in both HS ($F_{1,46} = 20.9$ $p < 0.001$) and a-MCI patients ($F_{1,46} = 15.1$, $p < 0.001$; see Figure 1, panel a). Conversely, the FAC effect was present in the HS only ($F_{1,46} = 20.3$, $p < 0.001$), while no facilitation was observed in a-MCI patients ($F_{1,46} = 3.54$, $p = 0.065$; see Figure 1, panel b). This indicates that, in a-MCI patients, the proportion of items retrieved in the Nrp condition is statistically higher than that retrieved in the Rp− conditions (RIF), whereas the proportion of items retrieved in the Nrp condition is not statistically higher than that retrieved in the Rp+ condition (FAC). Conversely, in the HS the proportions of items retrieved in the Nrp condition is statistically higher than that retrieved in Rp− and statistically lower than that retrieved in the Rp+ condition. These data are summarized in Table 4. When looking the raw accuracy in the typology of items, we found that a-MCI patients compared to HS showed a significantly lower retrieval of Nrp items ($F_{1,44} = 7.46$, $p = 0.009$), Rp+ items ($F_{1,44} = 15.76$, $p < 0.000$) and Rp− items ($F_{1,44} = 7.26$, $p = 0.010$; see Figure 2).

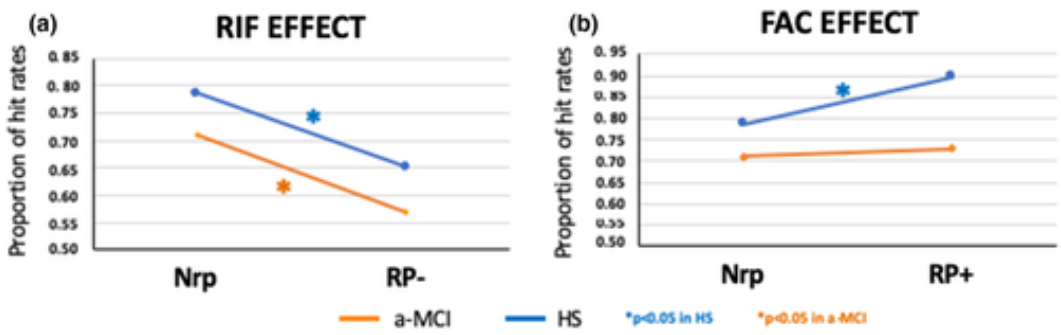


Figure 1.

The retrieval-practice paradigm: The RIF and FAC effect. The figure illustrates the RIF effect in panel (a) and FAC effect in panel (b) obtained at the retrieval-practice paradigm by patients and controls. The two-way MANCOVA analysis revealed in the a-MCI patients and in HS the presence of significant RIF effect (orange and cyan asterisks, respectively), The FAC effect was detected only in the HS group (cyan asterisk). Abbreviations: a-MCI, amnestic Mild Cognitive Impairment; HS, healthy subjects; Nrp, unpracticed items from unpracticed categories; Rp+, practiced items from practiced categories; Rp−, unpracticed items from practiced categories. See text for further details.

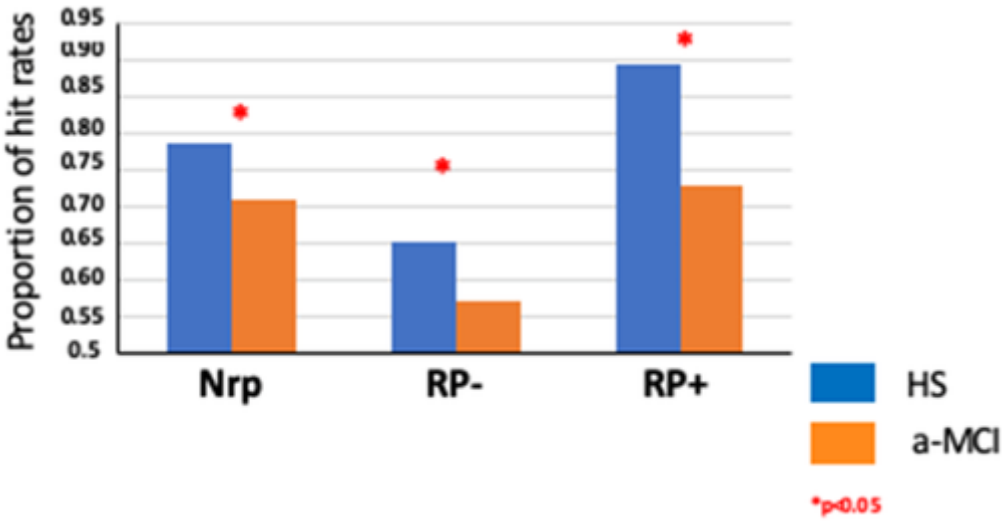


Figure 2.

The figure illustrates the significant differences between a-MCI patients and HS in the raw accuracy observed in the Nrp, Rp+ and Rp− items retrieved. Abbreviations: a-MCI, amnestic Mild Cognitive Impairment; HS, healthy subjects; Nrp, unpracticed items from unpracticed categories; Rp+, practiced items from practiced categories; Rp−, unpracticed items from practiced categories. See text for further details.

3.10.4 Discriminant analysis for RIF and FAC effects

The analysis showed a poor discriminant ability to correctly classify a-MCI and HS for pRIF ($\lambda = 1$, $df = 1$, $p = 0.885$; sensitivity = 57.9%; specificity = 41.4%; accuracy = 47.9%). Conversely pFAC showed a significant ability to correctly classify individuals belonging to either group ($\lambda = 0.868$; $df = 1$, $p = 0.011$; sensitivity = 57.9%; specificity = 75.9%; accuracy = 68.8%).

3.10.5 Correlations between retrieval-practice paradigm and ACE-R domains

In a-MCI patients, we found significant positive correlations between Nrp items and ACE-R ($r = 0.727$, $p < 0.001$), Executive Functions ($r = 0.763$, $p < 0.001$) and Language ability ($r = 0.826$, $p < 0.001$). We found also significant positive correlations between the Rp− items and ACE-R total score ($r = 0.604$, $p = 0.006$) and Visuo-spatial abilities ($r = 0.692$, $p = 0.001$). Finally, we found significant correlations between Rp+ and Memory performance ($r = 0.615$, $p = 0.005$). No significant correlations were identified in HS. When considering correlations with the proxy measure of RIF and FAC there were no significant differences in a-MCI patients and HS.

3.11 MRI relationships in a-MCI patients

VBM analyses in patients revealed a positive association between Nrp items and GM volumes in the precuneus and posterior cingulate cortex bilaterally and in the left occipital lateral cortex (Figure 3, panel a). Moreover, significant positive associations were found between patient Rp− items and GM volumes in the right hippocampus and parahippocampal

gyrus (Figure 3, panel b). No significant associations were found between Rp+ items and GM volumes.

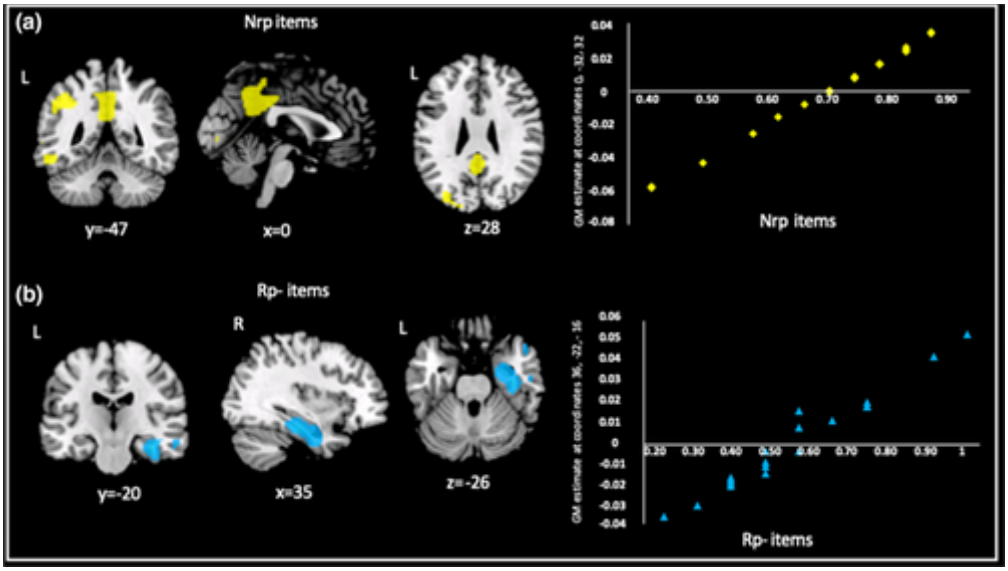


Figure 3.

Associations between the retrieval-practice paradigm and grey matter volumes in patients with a-MCI. Panel (a) shows direct association between Nrp items and GM volumes in the precuneus, posterior cingulate cortex bilaterally and occipito-lateral cortex in the left hemisphere. Panel (b) shows direct association between the Rp− items and GM volumes in the hippocampus, parahippocampal gyrus, in the right hemisphere. Scatter plots are also shown. The results are overlaid onto a T1-weighted template MNI coordinates are reported for each section. Abbreviations: GM, grey matter; Nrp, unpracticed items from unpracticed categories; L, left; R, right; Rp−, unpracticed items from practiced categories. See text for further details.

In addition, the analyses to test for associations between GM volumes and differential scores considered as proxy measures for RIF (pRIF) and FAC (pFAC) did not return any significant result.

3.12 Discussion

The RIF effect is due to the fact that repeated retrieval of an item reinforces that item and causes loss of retrieval access to other related items (Anderson et al., 1994). The FAC effect is due to an improved recall of items that were previously practised compared to those that were not, thus improving the accuracy of their retrieval. These effects have been consistently observed in young as well as in elderly healthy individuals (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009), while a single study only documented the presence of the RIF in patients with AD (Moulin et al., 2002). FMRI investigations have associated the RIF effect with integrity of the frontal cortex (Kuhl et al., 2007; Penolazzi et al., 2014; Wimber et al., 2008), which is known to be implicated in inhibitory mechanisms that are supposed to underlie the RIF effect. However, no previous studies have investigated the association between the RIF

effect and regional brain volumetrics in patients with neurodegenerative disorders. In the present study we first investigated the RIF and FAC effects in patients with a-MCI, and then possible associations with patient regional GM volumes. Our patients, all responding to the diagnosis of a-MCI due to AD, reported significantly lower scores than HS in several ACE-R domains, mainly Memory, Orientation/attention and Language.

We assessed in all recruited subjects (a-MCI patients and controls) the performance on RPP, a cognitive paradigm specifically devoted to investigation of both inhibitory and the faciliatory effects produced by retrieval of previously studied items. In contrast to previous studies on healthy elderly subjects and AD patients (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009; Moulin et al., 2002), we analysed subjects' performance considering both effects. We observed a significant main effect of Group due to the fact that a-MCI patients retrieved worse than HS all studied items independently from their being practised or unpractised. We found also a significant main effect of Condition. This was due to a better recall of Rp+ items (practiced items from practiced categories) in comparison to Nrp (unpractised items from unpractised categories – baseline condition) and Rp− items (unpractised items from practiced categories), indicating a general benefit deriving from practice effect. Interestingly, we found a significant Group by Condition interaction. Planned comparisons revealed that there was no significant difference in the RIF effect between groups, but there was a significant difference in the FAC effect. Indeed, the lack of between-group difference in the RIF was due to the fact that both HS and a-MCI patients showed a significantly lower accuracy for Rp− compared to Nrp items (i.e. measure of the RIF effect). Conversely, the significant difference observed in the FAC effect was due to higher accuracy for retrieval of Rp+ compared to the Nrp items (i.e. measure of the FAC effect) observed in HS but not in a-MCI.

Consistent to previous studies (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009), these data indicate a preservation of RIF effect in normal ageing as well as in the presence of neurodegeneration. Inhibition is the most relevant physiological mechanism underlying the RIF effect, whose function reduces the accessibility of interfering stimuli by inhibiting the recall of non-target stimuli. The forgetting phenomenon induced by retrieval is, therefore, due to unconscious control processes that limit the competition and interference of not-target stimuli (Levy & Anderson, 2002). Forgetting occurs because Rp+ items need to be recalled first, and this affects the recall of Rp− items. Our results are in line with the hypothesis that the inhibition mechanism underlying the RIF effect is an unintentional process requiring less modulation by executive functions (Hogge et al., 2008a, 2008b). Although there are only a few studies that investigated the RIF effect in elderly subjects, they all documented RIF integrity in normal ageing, thus demonstrating integrity of the inhibitory processes (Hogge et al., 2008a). These studies included participants whose average age was comparable to that of our subjects. This indicates the presence of intact automatic inhibitory abilities across ageing, which appear to decay only at most advanced stages (Aslan & Bäuml, 2012; Gómez-Ariza et al., 2009). Consistently, Aslan and Bäuml (2012) reported a significant RIF effect in older adults. All these results confirm that healthy elderly people benefit from well-functioning inhibitory processes in episodic memory despite their age.

Moreover, the first study performed on AD patients (Moulin et al., 2002) reported an intact RIF effect, indicating that its underlying inhibition mechanisms are substantially different from those subserving other cognitive tasks requiring inhibition (e.g. Stroop effect or similar), in which AD patients are well known to fail. Moulin et al. (2002) argued that the RIF effect is likely to be less dependent on executive functions than it has always been thought.

Coherently, a growing number of functional neuroimaging studies showed activation beyond prefrontal areas during inhibitory tasks (Amieva et al., 2004). Frontal regions and their cortical connections likely mediate inhibitory tasks involving controlled processes (Burgess & Shallice, 1996; Fuster, 1993), while more automatic inhibitory tasks are likely to involve more localized neural systems, such as subcortical structures (Collette and Van der Linden, 2002; Collette et al., 1999; Faust & Balota, 1997).

Similarly to Moulin et al. (2002), we observed in patients with mild memory impairment (a-MCI patients) the same RIF effect as that in HS. We interpreted these results arguing that the inhibitory mechanisms in patients with a-MCI parallel those observed in patients with AD (Moulin et al., 2002), which probably depend on an automatic, less demanding process for the executive functions. This process may be due to the resolution of interference related to a ‘blocking effect’ (Anderson et al., 1994). According to this hypothesis, the impairment in the recall of related items appears when the access to them is stopped by their successfully retrieved competitors, which are characterized by a stronger memory trace (Anderson et al., 1994).

In addition to Moulin et al. (2002) we investigated here also the facilitatory effect produced by retrieval of previously studied items. In line with our behavioural hypothesis, we documented the presence of the FAC effect in HS but not in a-MCI patients. This suggests that a-MCI patients do not benefit from repeated practice when required to retrieve studied items, which is probably due to impairment of an overlearning mechanism as a consequence of their memory disorder. The presence of RIF in both groups and the absence of FAC in MCI patients is reflected by a poor accuracy, sensitivity and specificity of RIF and a higher ability of FAC in discriminating between groups. In our opinion, the memory disorder of a-MCI patients may account for their lower amount of retrieved items when compared to HS. In support to this interpretation, we found a significant association between RPP items and cognitive function in the patient but not in the control group. Nrp and Rp− items were indeed significantly associated with patients' level of cognitive efficiency indicating that the severity of their cognitive impairment impacts on their RPP's performance. Interestingly, Rp+ items correlated with patients' memory scores, suggesting that retrieval of practiced items is strictly associated with the memory functions. This finding reinforces our idea that the normal overlearning mechanism underlying the FAC effect is no longer functioning in the presence of neurodegeneration. However, when correlating cognitive measures with proxy measures of RIF and FAC (estimated as differential scores) we did not obtain significant effects. This is likely due to the fact that these proxy measures are not able to estimate properly the RIF and FAC effect. In the literature, these effects have not been tested as differential scores but directly comparing the recollected items in different conditions.

Finally, we identified a significant association between patients' Nrp and Rp− items and their regional GM volumes. Specifically, the Nrp items correlated with GM volumes in the precuneus and posterior cingulate cortex bilaterally, while the Rp− items correlated with GM volumes in the right hippocampus and parahippocampal gyrus. All these brain regions are known to be critical for memory functions (Geib et al., 2017; Renoult et al., 2019) and involved in the early cognitive deficits observed in AD (McDonough et al., 2020; Serra et al., 2011; Serra et al., 2019). From a neurobiological viewpoint, the inhibitory mechanisms underlying the RIF effect are driven by integrity of the prefrontal cortex, mainly its dorsolateral portion. Previous studies highlighted the role of the right dorsolateral prefrontal cortex in retrieval suppression, a voluntary inhibitory mechanism that stops retrieval when a cue begins triggering a memory trace (see Anderson et al., 2016 for a review). Moreover, previous fMRI connectivity studies indicate that, in healthy subjects, the right dorsolateral prefrontal cortex actively couples with hippocampal and parahippocampal activation during retrieval suppression (Benoit et al., 2015; Benoit & Anderson, 2012). In addition, another study showed that the hippocampus improves progressively its activation with practice (Depue et al., 2007). Also, posterior regions of the brain such as the posterior cingulate cortex, the precuneus and angular gyrus contribute to this inhibitory network (Anderson et al., 2016). In the RPP procedure, retrieval-inhibitory forgetting is a non-voluntary mechanism, which explains why the prefrontal regions play a less prominent role. Against this background, our current findings suggest that, in a-MCI patients, RPP performances are sustained by integrity of the meso-temporal lobe and posterior regions rather than the frontal regions. In particular, the association between performance in Rp− condition and GM volumes in hippocampal regions could be interpreted in line with results previously reported in AD patients (Moulin et al., 2002). We hypothesized that the inhibitory mechanism involved in the RIF effect in neurodegenerative disorders is not related to the integrity of frontal lobes, but is based on the resolution of interference due to temporal lobes' functions. Indeed, the atrophic changes in the structures of the meso-temporal lobes in our a-MCI patients were ascertained by comparison with HS, while no differences were observed in the prefrontal cortices (dorsolateral prefrontal, ventrolateral or anterior cingulate cortex) reinforcing the idea that a-MCI patients suffer from a ‘meso-temporal lobe dysfunction’.

An important limitation of this study is the lack of direct evidence of neural correlates of RIF and FAC effects, as demonstrated by non-significant results obtained in the VBM analysis. However, this might depend on several factors including (as mentioned above) that the proxy measures of RIF and FAC used here are not able to estimate these effects properly. Another possible explanation is the fact that the differential scores flat the differences between items retrieved, making the detection of association with imaging data hard to be observed. In addition, structural MRI data are poorly sensitive to early brain tissue changes (e.g. synaptic disconnection), which are more likely to reflect RIF and FAC effects in our population. Future studies based on functional brain data are needed to clarify this issue. Another potential limitation of this study is the absence of MRI data in the control population. This did not allow us to investigate the neurobiological effects of RPP derived indexes and interactions with patients. Future studies are needed to fill this gap. Moreover, we did not consider any specific measure of intentional inhibitory abilities. Future studies should include

specific evaluations of executive functions mediated by the frontal lobe to distinguish better between automatic inhibitory processes and those requiring more frontal control. Finally, the age range of our participants was the same used in other studies on RIF. Consistently with those studies, we found an intact RIF in our sample. However, previous studies that divided older adults in young–old and old–old demonstrated the presence of RIF in young–old subjects only. This supports the hypothesis that inhibitory abilities decline late in life, similarly to other cognitive functions (Aslan & Bäuml, 2012). We did not consider older participants separately because of our small sample size. However, we recognize the importance to investigate by dedicated studies the presence of RIF in pathological populations considering young–old (age range 65–75 years) and old–old subjects (<75 years) separately.

In conclusion, we hypothesize that when a-MCI patients are challenged to retrieve previously presented items, the retrieval process is so much demanding for memory per se that it does not benefit from facilitation effects due to previous practicing. Conversely, cognitive efficiency, which is still substantially preserved in a-MCI patients, is likely to drive retrieval suppression of interfering stimuli instead of prefrontal inhibitory mechanisms. In this process it is possible to hypothesize that the meso-temporal lobe structures play an important role in managing the automatic mechanism leading to suppression of items. Thus, the presence of an intact RIF in a-MCI patients could indicate the efficiency of automatic, less attentional demanding, inhibitory mechanisms. This ability could be targeted by cognitive trainings in AD patients, developing memory tasks in which automatic inhibitory processes might help memorization of information. However, further studies are needed to disentangle the respective role of memory and inhibitory mechanisms in retrieval in the presence of pathological ageing.

Chapter IV

"Verbal and visual dissociation in retrieval practice paradigm in neurodegenerative diseases"

4.1 Aim

The aim of the present study was to document any verbal and visual dissociation in RPP and to test the hypothesis that representations in long-term visual memory are sufficiently ingrained to be immune to recognition-based impairment, unlike oblivion induced by the recovery of verbal material. This hypothesis was motivated, in the first place, by the evidence that long-term memory is superior for visual material compared to verbal material (Nelson, Reed, & Walling, 1976; Paivio, 1969, 1971) and, second, as evidence that retrieval-based memory deficits do not translate into similar recognition-based impairments (Anderson & Bjork, 1994; Butler, Williams, Zacks, & Maki, 2001; Hicks & Starns, 2004; Koustaal, Schacter, Johnson Galluccio, 1999; Macrae, 1999; Tversky, 1973). The aim of this project is also to investigate which brain areas are most involved in the processes of inhibition and facilitation in patients with different types of cognitive impairment.

4.2 Methods

4.2.1 Participants

23 HS (control group), 21 AD patients, 21 MCI patients, 16 SCD patients were recruited. Each recruited subject was required to sign an informed consent, after the detailed explanation of the protocol procedures.

Patients diagnosed with probable AD were selected according to the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (American Psychiatric Association APA, 2013; McKhann et al., 2011).

Patients diagnosed with MCI was defined according to current criteria (Albert et al., 2011). MCI patients were selected indiscriminately with single or multiple domain and did not meet the diagnostic criteria for major cognitive disorder (American Psychiatric Association APA, 2013), showing a CDR (Hughes et al., 1982) score not exceeding 0.5.

As for the SCD, the subjects did not have to report below normal scores in the neuropsychological assessment tests, and they did not have to be pathological at the ACE-R scores or in the total score of the MMSE. The SCD subjects had to go spontaneously to the clinic center, complaining of a subjective cognitive disorder, not subsequently found by neuropsychological tests.

The following inclusion and exclusion criteria will be used for the recruitment of SCD:

• Age between 60 and 80 years

• Right-handed

• Absence of neurological and cognitive deficits

• Absence of psychiatric pathologies

• Absence of exclusion criteria for the MR exam

The following inclusion and exclusion criteria will be used for the recruitment of healthy subjects:

• Age between 60 and 80 years

• Right-handed

• Absence of neurological and cognitive deficits

• Absence of psychiatric pathologies

• Absence of exclusion criteria for the MR exam

The following inclusion and exclusion criteria will be used for MCI patient recruitment:

• Age between 60 and 80 years

• Right-handed

• Absence of psychiatric pathologies

• Absence of exclusion criteria for the MR exam

The diagnosis of probable AD was defined according to the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (American Psychiatric Association APA, 2013; McKhann et al., 2011)

4.3 Neuropsychological assessment

- **Screening**

An extensive screening battery was used to assess cognitive functions in patients and healthy subjects (HS), which included the following tests: (a) verbal episodic long-term memory: 15-Word List (Immediate, 15-min Delayed recall and recognition; Carlesimo et al., 1996; Short Story Test (Immediate and 20-min Delayed recall; Carlesimo et al., 2002; (b) visuo-spatial long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall; Carlesimo et al., 2002); (c) short-term and working memory: Digit span (forward and backward) and the Corsi Block Tapping task (forward and backward) (Monaco et al., 2013); (d) executive functions: Phonological Word Fluency (Carlesimo et al.,1996) and Modified Card Sorting Test (Nocentini et al., 2002); (e) language: Naming objects subtest of the BADA (‘Batteria per l'Analisi dei Deficit Afasici’, Italian for ‘Battery for the analysis of aphasic deficits’) (Miceli et al., 1991); (f) Reasoning: Raven's Coloured Progressive Matrices

(Carlesimo et al., 1996); (g) constructional praxis: copy of simple drawings with and without landmarks (Carlesimo et al., 1996) and copy of Complex Rey's Figure (Carlesimo et al., 2002). For all of the tests, Italian normative data were available for both score adjustment (sex, age and education) and for defining normality cut-off scores, which were determined as the lower limit of the 95% tolerance interval for a confidence level of 95% (normative data for each test are reported in the corresponding references).

- **ACE-R and MMSE**

All participants underwent a cognitive assessment performed by administering the *Addenbrooke Cognitive Examination* test, ACE-R (Mathuranath et al., 2000); the ACE-R contains all the items provided for in the MMSE, it will therefore also be possible to calculate the final score of the MMSE (Folstein et al 1975).

4.4 Experimental procedure

Our experimental tasks are composed as follows: both visual and verbal tasks contain 8 categories, each consisting of 12 items; half of the categories are living and half non-living. The verbal stimuli chosen were converted into images, to have the same items in the form of images and words. The subjects will perform the two different behavioral paradigms randomly, half of the sample will perform the verbal task and the other half the visual one. For the choice of words, so that they could be similar in terms of word length and frequency of use, the database used was: *CoLFIS* (Bertinetto et al., 2005).

4.4.1 Experimental procedure: Verbal Task

The administration procedure consists of four phases:

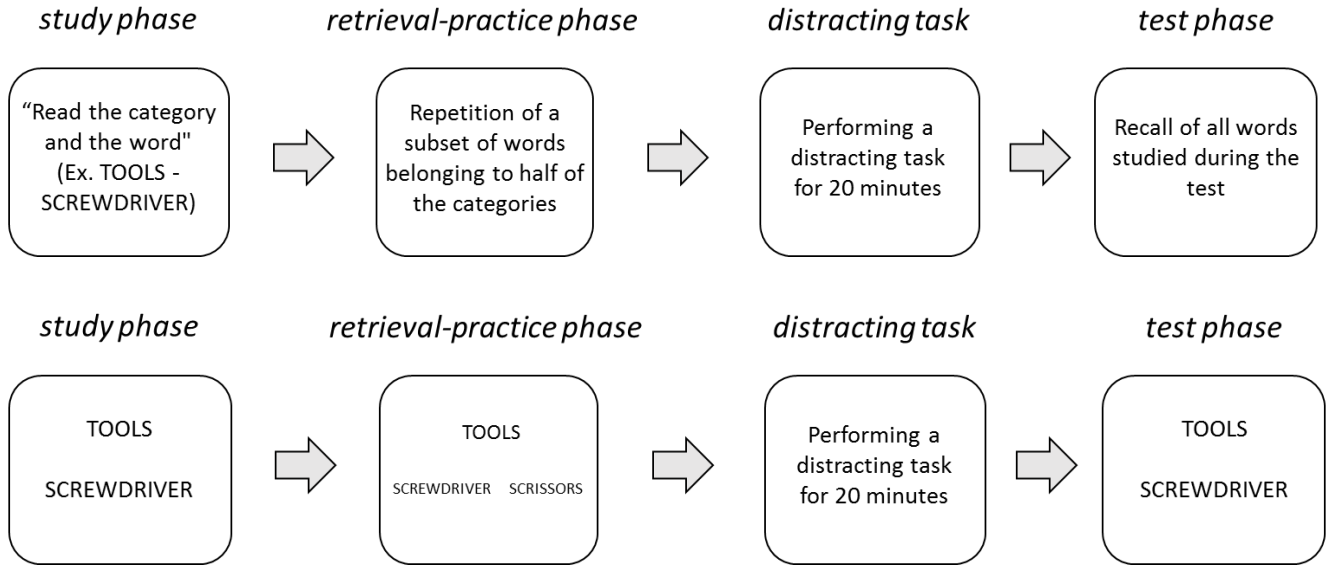
- *Study phase*: Participants underwent a list of words belonging to different categories (8 categories) for a total of 48 items (6 per category). In this first phase of the test, the subject is asked to read aloud a list of words, each slide shows the category at the top and below an item representative of that category. The stimuli are presented on a computer, at a distance of 2.5 seconds from each other, between one stimulus and another a cross appears on the PC screen, which will remain fixed on the monitor for 1.5 seconds.

- *Recognition practice phase*: 12 words belonging to half of the categories seen in the first phase (therefore 4 out of 8 categories) will be reviewed, together with a "bait" element never seen before, from the same category as the already known stimulus. The subject was asked to choose which of the two words he has seen before.

- *Interval phase*: about 20 minutes, during which the participants performed the ACE-R, except for the tests that could interfere with the experimental task.

- *Recognition phase*: participants performed a choice recognition test on all 48 stimuli presented in the study phase, to test the participants' memory for the items shown in the first phase (12 of which were reiterated). The subject had to answer (with a forced choice

between YES and NO) if the image presented has already been seen in any of the previous phases.



4.4.2 Experimental procedure: Visual Task

Like the verbal task, it also includes three different phases and a distracting task:

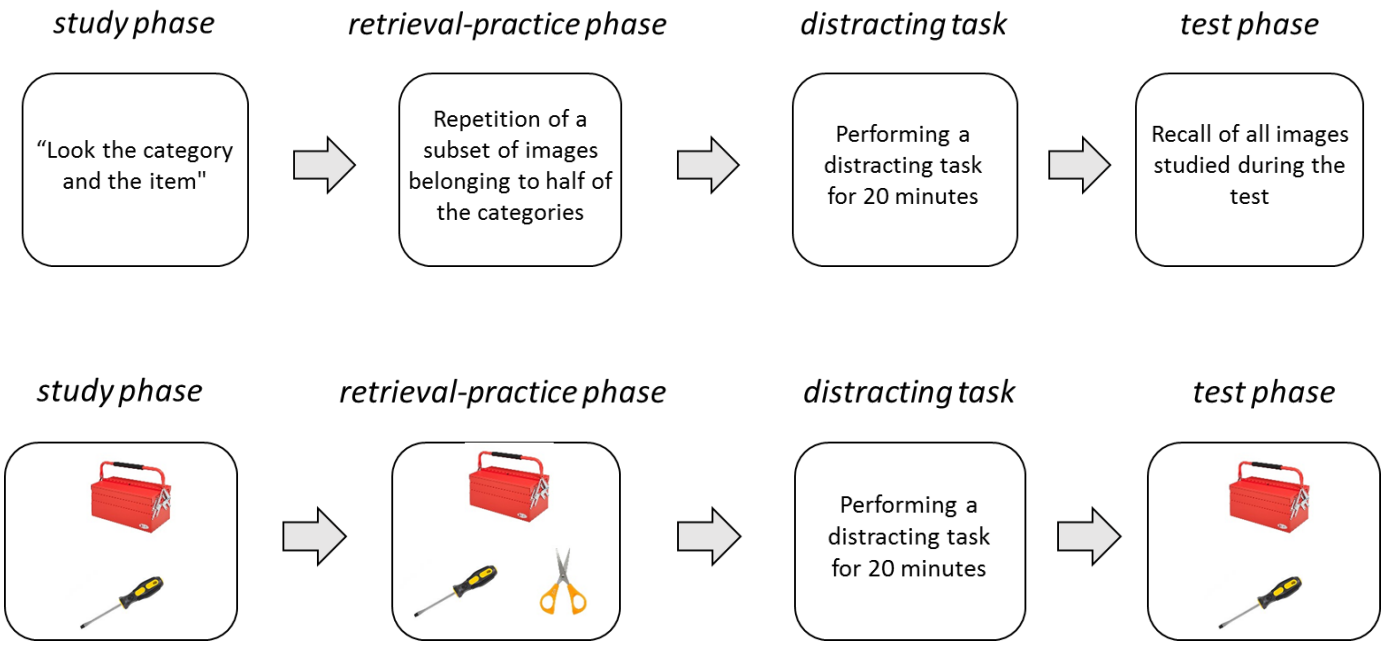
- *Study phase*: Participants underwent images belonging to different categories (eight categories) for a total of 48 items (6 per category). In this first phase of the test, the subject is asked to look at a list of images, each slide shows the category at the top and below an item representative of that category. The stimuli are presented on a computer, at a distance of 2.5 seconds from each other, between one stimulus and another a cross appears on the PC screen, which will remain fixed on the monitor for 1.5 seconds. During the visual task, while the images scroll, the subjects are engaged in a subvocalic repetition, in order to reduce the verbal coding of the items presented.

- *Recognition practice phase*: during which the participants underwent 12 stimuli selected from the study phase, combined with another specimen of the same category not shown previously (ex. a lemon already seen, from the FRUIT category and a "new pineapple item never seen "of the same category: FRUIT). Participants responded by pressing a button to indicate which element (image on the left or on the right combined with the button on the left or right) had already been seen in the previous phase.

- *Interval phase*: as for verbal task, about 20 minutes, during which the participants performed the ACE-R, except for the tests that could interfere with the experimental task.

- *Recognition phase*: Participants performed a choice recognition test on all 48 stimuli presented in the study phase to test the participants' memory for the items shown in the first

phase (12 of which were reiterated). The subject answered (with a forced choice between YES and NO) if the image presented has already been seen in any of the previous phases.



4.5. MRI acquisition

Some of the patients and healthy subjects who participated in the behavioral study, (for a total of 61 subjects), underwent a 3T-MRI examination (Siemens Magnetom Prisma). MRI scans will be obtained in a single session; the MRI protocol will include structural and functional scans:

(a) EPI Resting (TR =980 ms, TE1 = 12.80 ms, TE2=30.41 ms, TE3= 48.02 ms, Dynamic Measurement=488, Slice=52, Voxel Size=2.8x2.8x2.8 mm);
(b) 3D MEMPRAGE scan (TR = 2000 ms, TE1 = 1.67 ms, TE2= 3.48 ms, TE3= 5.29 ms, TE4= 7.1 ms, Matrix = 256 × 256, n. slices = 176, thickness = 1 mm)
(c) 3D fast-fluid attenuated inversion recovery (FLAIR; TR =8000 ms, TE = 314 ms, TI = 2350 ms);
(d) T2 Coronal Ippocampi (TR = 8020 ms, TE = 50 ms, slice = 30, thickness = 2mm, Matrix = 438× 448)
(e) pcAsl (TR = 4100 ms, TE = 18.98 ms, slice = 34, thickness = 2.5 mm, Matrix = 48× 64 , Labeling Duration=1800 ms)
(f) DTI (Direzioni=121, b-Value= 2500, TR = 3400 ms, TE = 80 ms, slice = 75, thickness = 1.8 mm, Voxel Size=1.8x1.8x1.8 mm, Matrix = 116× 116)
(g) QSM (TR = 39 ms, TE1 = 5 ms, TE2=10 ms, TE3= 15 ms TE4 = 20 ms TE5 = 25 ms, TE6 = 30 ms, TE7= 35 ms, slice = 144, thickness = 1 mm, Voxel Size=1x1x1 mm, Matrix = 192× 224)

The structural sequences DE and FLAIR were used for a macroscopic investigation (e.g., quantification, localization of any lesions) and for the exclusion of patients suffering from other pathology or concomitant, severe cerebrovascular disease.

The T1-weighted volumes were pre-processed using the VBM protocol (Ashburner & Friston, 2001, 2005) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), which consists of an iterative combination of segmentations and normalizations to produce a GM probability map (Ashburner & Friston, 2001, 2005) in the standard space (Montreal Neurological Institute, or MNI coordinates) for each subject.

To compensate for the expansion or compression that could occur during the deformation of the images, to make them match the model, the GM maps were "modulated" by multiplying the intensity of each voxel in the final images by the Jacobian determinant of the transformation, corresponding to the relative volume before and after deformation (Ashburner & Friston, 2001).

For each subject we calculated, from the images obtained from the previous step, the volumes of GM, WM and cerebrospinal fluid (CSF). All data were then smoothed using a 12 mm FWHM Gaussian kernel.

4.6 Statistical analysis

4.6.1 Behavioral and clinical data

Statistical analyses on demographic and cognitive data, were performed using SPSS-20.0.

One-way ANOVA models were used to compare age and years of formal education between all patients and HS. Chi-square was used to assess their sex distribution. For the screening neuropsychological battery, all patients and HS were compared using a series of one-way ANOVA. To avoid the type-I error, Bonferroni's correction was applied (*p* value threshold $\alpha = 0.05/24 = 0.002$).

The comparisons on each domain of the ACE-R and on each index of the RPP (for both visual and verbal tasks:) were studied using one-way ANOVA. The surviving results of the Bonferroni correction were taken into consideration, respectively for the analysis on the domains of the ACE-R and on the RPP indices.

All patients (AD, MCI and SCD) and HS were compared in each ACE-R domain (Memory, Orientation/Attention, Language, Visuospatial functions Executive) using one-way ANOVA models. To avoid the type-I error, Bonferroni's correction was applied (*p* value threshold $\alpha = 0.05/5 = 0.01$). Adjusted MMSE and total ACE-R scores were compared between groups using a one-way ANOVA model (*p* value threshold $\alpha = 0.05/2 = 0.025$ survived after Bonferroni's correction).

In each of the 4 groups, separately, Pearson's correlations were used to assess potential association between each domain of ACE-R (memory, executive functions, and language) and the three RPP indices (Nrp, RP +, Rp-) (*p* value threshold $\alpha = 0.05/6 = 0.008$, after Bonferroni's correction) divided into the three categories of membership: Baseline, FAC and RIF.

According to Anderson et al. (1994), behavioural analyses were performed to calculate, at a group level, the RIF and FAC effects.

The RIF effects was obtained contrasting Rp− items (unpractised items from practised categories) against Nrp items (unpractised items from unpractised categories – baseline condition). The FAC effect was obtained contrasting Rp+ (practised items from practised categories) against Nrp items.

RIF and FAC effects in all group were evaluated by comparing their performances using a repeated measures ANOVA, with Group as between factor (AD vs MCI vs SCD vs HS) and Conditions (Nrp, Rp−, Rp+) as within factor. Post-hoc planned comparisons were used

4.6.2 MRI and experimental tasks

After the behavioral study, we studied the magnetic resonance data of the 61 subjects (14 AD, 16 MCI, 14 SCD, and 18 HS) who were able to perform MRI.

For both experimental tasks, visual and verbal, for all participants, statistical analyses of regional GM volumes were performed on smoothed GM maps within the framework of the general linear model in SPM8. We investigated the potential association between patient GM volumes and all RPP indexes, with the aim of identifying possible neural correlates for Rp−, Rp+ and Nrp by using one simple t test model with RPP indices as covariate of interest.

All analyzes were performed separately for the visual and verbal tasks.

4.7 Results

4.7.1 Demographical characteristics

There were no significant differences between the four groups in age (F=2.02, *p*=0.117), in years of formal education (F=1.34, *p*=0.26). and sex distribution (χ^2=3.05, d.f.=3, *p*=0.384).

Results are reported in Table 1; Mean and standard deviation are reported. See text for further details.

Table 1. Demographic and clinical characteristics of studied subjects.

Demographical and clinical characteristics	AD	MCI	SCD	HS	*p* =
N°	21	21	16	23	
Mean (SD) age	72.48 (6.7)	71.43 (7.9)	68.63 (6.8)	67.52 (8.1)	0.117
Gender (M/F)	10\11	11\10	10\13	4\12	0.384
Mean (SD) years of formal education	11.62 (4.37)	13.48 (3.64)	13.25 (3.41)	13.65 (3.27)	0.26

4.7.2 Neuropsychological assessment

- ***Screening***

Average performance scores of the experimental groups on the tests of the neuropsychological battery are reported in Table 2. The series of performed one-way ANOVAs for most tests showed significant differences between four groups, except for Delayed recall of the Short Story test, Forward and Backward Digit Span. Note that the significant differences between four groups on the tests Phonological Word Fluency, Naming of objects, Copy of drawings and Copy of drawings with landmarks do not survive after Bonferroni's correction.

In general, as expected, HS performed better than MCI and AD groups on all tests. On the neuropsychological battery, SCD and HS showed similar performances. The SCD group tend to behave similarly to HS when compared to patients (MCI and AD) but show comparable scores to MCI patients on tests of Copy of Rey's Complex Figure, Phonological Word Fluency, Copy of drawings and Copy of drawings with landmarks. The patients' groups (MCI and AD) had different mean scores on Immediate Recall of 15-Word List (*p*=0.002), on TMT (*p*<0.001), Copy of Rey's Complex Figure (*p*=0.001), on number of achivied criteria on Modified Card Sorting Test (*p*=0.002), due to better performances of MCI group to AD.

Table 2 summarizes the performance obtained by all study participants on the neuropsychological screening battery.

Table 2. Performance scores obtained by all groups on the tests of the screening neuropsychological battery.

Test	AD	MCI	SCD	HS	*F*	*p* -Level
Rey's 15-word list:						
Immediate recall (cut-off ≥ 28.5)	22.25 (2.70)	33.33 (7.49)	44.80 (10.31)	49.38 (7.76)	30.87	< 0.001
Delayed recall (cut-off ≥ 4.6)	1.42 (1.31)	4.83 (2.98)	9.47 (3.44)	11.23 (2.24)	35.22	< 0.001
Recognition: hit rates	9.17 (4.56)	11.75 (2.70)	14.00 (0.92)	14.83 (0.38)	11.57	< 0.001
Recognition: false	6.58 (5.12)	2.92 (2.99)	1.13 (1.24)	0.50 (0.52)	10.49	< 0.001
Short story test:						
Immediate recall (cut-off ≥ 3.1)	3.22 (1.83)	4.44 (1.84)	6.25 (1.35)	6.66 (0.91)	13.57	< 0.001
Delayed recall (cut-off ≥ 2.6)	2.25 (1.77)	4.21 (1.72)	6.05 (1.13)	6.29 (0.90)	0.93	NS
Rey's Complex figure:						
Immediate recall (cut-off ≥ 6.4)	3.41 (2.10)	9.16 (5.06)	14.61 (5.75)	14.76 (4.39)	10.09	< 0.001
Delayed recall (cut-off ≥ 6.3)	4.03 (3.06)	8.62 (5.18)	14.73 (6.20)	13.46 (4.47)	7.6	< 0.001
Digit span forward (cut-off ≥ 3.7)	5.09 (1.04)	5.18 (1.16)	6.00 (1.19)	5.69 (1.25)	1.72	NS
Corsi span forward (cut-off ≥ 3.5)	3.75 (0.63)	4.25 (0.70)	5.25 (1.13)	5.17(0.71)	7.25	0.001
Digit span backward	3.64 (0.80)	3.82 (1.53)	4.53 (1.12)	4.62 (0.87)	2.42	NS
Corsi span backward	3.29 (0.95)	3.63 (0.91)	4.67 (0.77)	5.00 (0.73)	8.92	< 0.001
Phonological word fluency (cut-off ≥ 17.3)	26.75 (12.37)	37.00 (9.63)	39.64 (8.03)	39.25 (9.21)	4.61	0.007
Modified Card Sorting Test						
Criteria achieved (cut-off ≥ 4.2)	2.75 (2.06)	4.75 (1.58)	6.00 (0.00)	5.77 (0.59)	12.7	< 0.001
Trail Making Test (TMT):						
TMT_A	84.08 (29.55)	61.50 (28.56)	42.20 (13.33)	38.08 (10.75)	11.99	< 0.001
TMT_B	348.17 (128.38)	202.33 (95.38)	103.40 (30.99)	111.15 (37.40)	25.35	< 0.001
TMT_B-A	264.08 (106.02)	140.00 (100.74)	61.20 (28.95)	73.08 (29.88)	20.48	< 0.001
Perseverative errors						
Naming of objects (cut-off ≥ 22)	27.64 (2.50)	29.09 (1.22)	29.50 (1.16)	29.92 (0.27)	5.41	0.003
Raven's Coloured Progressive matrices (cut-off ≥ 18.9)	22.50 (7.04)	25.50 (4.00)	31.58 (2.70)	32.67 (2.93)	13.75	< 0.001
Copy of drawings (cut-off ≥ 7.1)	7.25 (3.64)	8.83 (2.20)	9.92 (0.86)	9.69 (0.75)	3.86	0.015
Copy of drawings with landmarks (cut-off ≥ 61.8)	62.63 (7.67)	67.40 (4.00)	69.00 (2.00)	68.08 (1.62)	4.03	0.014
Copy of Rey's Complex figure (cut-off ≥ 23.7)	19.35 (12.29)	30.50 (6.37)	32.73 (2.63)	30.03 (3.88)	7.32	0.001

- ***ACE-R and MMSE***

As reported in Table 3, there were expected differences between patients and controls in their MMSE and total ACE-R scores.

Mean MMSE score, ACE-R total score and all ACE-R domain scores (AO, M, EF, L, VS) significantly differed among the experimental groups (respectively, F=33,4, F=46,2, F=31,9, F=63,7, F=19,8, F=9,8, F= 13,6, p<.001 in all cases). In fact, as expected, the control group performed better than other pathological groups (AD and MCI group) (p<.05 in all comparisons), but they obtained similar performance when compared to SCD group.

Table 3. Performance scores obtained by all groups at neuropsychological test.

ACE-R & MMSE	AD	MCI	SCD	HS	*p - Level*
Memory score Mean (SD)	9.86 (3.96)	19.19 (4.40)	23.25 (3.04)	24.04 (3.15)	<.001
Orientation/Attention score Mean (SD)	14.05 (2.39)	17.10 (1.64)	17.88 (0.34)	18 (0.00)	<.001
Language score Mean (SD)	22.95 (2.69)	24.10 (2.73)	25.69 (0.62)	25.83 (0.38)	<.001
Visuospatial functions (SD)	10.57 (3.88)	14.62 (3.15)	15.31 (1.19)	14.96 (1.43)	<.001
Executive Functions score Mean (SD)	6.24 (3.09)	9.48 (2.08)	11.25 (2.43)	11.39 (2.03)	<.001
Total ACE-R (SD)	63.16 (12.05)	79.48 (8.33)	89.35 (6.12)	89.14 (3.62)	<.001
MMSE score Mean (SD)	23.42 (3.09)	27.01 (2.56)	29.02 (1.53)	29.66 (0.95)	<.001

4.7.3 Results of the Verbal Paradigm (RPP)

Table 4 illustrates the proportions of the three conditions in AD, MCI, SCD patients and controls. Figure 1 illustrates the performance of the 4 groups, in the Nrp, Rp+ and Rp- conditions. Table 5 shows the Mean and standard deviation (SD), of FAC and RIF, in all groups. Figure 2 show the RIF effect in panel (a) and FAC effect in panel (b) obtained at the retrieval-practice paradigm by patients and controls, in the verbal task

For the verbal task, in the first one-way ANOVA we observed a significant between-group difference in Nrp items (F=3,56, *p*=.023). Turkey's post-hoc showed that the proportion of items in the Nrp condition is statistically higher in HS group than AD group. Moreover, we found a significant effect of group (F=8.23, *p*<.001) in Rp+ items: planned comparisons revealed a significant difference between AD and SCD (*p*=.002) and between AD and HS (p<.001). Interestingly, the tendency of significance was present on the comparison between AD and MCI (*p*=.065). No significant differences were observed between MCI and SCD (*p*=.531) and between MCI and HS (*p*=.322). Similarly, HS and SCD groups showed comparable performance on Rp+ items (*p*=.994). Finally, the one-way ANOVA applied to the performance on Rp- items revealed no difference between four participant groups (F=1.83, *p*=.16).

Respecting the FAC effect, we observed a significant main effect of group ($F_{3, 36}$=7.21, *p*=.001): Tukey's post-hoc revealed significant comparisons between AD and SCD (*p*=.005) and between AD and HS (*p*<.001). We found also a significant main effect of Condition ($F_{1, 36}$=42.1, *p*<.001), due to the fact that the proportion of items retrieved in the Rp+ condition (mean= 0.88) is statistically higher than that retrieved in the Nrp condition (mean= 0.71). Finally, we found no significant Group by Condition interaction ($F_{3, 36}$=1.29, *p*=.292): the planned comparisons showed that the facilitation effect was present in all groups, in AD ($F_{1, 36}$=7.46, *p*=.009), in MCI ($F_{1, 36}$=22.05, *p*<.001), in SCD ($F_{1, 36}$=8.29, *p*=.006), in HS ($F_{1, 36}$=6.60, *p*=.014).

Finally, regarding the RIF effect, we observed a significant main effect of group ($F_{3, 36}$=3.54, *p*=.024), due to a significant difference exclusively between AD and HS groups; we revealed no significant effect of condition ($F_{1, 36}$=0.17, *p*=.677): indeed, in this case the means of item retrieved in two conditions Nrp (mean= 0.71) and Rp- (mean= 0.70) were almost the same. Finally, we found a significant Group by Condition interaction ($F_{3, 36}$=5.26, *p*=.004) The planned comparisons showed that the RIF effect was present in the SCD only ($F_{1, 36}$= 11.70, *p*=.001), but no RIF effect was observed in AD ($F_{1, 36}$=1.51, *p*=0.22), in MCI ($F_{1, 36}$=2.65, *p*=0.11) and HS groups ($F_{1, 36}$=0.04, *p*=0.83)

Table 4 Proportions of the retrieved items in the RPP in all participants.

Verbal Retrieval Practice (RPP) Results	AD	MCI	SCD	HS
Nrp Mean (SD)	0.58 (0.27)	0.64 (0.21)	0.80 (0.14)	0.85 (0.12)
Rp+ Mean (SD)	0.72 (0.21)	0.89 (0.11)	0.95 (0.06)	0.97 (0.04)
Rp- Mean (SD)	0.63 (0.26)	0.71 (0.20)	0.66 (0.09)	0.84 (0.14)

Figure 1 Performance of the four groups, in the Nrp, Rp+ and Rp- conditions

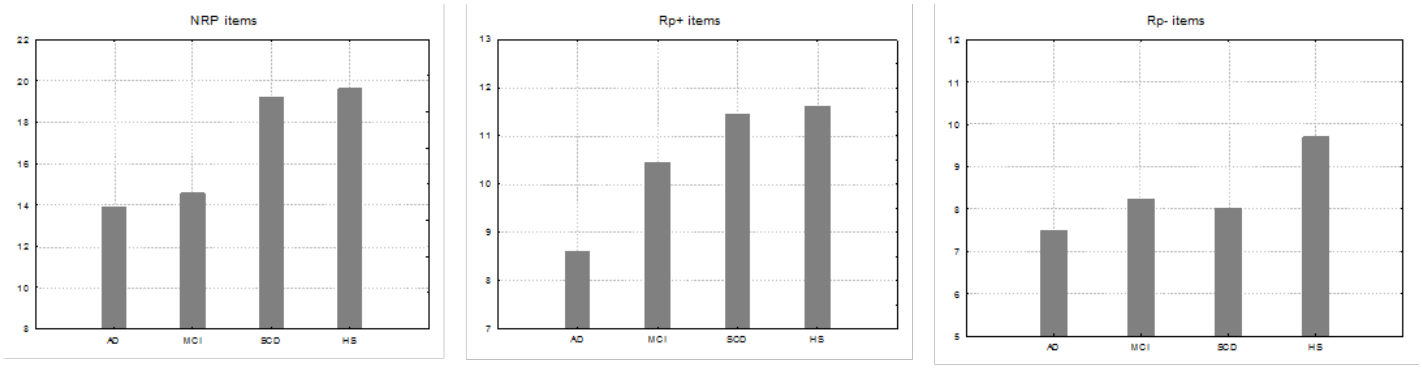
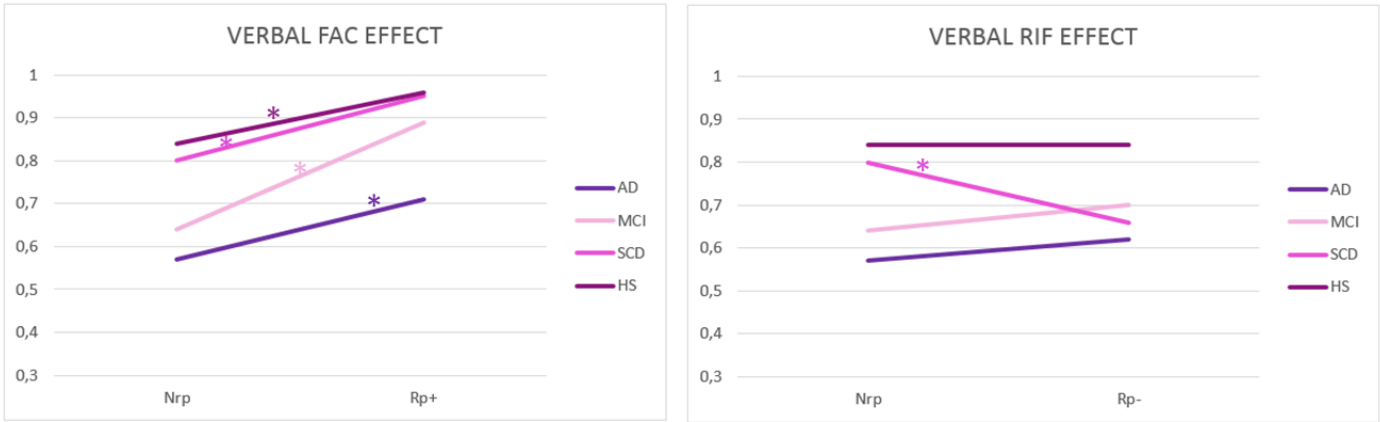


Table 5 Shows the Mean and standard deviation (SD), of FAC and RIF, in all groups

Verbal FAC	*Nrp*	*Rp+*	*p* - Level
AD Mean (SD)	0.57 (0.27)	0.71 (0.21)	.009
MCI Mean (SD)	0.64 (0.21)	0.89 (0.10)	<.001
SCD Mean (SD)	0.8 (0.14)	0.95 (0.06)	.006
HS Mean (SD)	0.84 (0.11)	0.96 (0.04)	.014

Verbal RIF	*Nrp*	*Rp-*	*p* - Level
AD Mean (SD)	0.57 (0.27)	0.62 (0.26)	0.22
MCI Mean (SD)	0.64 (0.21)	0.70 (0.19)	0.11
SCD Mean (SD)	0.8 (0.14)	0.66 (0.09)	.001
HS Mean (SD)	0.84 (0.11)	0.84 (0.13)	0.83

Figure 2 Show the RIF effect in panel (a) and FAC effect in panel (b) obtained at the retrieval-practice paradigm by patients and controls, in the verbal task.



FAC effect: *p=0.009 in AD; *p<0.001 in MCI; *p=0.006 in SCD; *p=0.01 in HS.

RIF effect: *p=0.001 in SCD.

4.7.4 Results of the Visual Paradigm (RPP)

Table 6 illustrates the proportions of the three conditions in AD, MCI, SCD patients and controls. Figure 3 illustrates the performance of the 4 groups, in the Nrp, Rp+ and Rp- conditions. Table 7 shows the Mean and standard deviation (SD), of FAC and RIF, in all groups. Figure 4 show the RIF effect in panel (a) and FAC effect in panel (b) obtained at the retrieval-practice paradigm by patients and controls, in the visual task

For the visual task, no significant differences were observed between four participant groups in Nrp items (F=2,17, p=.11), RP+ items (F=1,44, p=.25), RP- items (F=.265, p=.26).

Finally, as regards the FAC effect, we observed a significant main effect of group ($F_{3, 37}$=3.09, *p*=.039), due to a significant difference exclusively between AD and HS groups. We found also a significant main effect of Condition ($F_{1, 37}$ =50.9, *p*<.001): in this case, the Rp+ items (mean= 0.91) were better recalled than Nrp items (mean= 0.59); finally , we observed no significant Group by Condition interaction ($F_{3, 37}$=0.49, *p*=0.690), due to the fact that, as the planned comparisons revealed, the FAC effect was present in all groups, in AD ($F_{1, 37}$ =22.89, *p*<.001), in MCI ($F_{1, 37}$=10.99, *p*=.002), in SCD ($F_{1, 37}$=7.83, *p*=.008), in HS ($F_{1, 37}$ =13.29, *p*=.008).

Furthermore, about the RIF effect, in the verbal task, we observed no significant main effect of group ($F_{3, 37}$=1.58, *p*=.208), but significant main effect of Condition ($F_{1, 37}$=5.11, *p*=.030), due to the fact that the Nrp items (mean= 0.59) were better recalled than Rp- items (mean= 0.53). Moreover, we found no significant Group by Condition interaction ($F_{3, 37}$=1.87, *p*=.150): in this case, the planned comparisons revealed that the RIF effect was present in the SCD only ($F_{1, 37}$=5.81, *p*=.02), while no inhibitory effect was observed in AD ($F_{1, 37}$=0.02, *p*=0.59), in MCI ($F_{1, 37}$=3.12, *p*=.08) and in HS ($F_{1, 37}$=0.37, *p*= 0.54).

Table 6 Proportions of the retrieved items in the RPP in all participants.

Visual Retrieval Practice (RPP) Results	AD	MCI	SCD	HS
Nrp Mean (SD)	0.44 (0.32)	0.65 (0.14)	0.63 (0.26)	0.67 (0.26)
Rp+ Mean (SD)	0.83 (0.24)	0.91 (0.13)	0.92 (0.10)	0.97 (0.06)
Rp- Mean (SD)	0.46 (0.32)	0.56 (0.15)	0.48 (0.24)	0.64 (0.21)

Figure 3 Performance of the four groups, in the Nrp, Rp+ and Rp- conditions

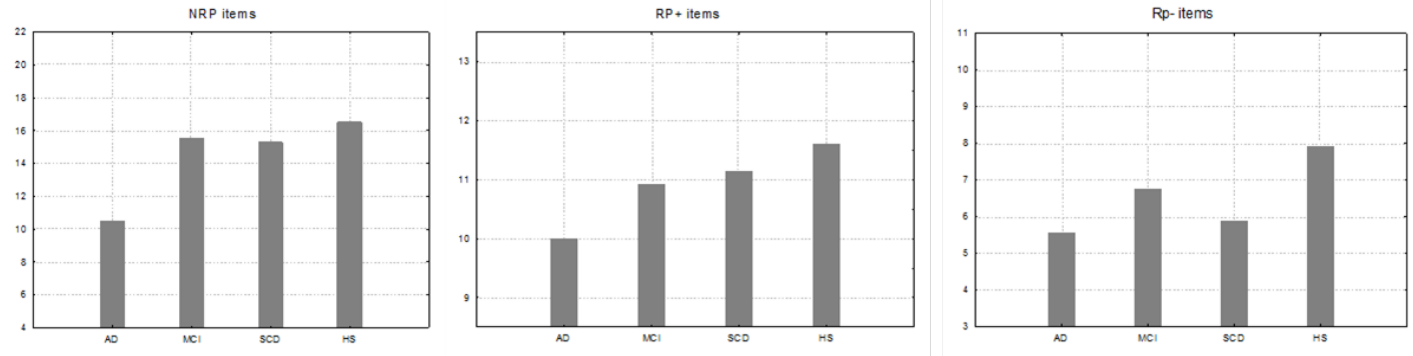


Table 7 Shows the Mean and standard deviation (SD), of FAC and RIF, in all groups.

Visual FAC	*Nrp*	*Rp+*	*p* - Level
AD Mean (SD)	0.43 (0.31)	0.83 (0.23)	<.001
MCI Mean (SD)	0.64 (0.13)	0.90 (0.12)	.002
SCD Mean (SD)	0.63 (0.26)	0.92 (0.10)	.008
HS Mean (SD)	0.66 (0.25)	0.96 (0.05)	.008

Visual RIF	*Nrp*	*Rp-*	*p* - Level
AD Mean (SD)	0.43 (0.31)	0.46 (0.31)	0.59
MCI Mean (SD)	0.64 (0.13)	0.56 (0.15)	.08
SCD Mean (SD)	0.63 (0.26)	0.48 (0.24)	.02
HS Mean (SD)	0.66 (0.25)	0.63 (0.20)	0.54

Figure 4 show the RIF effect in panel (a) and FAC effect in panel (b) obtained at the retrieval-practice paradigm by patients and controls, in the visual task.

FAC effect: *p<0.001 in AD; *p=0.002 in MCI; *p<0.001 in SCD; *p<0.001 in HS.

RIF effect: *p=0.002 in SCD

Overall summary

Table 8 shows for both tasks the FAC and RIF effect, in each group.

Verbal	FAC	RIF
AD	+	-
MCI	+	-
SCD	+	+
HS	+	-

Visual	FAC	RIF
AD	+	-
MCI	+	-
SCD	+	+
HS	+	-

Comparing the groups individually, no significant dissociation emerged between two tasks, verbal and visual. There is only a tendency in SCD, due to greater accuracy of subjects who performed the verbal task, compared to those who performed the visual task, in the Rp- condition (F=4.15, p=0.006).

4.7.5 Correlations between Retrieval-Practice Paradigm and ACE-R domains

After Bonferroni's correction (*p* value threshold α =0.05/6 = 0.008) the only significant positive correlation identified was in AD patients, between the Memory domain and the proportion of items Rp+ (*r Pearson's*= 0.64; *p* = 0.002).

Further correlation analyzes were performed separately on two different samples: on subjects who performed the verbal task, and those who performed the visual task.

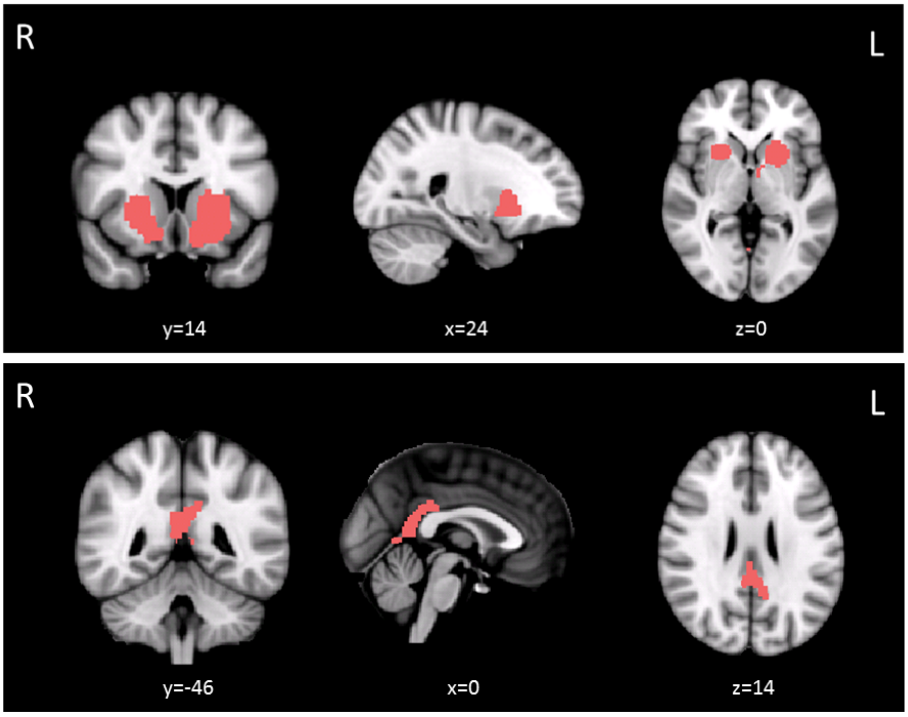
- ***Verbal task:*** After Bonferroni's correction (*p* value threshold α =0.05/6 = 0.008) the correlation analyses showed significant correlation between proportions of items Nrp and ACE-R-total (*r Pearson's*= 0.451; *p* = 0.003), Memory's Domain (*r Pearson's*= 0.508; *p* = 0.001) and Visuo-Spatial's Domain (*r Pearson's*= 0.435; *p* = 0.004). We also find positive correlations between proportions of items Rp+ and all domains of ACE-R: total *r Pearson's*= 0.604, OA *r=0.*534, M *r=0.*705, EF *r=0.*441, L *r=0.*451, VS *r=0.*493, *p*<0.004 in all cases). Finally, we find significant positive correlation between proportions of items Rp- and Memory's Domain (*r Pearson's*= 0.416; *p* = 0.007).
- ***Visual task:*** After Bonferroni's correction (*p* value threshold α =0.05/6 = 0.008) the correlation analyses showed significant correlation between proportions of items Nrp and EF (*r Pearson's*= 0.546; *p* < 0.001). Finally, we find significant positive correlation between proportions of items Rp+ and ACE-R total (*r Pearson's*= 0.586; *p* < 0.001), OA (*r Pearson's*= 0.655; *p* < 0.001), and L (*r Pearson's*= 0.598; *p* < 0.001).

5.1 MRI analysis

After the behavioral study, we studied the magnetic resonance data of the 61 subjects (14 AD, 16 MCI, 14 SCD, and 18 HS) who were able to perform MRI. Below the results.

5.1.2 Voxel Based Morphometry Results: Correlation between RPP Paradigm Indicators and Gray Matter Volume in Verbal Task.

VBM analyzes in AD patients, who performed the verbal task, revealed a positive association between Rp- items and GM volumes in the Right Putamen, Cingulus Gyrus and Left Putamen (Figure 5).

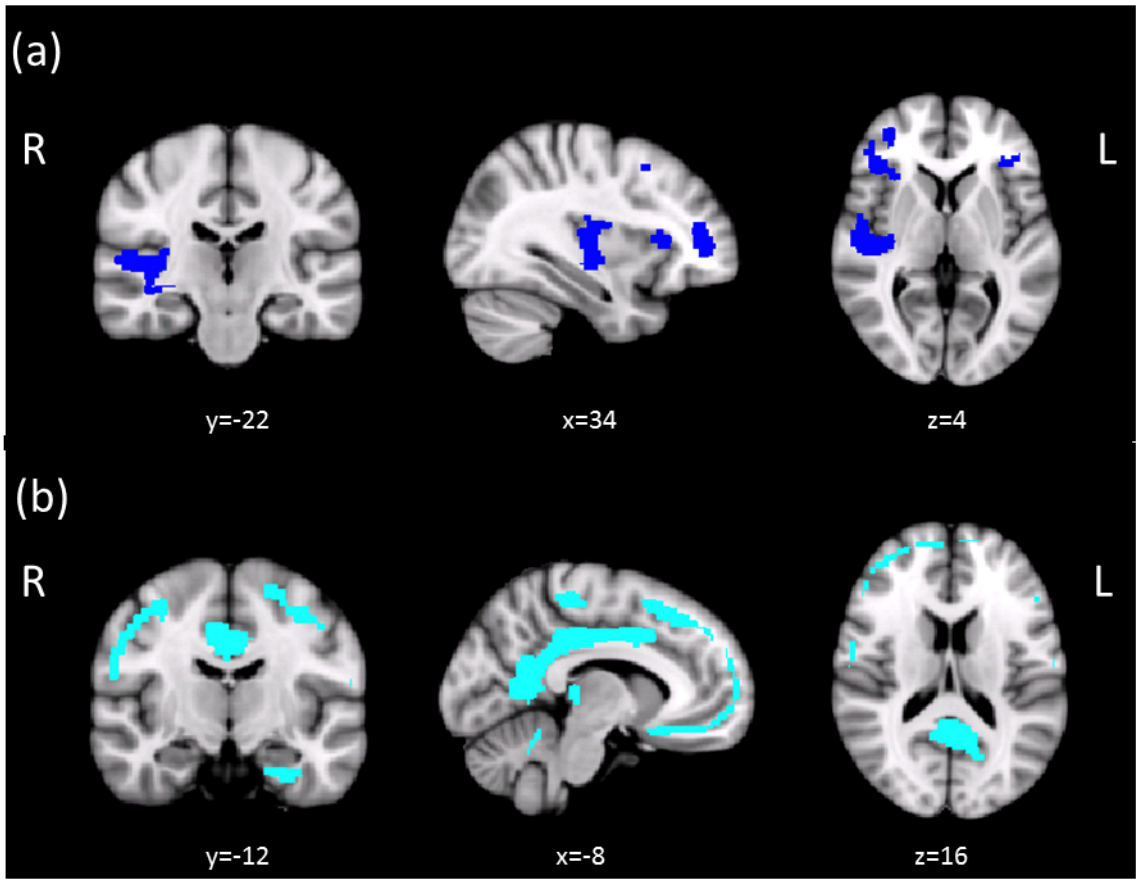


Associations between the recovery practice paradigm and GM volumes in AD patients. Figure 5 shows the direct association between Rp- items and GM volumes in the Right Putamen, Cingulus Gyrus and Left Putamen. See text for further details

5.1.3 Voxel Based Morphometry Results: Correlation between RPP Paradigm Indicators and Gray Matter Volume in Visual Task.

VBM analyzes in AD patients, who performed the visual task, revealed a positive association between Nrp items and GM volumes in the Middle Frontal Gyrus, Inferior Frontal Gyrus, pars triangularis, Inferior Frontal Gyrus. pars opercularis and Insular Cortex (Figura 6, panel a).

In addition, in SCD subjects, significant positive associations were found between Rp- items and GM volumes in the Postcentral Gyrus, Supramarginal Gyrus. anterior division, Superior Frontal Gyrus, and Precuneous Cortex (Figura 6, panel b).



Associations between the recovery practice paradigm and GM volumes in AD and SCD.

Figure 5 panel a) shows the direct association between Nrp items and GM volumes, in AD patience, in the Middle Frontal Gyrus, Inferior Frontal Gyrus, pars triangularis, Inferior Frontal Gyrus. pars opercularis and Insular Cortex. See text for further details

Figure 5 panel b) shows the direct association between Rp- items and GM volumes, in SCD subjects, in the Postcentral Gyrus, Supramarginal Gyrus. anterior division, Superior Frontal Gyrus, and Precuneous Cortex. See text for further details

6.1 Discussion

As we have previously explained, two effects emerge from the retrieval-induced forgetting paradigm: the RIF effect, which is due to the fact that by repeating an element several times, it is strengthened to the detriment of the other related elements, whose access in the retrieval phase (Anderson et al., 1994) and the FAC effect, which, on the other hand, is due to the better recall of items that have been previously practiced, compared to those that have not been repeated, thus improving the accuracy of their retrieval (Serra et al., 2022).

These two effects have been repeatedly studied and observed, both in young elderly people and in HS (Aslasn & Bauml., 2012; Gomez-Ariza., 2009), while there was only one single study that documented the presence of RIF only in AD patients (Moulin et al., 2002).

The purpose of the RPP is to evaluate the role of inhibition processes in memory, specifically the RIF effect, the retrieval-induced forgetting. Specifically, inhibition is a functional mechanism that acts with the aim of reducing the accessibility of interfering stimuli and a non-target stimulus is inhibited if its recall does not occur. The RIF effect is therefore the consequence of control processes that help limit competition and interference from non-target stimuli (Anderson, 2003).

Anderson and colleagues (1994) defined RIF as a consequence of Rp+ item retrieval practice resulting in lower recall of Rp- items than Nrp items, suggesting that Rp+ item “retrieval practice” impairs subsequent recall of Rp items.

However, retrieval practice can enhance subsequent recall of unpracticed items, Rp- items, and instead of being inhibited by retrieval practice, they are strengthened, a phenomenon known as retrieval-induced facilitation (FAC) (Burgess & Shallice, 1996; Chan et al., 2006). It may happen that the retrieval practice of a certain item can cause the inhibition of other items (the Nrp items), but this inhibition can be observed more in the Rp- items, as they are considered competing stimuli in the retrieval of the Rp+ items (Anderson et al., 1994; Anderson & Spellman, 1995 and Racsmany & Conway, 2006).

Cognitive and neuropsychological studies have demonstrated the integrity of inhibitory processes in normal aging (Hogge et al., 2008): Aslan and colleagues (2007) found significant RIF effects in older adults. The results of these studies confirmed that healthy elderly people can benefit from inhibitory processes despite their age. In contrast to the healthy elderly, MCI patients, in a study by Hogge and colleagues (2008) showed particularly

compromised performance when they had to inhibit the retrieval of interfering stimuli. Performance is preserved under normal aging and confirms data obtained by Aslan and colleagues (2007) who found significant and similar RIF effects for the young and the elderly. These data suggest that inhibitory processes are conserved in normal ageing.

Still, the literature shows the presence of an inhibitory difficulty in MCI, which is also reflected in our study. Using different methods to evaluate the inhibitory processes in the responses of a-MCI patients, such as Go-NoGo test or Stroop Test, it emerged that the inhibitory responses of AD patients decrease compared to healthy elderly (Traykov et al., 2011). Belanger & Belleville (2009) observed inhibitory abilities in both Alzheimer's disease and MCI patients. Furthermore, longitudinal analysis demonstrated that the performance of MCI patients was predictive of cognitive decline. Specifically investigating the RPP paradigm, Ortega and colleagues (2012) observed how the RIF in the elderly is absent or reduced after the assignment of a demanding task during which the subjects had to be able to maintain attention on a list of words that a five-digit list was also presented to them and subsequently also added, while in MCI patients, the RIF was absent after the presentation of an even less demanding memory task. These studies are in line with our findings, where in both AD and MCI, in both tasks, we do not find the RIF effect.

Impairment of executive functions, that is the mechanisms that modulate the functioning of various cognitive subprocesses (Muyake et al., 2000), is recognized as a relatively common condition among elderly individuals with mild cognitive impairment (Brandt et al., 2009).

Some fMRI studies have shown the association between the integrity of the frontal cortex (Kuhlet al., 2007, Penolazzi et al., 2014; Wimberet al., 2008) and the RIF effect. As is known, the frontal cortex is implicated in the processes of inhibitory mechanisms, which could underlie the RIF effect (Serra et al., 2022).

In a structural magnetic resonance study by Serra and collaborators (2010) a group of a-MCI patients were compared with a group of non-amnesic MCI patients (na-MCI) characterized by executive impairment. It emerged that in a-MCI patients, brain atrophy was localized in the hippocampus and tempor structures and correlated with the observed episodic memory deficit; in contrast, in na-MCI dysexecutive patients, atrophy was localized in the prefrontal cortex and basal ganglia and correlated with impaired performance on an executive test (the Wisconsin Card Sorting Test).

The a-MCI patients scored lower than the control group in the ACE-R test in the attention domain, showing a significant difference compared to the score obtained by the healthy subjects (Serra et al., 2022). Attention deficits in MCI, specifically in a-MCI patients, are considered predictors of conversion from MCI to AD (Saunders & Summers, 2011),

In the present study, we wanted to first study the effects of RIF and FAC in the different clinical stages of Alzheimer's disease, in AD (21), MCI (21) and SCI (16) patients, as well as in HS (23), in two different recognition tasks, where the same typology of items were submitted, in one group of subjects, in the form of a visual task, and in another group in the form of a verbal task. Next, we wanted to study whether there were associations with regional GM volumes in the different types of subjects who participated in the study.
There is only one previously study that investigated the association between brain volume and the RIF effect, in a-MCI subjects (Serra et al., 2022).

Saunders & Summers (2011) examined neuropsychological functioning in a sample of 60 a-MCI patients, 32 AD patients, and 25 healthy subjects. The a-MCI and AD patients showed significant impairments in attentional processes, working memory and semantic skills.

It has been observed that patients inhibit interfering stimuli less than healthy elderly subjects.

In our study, all subjects were compared in each ACE-R domain using one-way ANOVA models, there were expected differences between patients and controls in their MMSE and total ACE-R scores. Mean MMSE score, ACE-R total score and all ACE-R domain scores (AO, M, EF, L, VS) significantly differed among the experimental groups. In fact, as expected, the pathological groups (AD and MCI group), performed worse than control group, but the patients obtained similar performance when compared to SCD group.

There were no significant differences between the four groups in age, in years of formal education and sex distribution. In this regard, it is possible to hypothesize that the lower performance of the groups of patients with respect to the HS is due to the pathology and does not depend on age.

According to Anderson et al. (1994), behavioral analyses were performed to calculate, at a group level, the RIF and FAC effects.

What we observed for our tasks was, regarding the verbal paradigm, in the first one-way ANOVA a significant between-group difference in Nrp items. Moreover, we found a

significant effect of group in Rp+ items: planned comparisons revealed a significant difference between AD and SCD and between AD and HS. About this, although we know that the planned comparisons cannot be explored unless they are meaningful, we still wanted to study them in an exploratory way to see the general trend of the patients, waiting for a larger sample of subjects on which to redo the analyses.

Interestingly, the tendency of significance was present on the comparison between AD and MCI. No significant differences were observed between MCI and SCD and between MCI and HS. Similarly, HS and SCD groups showed comparable performance on Rp+ items.

Finally, on Rp- items, no significant differences were revealed between the four groups of participants.

Regarding the FAC effect, we observed a significant main effect of the groups: we found significant comparisons between AD and SCD and between AD and HS. Furthermore, there was a significant main effect of the condition, due to the fact that the proportion of items recovered in the Rp+ condition is statistically higher than that recovered in the Nrp condition.

No significant interaction was found. Group by condition, the facilitation effect was present in all groups.

Regarding the RIF effect, we observed a significant main effect of the group, due to a significant difference exclusively between the AD and HS groups, this because, as we expected, patients with Alzheimer's disease, being more compromised, go worse at task.

We did not detect any significant conditional effect, on the contrary, in this case the means of the items retrieved in the two conditions Nrp and Rp- were almost equal.

This significance, which we expected to find among the conditions, and which was not found in this specific task, could be due to the type of material used (verbal items) given that it is not present in the other task. We need further analyzes to explain this unexpected result.

Finally, we found a significant interaction Group by condition. The RIF effect is present only in SCD, but no RIF effect was observed in the other groups.

As for the visual paradigm, no significant differences were observed between four participant groups in the three conditions: Nrp, RP+ and RP- items.

Regarding the FAC effect, we observed a significant group main effect, due to a significant difference exclusively between the AD and HS groups. We also found a significant Condition main effect: in this case, Rp+ items were better remembered than Nrp items.

Furthermore, we did not observe any significant interactions Group by condition, because the FAC effect was present in all four groups.

Regarding the RIF effect, in the visual task, we did not observe any significant main effect of the group, but a significant main effect of the condition, because Nrp items were remembered better than Rp- items. Furthermore, we did not find any significant Group by Condition interaction: in this case, we saw that the RIF effect was present only in SCD, while no inhibitory effect was observed in the other three groups.

So, in contrast to previous studies (Aslan & Bauml, 2012; Gomez-Ariza et al, 2009; Serra et al., 2022) which indicate a conservation of the RIF effect both in aging and in the presence of neurodegeneration, in both our tasks, except for the group of SCD which exhibit the RIF effect in both tasks, there is no significant inhibition effect in the other groups (AD, MCI, HS).

This interesting finding could be caused by the fact that both tasks implied recognition and not recall processes, which could have greatly facilitated our subjects.

What will be interesting to study next is why SCD exhibits a RIF effect while there is none in the other groups. Our hypothesis is that, since inhibition is a functional mechanism that acts with the aim of reducing the accessibility of interfering stimuli (and a non-target stimulus is inhibited if its recall does not occur), the forgetting induced by retrieval in Our SCD patients are functional, as this group of subjects are not yet cognitively impaired. Consequently, coherently with cognitive and neuropsychological studies, our task strengthens the hypothesis of the integrity of inhibitory processes in normal aging (Aslan et al., 2007; Hogge et al., 2008).

Since retrieval-induced forgetting is the consequence of control processes that help limit competition and interference from non-target stimuli (Anderson, 2003), our result confirms that our SCD subjects manage to benefit from inhibitory processes, despite report initial memory problems and despite their age, unlike the other subjects (AD and MCI) who do not benefit from this effect, as they are more cognitively compromised.

From our results there is no verbal-visual dissociation, as all groups behave in the same way both in the verbal and visual task.

As we expected the worse the pathology gets, the less the subjects remember in both tasks. We therefore have that, in both tasks, the Rp+ items are remembered more by the HS, then by the SCD, followed by the MCI and finally by the AD. Since we don't have similar experiments (about verbal and visual dissociation in a recognition task), unfortunately we cannot compare our results with other recall tasks that study verbal and visual dissociation with the same items.

When considering the VBM analyses in the Verbal task AD patients revealed a positive association between Rp- items and GM volumes in the Right Putamen, Cingulus Gyrus and Left Putamen.

In the Visual task AD patients revealed a positive association between Nrp items and GM volumes in the Middle Frontal Gyrus, Inferior Frontal Gyrus, pars triangularis, Inferior Frontal Gyrus pars opercularis and Insular Cortex.

Moreover, in SCD subjects, significant positive associations were found between Rp- items and GM volumes in the Postcentral Gyrus, Supramarginal Gyrus, anterior division, Superior Frontal Gyrus, and Precuneous Cortex.

From a neurobiological point of view, our study confirms that the episodic memory deficit of AD patients is predominant over other cognitive processes. In this case, in patients with AD, the deficit manifests itself in the form of "loss" of the items studied at baseline, which are forgotten, therefore of the items that express a "pure" memory process.

The correlation that we observe, in the VBM, regarding the items that imply a retrieval of recognition, is mediated by processes that have to do with both the phenomenon of familiarity and recollection, and not only with recollection, as happens in recall tasks.

These processes are mediated by a structural network, which involves both the cingulate gyrus (and the connections it has with the hippocampus), and structures such as the basal ganglia, which, thanks to the fronto-striatal circulation, also directly involve the frontal lobe (Yonelinas et al., 2005; Turriziani et al., 2008; Serra et al., 2010; Lombardi et al., 2016).

Basically, the cingulate relates to the hippocampus and this explains the memory impairment. In severely ill patients, such as those with Alzheimer's disease, the memory impairment is mediated by both hippocampal and more frontal processes. This also occurs in the "more basic" episodic memory processes, where there appears to be a large involvement of the damage in the frontal structures.

Consequently, in our patients, even when we go to administer a "simple" task such as that of recognition, it is deficient, as there is an involvement of the memory disorder both due to a hippocampal disorder and a frontal type of disorder.

Thus, as we have said, recognition memory processes are familiar and recollection processes, which are known to be involved and impaired in the more advanced stages of Alzheimer's disease. We know that recollection processes are directly dependent on the hippocampus, while familiarity processes involve an extensive network involving both the frontal cortices and the precuneus (Andrew et al., 2005; Turriziani et al., 2008; Serra et al., 2010; Lombardi et al., 2016). As documented, a memory problem in the most advanced stages of the disease is certainly due to both recollection and familiarity, a deficit found in both our verbal and visual tasks.

As for those with milder impairments (SCD), they probably have a lower impairment because the memory test is easier for them. Even if we find less correlation, the areas that correlate are still involved in memory, especially the precuneus cortex, which is a pole of the default mode network. Even if we hypothesize that in these subjects it is the more strictly frontal aspect of the memory task that is somehow involved in the retrieval of previously studied items.

In conclusion, our study, in line with other experiments (Hogge et al., 2008; Saunders and Summers., 2011; Traykov et al., 2011; Ortega et al., 2012; Serra et al., 2022), shows the presence of an inhibitory difficulty in patients with memory impairment: the RIF is not evident in the pathological group of AD and MCI, but not even in healthy subjects, which generally show good inhibition capacity; this result could be because the recall task was too simple for healthy subjects, who were able to recall multiple items without distinction.

Although there is a trend, in both tasks, in favor of a RIF effect as the pathology increases. As the severity of the disease increases, the inhibition worsens.

We can also hypothesize that the worse performance observed in the RIF obtained from patients is not a direct expression of an inhibitory deficit but could depend on a general deficit of episodic long-term memory processes.

Consistently, the inhibitory deficit reported in the literature is usually measured with tests that do not require learning of material and its subsequent recognition, as occurs in our tasks, but simply the inhibition of interfering responses (e.g., Stroop Test, Go- NoGo). On

the contrary, RPP is in fact a memorization task where the inhibitory effect on the interfering material should allow a better recall of the target stimulus.

Since our patients have a documented episodic memory deficit, their impaired performance in the RPP and the consequent attenuation of the RIF effect, could depend on a basic deficit coding.

In support of our hypothesis, Guez and Naveh-Benjamin (2015) show that the difficulties in recalling verbal material in healthy elderly people depend on a purely mnemic deficit and are not the consequence of an impairment of the inhibitory abilities proper.

A further hypothesis may be that the recognition tasks are simpler than the recall ones, and we hypothesize that when our patients are asked to recognize previously shown elements, the recognition process is not so challenging, to do not activate the RIF effect, but benefit from the facilitation effect (FAC) due to the previous practice.

A limitation of the study is that, while the results of the first study conform and are consistent with both our expectations and with the literature, the results of the second experiment strongly disagree with both the results of the first experiment and our expectations. As already mentioned, the result of this discrepancy is probably due to a limitation of the procedure used in the second experiment.

Probably the retrieval procedure based on the "yes/no" recognition is not suitable for demonstrating the processes of facilitation and, above all, of inhibition in memory tasks.

It could be interesting to create tasks for cognitive training purposes for patients with mild memory disorders, where through automatic inhibitory processes the memorization of new information and its retention could be helped.

We plan to review the procedure, expand the sample, and look for new results on the RIF phenomenon.

BIBLIOGRAPHY

Albert M.S., Moss M.B., Tanzi R., Jones K., (2001) Preclinical prediction of AD using neuropsychological tests, Journal of the international neuropsychological society; pp. 631-639.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 7, 270–279.

Amariglio R.E, Mormino E.C., Pietras A.C., et al. Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly. *Neurology* 2015; 85: 56–62.

American Psychiatric Association (APA). (2013). *Diagnostic and statistical manual of mental disorders* (5th Ed.). American Psychiatric Association.

Amieva H, Le Goff M, Millet X, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol 2008; 64: 492–98.

Amieva, H., Lafont, S., Rainville, C., Dartigues, J. F., & Fabrigoule, C. (1998). Analysis of inhibitory dysfunction in patients with Alzheimer's disease and normal elderly adults in two verbal tasks. *Brain and Cognition*, 37, 58–60.

Amieva, H., Phillips, L. H., Della Sala, S., & Henry, J. D. (2004). Inhibitory functioning in Alzheimer's disease. *Brain*, 127(5), 949–964.

Anderson M.C. (2003) Rethinking interference theory: Executive control and the mechanisms of forgetting. Journal of Memory and Language, 49, 415-445.

Anderson M.C., Bjork E.L., Biork R.A. (2000), Retrieval induced forgetting: evidence for a recall-specific mechanism, in Psychonomic Bulletin & Review 7, 522-530.

Anderson M.C., Bjork R.A., Bjork E.L. (1994) Remembering can cause forgetting: retrieval dinamics in long-term memory, in Journal of experimental psychology, learning, memory and cognition, 20(5), 1063-1087.

Anderson, M. C., Bell, T. (2001). Forgetting our facts: The role of inhibitory processes in the loss of propositional knowledge. Journal of Experimental Psychology: General, 130, 544-570

Anderson, M. C., Bunce, J. G., & Barbas, H. (2016). Prefrontal-hippocampal pathways underlying inhibitory control over memory. *Neurobiology of Learning and Memory*, 134, 145–161

Anderson, M.C. & Spellman, B.A. (1995) On the status of inhibitory mechanisms in cognition: memory retrieval as a model case. Psychol. Rev. 102, 68-100

Ashburner J., & Friston K.J. (2001) Why voxel-based morphometry should be used, in Neuroimage Vol. 14, 1238-1243.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, 26, 839– 851.

Aslan, Bäuml A., Heinz K.T., (2012) Retrieval-induced forgetting in old and very old age, in Psychology and Aging 27 (4), S. 1027-1032.

Baddeley A., Logie R., Bressi S., Della Sala S., Spinnler H., Dementia and Working Memory (1986), The Quarterly Journal of Experimental Psychology Section A, Volume: 38 issue: 4, page(s): 603-618.

Bandera, L., Della Sala, S., Laiacona, M., Luzzatti, C., & Spinnler, H. (1991). Generative associative naming in dementia of Alzheimer's type. *Neuropsychologia*, 29(4), 291– 304.

Basser, P. J. & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusiontensor MRI. *J Magn Reason*, B111, 209-219.

Basser, P. J., Mattiello, J., LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. Biophys *J*, 66, 259-267.

Bélanger, S., & Belleville, S. (2009), Semantic inhibition impairment in mild cognitive impairment: A distinctive feature of upcoming cognitive decline? *Neuropsychology*, 23(5), 592–606.

Benoit, R. G., & Anderson, M. C. (2012). Opposing mechanisms support the voluntary forgetting of unwanted memories. *Neuron*, 76, 450– 460.

Benoit, R. G., Hulbert, J. C., Huddleston, E., & Anderson, M. C. (2015). Adaptive top-down suppression of hippocampal activity and the purging of intrusive memories from consciousness. *Journal of Cognitive Neuroscience*, 27, 96– 111.

Bertinetto, P. M., Burani, C., Laudanna, A., Marconi, L., Ratti, D., Rolando, C., & Thornton, A. M. (2005). CoLFIS (Corpus e Lessico di Frequenza dell'Italiano Scritto). Available on http://www. istc. cnr. it/material/database, 67-73

Bjorklund, D. F., & Harnishfeger, K. K. (1995). The evolution of inhibition mechanisms and their role in human cognition and behavior. In F. N. Dempster & C. J. Brainerd (Eds.), *Interference and inhibition in cognition* (pp. 141– 173). Academic Press.

Blennow K., Hampel H. (2003), Cerebrospinal fluid markers for incipient Alzheimer's disease. Lancet Neurology;2:605–13

Bondi W.M., Serody A.B., Chan A.S., Eberson-Shumate S.C., Delis D.C., Hansen L.A., Salmon D.P. (2002), Cognitive and neuropathologic correlates of stroop color-word test performance in Alzheimer's disease, *Neuropsychology*, 16(3), 335-343.

Boyle PA et al. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann. Neurol 83, 74–83 (2018). A clinical-neuropathological analysis of >1,000 persons demonstrating how multiple aetiologies relate to late-life cognition.

Bozzali, M., Falini, A., Franceschi, M., et al. (2002). White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. *J Neurol Neurosurg Psychiatry*, 72, 742–746.

Bozzali, M., Serra, L. & Cercignani, M. (2016). Quantitative MRI to understand Alzheimer's disease pathophysiology. *Current Opinion Neurology,* 29, 437–444.

Brandt, J., Aretouli E., Neijstrom E., Samek J., Manning K., Albert M. S., & Bandeen- Roche K. (2009). Selectivity of executive function deficits in mild cognitive impairment. *Neuropsychology*, 23(5), 607–618.

Burgess P. W, Shallice T. Confabulation and the control of recollection. *Memory*. 1996 Jul;4(4):359-411.

Burgess, P. W., & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia*, 34(4), 263– 272.

Büsch, D., Hagemann, N., & Bender, N. (2010). The dimensionality of the Edinburgh handedness inventory: An analysis with models of the item response theory. *Laterality*, 15, 610– 628.

Butler K. M., Williams C. C., Zacks R. T., & Maki R. H. (2001). A limit on retrieval-induced forgetting. Journal of Experimental Psychology: Learning, Memory, and Cognition, 27(5), 1314–1319.

Camp G., Pecher D., Schmidt H. G. (2007) No Retrieval-Induced Forgetting Using Item-Specific Independent Cues: Evidence Against a General Inhibitory Account. J Exp Psychol Learn Mem Cogn. 2007 Sep; 33 (5):950-8. doi: 10.1037/0278-7393.33.5.950.

Cantagallo A., Spintoni G. e Antonucci G., "Le funzioni esecutive. Valutazione e riabilitazione" (2010).

Canu E, McLaren DG, Fitzgerald ME, Bendlin BB, Zoccatelli G, Alessandrini F, Pizzini FB, Ricciardi GK, Beltramello A, Johnson SC, Frisoni GB. Mapping the structural brain changes in Alzheimer's disease: the independent contribution of two imaging modalities. J Alzheimers Dis. 2011;26 Suppl 3(Suppl 3):263-74. doi: 10.3233/JAD-2011-0040. PMID: 21971466; PMCID: PMC3267543.

Carlesimo, G. A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lo Russo, S., Bevilacqua, G., & Caltagirone, C. (2002). Standardizzazione di due test di memoria per uso clinico: Breve Racconto e Figura di Rey. *Nuova Rivista di Neurologia*, 12, 1– 13.

Carlesimo, G. A., Caltagirone, C., & Gainotti, G. (1996). The mental deterioration battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the mental deterioration battery. *European Neurology*, 36, 378– 384.

Carlson M.C., Hasher L., Zacks R.T., Connelly S.L., (1995) Aging, distraction, and the benefits of predictable location. Psychology Aging.; 10(3):427-36.

Caselli RJ, Chen K, Locke DEC, et al. Subjective cognitive decline: self and informant comparisons. Alzheimers Dement 2014; 10: 93–98.

Chan J.C.K., McDermott K. B., & Roediger H. L. (2006). Retrieval-induced facilitation: initially nontested material can benefit from prior testing of related material. *Journal of Experimental Psychology General*, 135, 553–571.

Chètelat, G., Landeau, B., Eustache, F., Mézenge, F., Viader, F., Sayette, V. et al. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *NeuroImage*, 27, 934-946.

Cid, R. E. C., Crocco, E. A., Duara, R., Garcia, J. M., Rosselli, M., DeKosky, S. T., Smith, G., Bauer, R., Chirinos, C. L., Adjouadi, M., Barker, W., & Loewenstein, D. A. (2020). A novel method of evaluating semantic intrusion errors to distinguish between amyloid positive and negative groups on the Alzheimer's disease continuum. *Journal of Psychiatric Research*, 124, 131– 136.

Ciranni, M. A., & Shimamura, A. P. (1999). Retrieval-induced forgetting in episodic memory. Journal of Experimental Psychology: Learning, Memory, and Cognition, 25(6), 1403–1414

Collette F., Schmidt C., Scherrer C., Adam S., Salmon E., (2009). Specificity of inhibitory deficits in normal aging and Alzheimer’s disease. Neurobiology Aging.;30:875–889.

Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and biobehavioral reviews*, 26(2), 105– 125.

Collette, F., Van der Linden, M., & Salmon, E. (1999). Executive dysfunction in Alzheimer's disease. *Cortex*, 35(1), 57– 72.

Conway, M. A., & Fthenaki, A. (2003). Disruption of inhibitory control of memory following lesions to the frontal and temporal lobes. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior*, 39(4–5), 667– 686.

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*, 317, 215– 219.

Dhanjal N.S., Wise R.J., Frontoparietal cognitive control of verbal memory recall in Alzheimer's disease. Ann Neurol. 2014; 76(2):241-51.

Di Carlo A.; Lamassa M.; Baldereschi M.; Inzitari M.; Scafato E.; Farchi G.; Inzitari D., (2007) CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology; 68(22):1909-16

Diamond A. (2013). Executive functions. Annual review of psychology, 64, 135–168.

El Haj M., Antoine P., Kapogiannis D., (2015). Similarity between remembering the past and imagining the future in Alzheimer's disease: implication of episodic memory. Neuropsychologia; 66:119–125.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & psychophysics*, *16*(1), 143-149.

Estévez-González A., García-Sánchez C., Boltes A., Otermín P., Pascual-Sedano B., Gironell A., Kulisevsky J., (2004) Semantic knowledge of famous people in mild cognitive impairment and progression to Alzheimer's disease. Dementia and Geriatric Cognitive Disorders; 17(3): 188-195.

Falini, A., Bozzali, M., Magnani, G., Pero, G., Gambini, A., Benedetti, B., Mossini, R., Franceschi, M., Comi, G., Scotti, G., & Filippi, M. (2005). A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment. *NeuroImage*, 26, 1159– 1163.

Faust, M. E., & Balota, D. A. (1997). Inhibition of return and visuospatial attention in healthy older adults and individuals with dementia of the Alzheimer type. *Neuropsychology*, 11(1), 13– 29.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov; 12(3): 189-98. doi: 10.1016/0022-3956(75)90026-6. PMID: 1202204.

Fuster, J. M. (1993). Frontal lobes. *Current Opinion in Neurobiology*, 3(2), 160– 165.

Ganguli M., Dodge H.H., Shen C., DeKosky S.T. (2004) Mild cognitive impairment, amnestic type: an epidemiologic study. Neurology; 63:115–121.

Ganguli, M., Chang, C. C., Snitz, B. E., Saxton, J. A., Vanderbilt, J., & Lee, C. W. (2010).

Geib, B. R., Stanley, M. L., Dennis, N. A., Woldorff, M. G., & Cabeza, R. (2017). From hippocampus to whole-brain: The role of integrative processing in episodic memory retrieval. *Human Brain Mapping*, 38, 2242– 2259.

Giulietti, G., Bozzali, M., Figura, V., Spanò, B., Perri, R., Marra, C., Lacidogna, G., Giubilei, F., Caltagirone, C., & Cercignani, M. (2012). Quantitative magnetization transfer provides information complementary to grey matter atrophy in Alzheimer's disease brains. *NeuroImage*, 59, 1114– 1122.

Gòmez-Ariza C.J., Pelegrina S., Lechuga M.T., Suàrez A., Bajo M.T. (2009) Inhibition and retrieval of facts in young and older adults, Experimental aging research; 35(1):83-97.

Guez J. & Naveh-Benjamin M., (2015) Proactive interference and concurrent inhibitory processes do not differentially affect item and associative recognition: Implication for the age-related associative memory deficit, *Memory*, 24:8, 1091-1107.

Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., Ross Russell, R. W., & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology*, 32, 632– 637.

Haj M.E., Postal V., Gall D.L., Allain P., (2011). Directed forgetting of autobiographical memory in mild Alzheimer's disease. Memory; 19(8):993-1003.

Hanyu, H., Sakurai, H., Iwamoto, T., et al. (1998). Diffusion-weighted MR imaging of the hippocampus and temporal white matter in Alzheimer's disease. *J Neurol Sci*, 156, 195–200.

Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med 2013; 29: 737–52.

Hasher L., & Zacks R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Bower (Ed.), The psychology of learning and motivation. Vol. 22 (pp. 193-225).

Hicks, J. L., Starns, J. J. (2004). Retrieval-induced forgetting occurs in tests of item recognition. Psychonomic Bulletin and Review, 11, 125-130.

Hogge M., Adam S., Collette F. (2008) Retrieval-induced forgetting in normal aging, Journal of neuropsychology 2 (pt 2): 463-76.

Hogge, M., Adam, S., & Collette, F. (2008b). Directed forgetting and aging: The role of retrieval processes, processing speed, and proactive interference. *Aging Neuropsychology and Cognition*, 15, 471– 491.

Hoogendam YY, Hofman A, Van Der Geest JN, Van Der Lugt A, Ikram MA. Patterns of cognitive function in aging: the Rotterdam study. Eur J Epidemiol 2014; 29: 133–40.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry*, 40, 566– 572.

Jahn H. (2013). Memory loss in Alzheimer's disease. *Dialogues in clinical neuroscience*, *15*(4), 445–454.

Jessen F, Spottke A, Boecker H, et al. Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). Alzheimers Res Ther 2018; 10: 15.

Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry 2010; 67: 414–22.

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., & Wagner, M. (2020). The characterisation of subjective cognitive decline. The Lancet Neurology, 19(3), 271-278

Karas, G., Scheltens, P., Rombouts, S., Visser, P., van Schijndel, R., Fox, N., & Barkhof, F. (2004). Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage*, 708-716.

Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, Nixon RA, Jones DT. Alzheimer disease. Nat Rev Dis Primers. 2021 May 13;7(1):33. doi: 10.1038/s41572-021-00269-y. PMID: 33986301; PMCID: PMC8574196.

Koivisto K., Reinikainen K.J., Hanninen T. et al., (1995). Prevalence of age-associated Memory impairment in a randomly selected population from eastern Finland. Neurology; 45:741–747.

Koutstaal W., Schacter D. L., Johnson M. K., & Galluccio L. (1999). Facilitation and impairment of event memory produced by photograph review. Memory & Cognition, 27(3), 478–493.

Kramer, A. F., Humphrey, D. G., Larish, J. F., & Logan, G. D. (1994). Aging and inhibition: Beyond a unitary view of inhibitory processing in attention. *Psychology and Aging*, 9(4), 491– 512.

Kuhl, B. A., Dudukovic, N. M., Kahn, I., & Wagner, A. D. (2007). Decreased demands on cognitive control reveal the neural processing benefits of forgetting. *Nature Neuroscience*, 10, 908– 914.

La Joie R, Perrotin A, Egret S, et al. Qualitative and quantitative assessment of self-reported cognitive difficulties in nondemented elders: association with medical help seeking, cognitive deficits, and β-amyloid imaging. Alzheimers Dement (Amst) 2016; 5: 23–34.

Larrieu S., Letenneur L., Orgogozo J.M., Fabrigoule C., Amieva H., Le Carret N., Barberger–Gateau P., Dartigues J.F. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology Nov 2002, 59 (10) 1594-1599.

Le Moal, S., Reymann, J. M., Thomas, V., Cattenoz, C., Lieury, A., & Allain, H. (1997). Effect of normal aging and of Alzheimer's disease on episodic memory. *Dementia and Geriatric Cognitive Disorders*, 8(5), 281– 287.

Levy B. J., & Anderson M. C., (2002) Inhibitory processes and the control of memory retrieval. Cognitive Sciences Vol.6 No.7 July 2002

Lezak M, Howieson D, Bigler E, Tranel D. Neuropsychological Assessment. 5. New York: Oxford University Press; 2012.

Loewenstein, D. A., Curiel, R. E., DeKosky, S., Bauer, R. M., Rosselli, M., Guinjoan, S. M., Adjouadi, M., Peñate, A., Barker, W. W., Goenaga, S., Golde, T., Greig-Custo, M. T., Hanson, K. S., Li, C., Lizarraga, G., Marsiske, M., & Duara, R. (2018). Utilizing semantic intrusions to identify amyloid positivity in mild cognitive impairment. *Neurology*, 91(10), e976– e984.

Lombardi MG, Fadda L, Serra L, Di Paola M, Caltagirone C, Carlesimo G.A. Recollection and familiarity components of recognition: effect of side of mesio-temporal damage. *Neurocase* 2016; 22(1):1-11.

Macrae, C. N., Macleod, M. D. (1999). On recollections lost: When practice makes imperfect. Journal of Personality and Social Psychology, 77, 463-473.

Manenti R., Cotelli M., Robertson I.H., Miniussi C., (2012). Transcranial brain simulation studies of episodic memory in young adults, elderly adults and individuals with memory dysfunction: a review. Brain stimulation journal 103-109. MEd.; 256 (3): 183-94.

Mathuranath, P.S., Nestor P.J., Berrios G.E., et al. 2000 A briefcognitive test battery to differentiate Alzheimer’s disease and frontotemporal dementia. Neurology 55(11): 1613-1620.

Matsuo, K., Mizuno, T., Yamada, K., Akazawa, K., Kasai, T., Kondo, M. et al. (2008). Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. *Neuroradiology*, 50, 605-611.

Maxcey A. M. & Woodman G. F. (2014) Forgetting induced by recognition of visual images. Vis cogn. Jul; 22(6): 789–808.doi: 10.1080/13506285.2014.917134

McDonough, I. M., Festini, S. B., & Wood, M. M. (2020). Risk for Alzheimer's disease: A review of long-term episodic memory encoding and retrieval fMRI studies. *Ageing Research Reviews*, 62, 101133.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr, Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association, 7(3), 263–269.

Measso, G., Cavarzeran, F., Zappalà, G., & Grigoletto, F. (1993). The mini-mental state examination: Normative study of an Italian random sample. *Developmental Neuropsychology*, 9, 77– 85.

Miceli, G., Laudanna, A., Burani, C., & Capasso, R. (1991). *Batteria per l'analisi dei deficit afasici. Ass.ne per lo sviluppo delle ricerche neuropsicologiche*. Berdata.

Miebach L, Wolfsgruber S, Polcher A, et al. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res Ther 2019; 11: 66.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's cognitive examination revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21, 1078– 1085.

Mitchell A, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. Acta Psychiatr Scand 2014; 130: 439–51.

Miyake A., Friedman N. P., Emerson M. J., Witzki A. H., Howerter A., Wager T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cogn. Psychol.* 41 49–100.

Monaco, M., Costa, A., Caltagirone, C., & Carlesimo, G. A. (2013). Forward and backward span for verbal and visuo-spatial data: Standardization and normative data from an Italian adult population. *Neurological Sciences*, 34, 749– 754.

Moulin, C. J., Perfect, T. J., Conway, M. A., North, A. S., Jones, R. W., & James, N. (2002). Retrieval-induced forgetting in Alzheimer's disease. *Neuropsychologia*, 40, 862– 867.

Mufson E. J., Binder L., Counts S. E., DeKosky S. T., de Toledo-Morrell L., Ginsberg, S. D., Scheff, S. W. (2012). Mild cognitive impairment: pathology and mechanisms. Acta neuropathologica, 123(1), 13–30.

Murphy KJ, Troyer AK, Levine B, Moscovitch M. Episodic, but not semantic, autobiographical memory is reduced in amnestic mild cognitive impairment.

Neuropsychologia. 2008 Nov; 46(13): 3116-23. doi: 10.1016/j.neuropsychologia.2008.07.004. Epub 2008 Jul 12. PMID: 18675285; PMCID: PMC2629588.

Nelson D. L., Reed V., & Walling. J. R. (1976) The pictorial superiority effect. Journal of Experimental Psychology: Human Learning and Memory. 1976. 2. 523·528.

Nelson PT et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol*. 121, 571–587 (2011).

Nestor, P. G., Piech, R., Allen, C., Niznikiewicz, M., Shenton, M., & McCarley, R. W. (2005). Retrieval-induced forgetting in schizophrenia. *Schizophrenia Research*, 75(2–3), 199– 209.

Nicholas CR, Dowling NM, Racine AM, et al. Longitudinal assessment of self- and informant-subjective cognitive complaints in a sample of healthy late-middle aged adults enriched with a family history of Alzheimer's disease. J Int Neuropsychol Soc 2017; 23: 617–26.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin*, 126(2), 220– 246.

Niu H, Álvarez-Álvarez I, Guillén-Grima F & Aguinaga-Ontoso I Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. *Neurologia* 32, 523–532 (2017)

Nocentini, U., Di Vincenzo, S., Panella, M., Pasqualetti, P., & Caltagirone, C. (2002). La valutazione delle funzioni esecutive nella pratica neuropsicologica: dal Modified Card Sorting Test al Modified Card Sorting Test-Roma Version. Dati di standardizzazione. *Nuova Rivista di Neurologia*, 12, 14– 24.

Ortega A., Gòmez-Ariza C.J., Romàn P., Bajo M.T., (2012). Memory inhibition, aging, and the executive deficits hypothesis, Journal of experimental psychology. *Learning, memory, cognition*, 38(1): 178-186.

Paivio A. (1969) Mental imagery in associative learning and memory. *Psychological Review*. 76. 241·263.

Paivio A. (1971) Imagery in recall and recognition. In J. Brown (Ed.). Recall and recognition. New York: Wiley

Penolazzi B., Stramaccia D. F., Braga M., Mondini S., Galfano G. (2014) Human memory retrieval and inhibitory control in the brain: beyond correlational evidence, *Journal of Neuroscience*, 34, 6606-6610.

Perri R., Carlesimo G.A., Serra L., Caltagirone C., and the early diagnosis group of the italian interdisciplinary network on Alzheimer's disease, (2005). Characterization of memory profile

in subjects with amnestic mild congnitive impairment. Journal of Clinical and Experimental Neuropsychology, 27, 1033-1055.

Petersen R.C., Mild Cognitive Impairment, Continuum (Minneap Minn), 2016, 22 (2 Dementia): 404-18.

Petersen R.C., Roberts R.O., Knopman D.S., Geda Y.E., Cha R.H., Pankratz V.S., Boeve B.F., Tangalos E.G., Ivnik R.J., Rocca W.A. (2010) Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging, Neurology; 75 (10): 889-97.

Petersen RC Mild cognitive impairment as a diagnostic entity. *J. Intern. Med* 256, 183–194 (2004)

Pigliautile, M., Ricci, M., Mioshi, E., Ercolani, S., Mangialsche, F., Monastero, R., Croce, M. F., Federici, S., & Mecocci, P. (2011). Validation study of the Italian Addenbroke's cognitive examination revised in a young-old and old-old population. *Dementia and Geriatric Cognitive Disorders*, 32, 301– 307.

Prince M et al. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res. Ther* 8, 23 (2016)

Racsmány M, Conway MA. Episodic inhibition. *J Exp Psychol Learn Mem Cogn*. 2006 Jan;32(1):44-57.

Radvansky G. A., Zacks R. T., & Hasher L. (1996). Fact retrieval in younger and older adults: The role of mental models. *Psychology and Aging*, 11, 258-271.

Rami L, Mollica MA, García-Sanchez C, et al. The subjective cognitive decline questionnaire (SCD-Q): a validation study. J Alzheimers Dis 2014; 41: 453–66.

Rattanabannakit C, Risacher S.L, Gao S, et al. The cognitive change index as a measure of self and informant perception of cognitive decline: relation to neuropsychological tests. J Alzheimers Dis 2016; 51: 1145–55.

Renoult, L., Irish, M., Moscovitch, M., & Rugg, M. D. (2019). From knowing to remembering: The semantic-episodic distinction. *Trends in Cognitive Sciences*, 23, 1041– 1057.

Roberts R. & Knopman D.S. (2013) Classification and epidemiology of MCI, Clin Geriatric Med., 753-72.

Roberts R.O., Geda Y.E., Knopman D.S., Cha R.H., Pankratz V.S., Boeve B.F., Tangalos E.G., Ivnik R.J., Rocca W.A., Petersen R.C., The incidence of MCI differs by subtype and is higher in men Neurology Jan 2012, 78 (5) 342-351.

Roediger, H. L., & Schmidt, S. R. (1980). Output interference in the recall of categorized and paired-associate lists. Journal of Experimental Psychology: Human Learning and Memory, 6(1), 91–105.

Roehr S, Villringer A, Angermeyer MC, Luck T, Riedel-Heller SG. Outcomes of stable and unstable patterns of subjective cognitive decline - results from the Leipzig longitudinal study of the aged (LEILA75+). BMC Geriatr 2016; 16: 180.

Rose, S. E., Janke, A. L., Chalk, J. B. (2008). Gray and white matter changes in Alzheimer's disease: a diffusion tensor imaging study. *J Magn Reson Imaging*, 27, 20-26.

Sanford A.M. (2017), in Mild Cognitive Impairment, Clinical Geriatric Med. 2017; 33(3):

Saunders J. & Mcleod M.D., (2006), Can inhibition resolve retrieval competition through the control of spreading activation, in Memory and cognition 34, 307-322.

Saunders N.L. e Summer M.J., (2010). Attention and working memory deficits in Mild Cognitive Impairment, J. Clin. Exp. Neuropsychological, 32 (4), 350-7.

Scheltens, P., Launer, L. J., Barkhof, F., Weinstein, H. C., & van Gool, W. A. (1995). Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: Interobserver reliability. *Journal of Neurology*, 242, 557– 560.

Schneider JA, Arvanitakis Z, Leurgans SE & Bennett DA The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann. Neurol* 66, 200–208 (2009).

Selkoe D., (2005). Defining molecular targets to prevent Alzheimer's disease. Arch Neurol.; 62:192–5.

Serra L, Bechi Gabrielli G, Tuzzi E, Spanò B, Giulietti G, Failoni V, Marra C, Caltagirone C, Koch G, Cercignani M, Bozzali M. (2017) Damage to the Frontal Aslant Tract Accounts for Visuo Constructive Deficits in Alzheimer's Disease. *J Alzheimers Dis*. 2017; 60(3):1015-1024. doi: 10.3233/JAD-170638. PMID: 28984608.

Serra L, Bozzali M, Cercignani M, Perri R, Fadda L, Caltagirone C, Carlesimo G.A. Recollection and familiarity in amnesic mild cognitive impairment. *Neuropsychology* (2010) May;24(3):316-26.

Serra L., Bechi Gabrielli G., Di Domenico C., Del Bono C., Marra C., Lopiano L., Caltagirone C., Bozzali M. (2022) "Are the inhibitory and faciliatory effects during retrieval of semantically related items present in amnestic mild cognitive impairment?" *J Neuropsychol*. 2022 Aug 15. doi: 10.1111/jnp.12286.

Serra, L., Cercignani, M., Lenzi, D., Perri, R., Fadda, L., Caltagirone, C., Macaluso, E., & Bozzali, M. (2010). Grey and white matter changes at different stages of Alzheimer's disease. *Journal of Alzheimer's Disease*, 19, 147– 159.

Serra, L., Cercignani, M., Petrosini, L., Basile, B., Perri, R., Fadda, L., Spanò, B., Marra, C., Giubilei, F., Carlesimo, G. A., Caltagirone, C., & Bozzali, M. (2011). Neuroanatomical correlates of cognitive reserve in Alzheimer disease. *Rejuvenation Research*, 14, 143– 151.

Serra, L., Giulietti, G., Cercignani, M., Spanò, B., Torso, M., Castelli, D. & al. (2013). Mild Cognitive Impairment: Same Identity for Different Entities. *Journal of Alzheimer's Disease*, 33, 1157-1165.

Serra, L., Petrosini, L., Salaris, A., Pica, L., Bruschini, M., Di Domenico, C., Caltagirone, C., Marra, C., & Bozzali, M. (2019). Testing for the myth of cognitive reserve: Are the static and dynamic cognitive reserve indexes a representation of different reserve warehouses? *Journal of Alzheimer's Disease*, 72, 111– 126.

Slot R., Sikkes S., Berkhof J, et al. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. Alzheimers Dement 2019; 15: 456–76.

Snitz BE, Wang T, Cloonan YK, et al. Risk of progression from subjective cognitive decline to mild cognitive impairment: the role of study setting. Alzheimers Dement 2018; 14: 734–42.

Tempel, T., Ludwig, M., & Stolte, J. (2021). Disrupted memory inhibition in dementia of Alzheimer's type. *Journal of Neuropsychology*, 15(2), 151– 161.

Tomaszewski Farias S, Mungas D, Harvey DJ, Simmons A, Reed BR, Decarli C. The measurement of everyday cognition: development and validation of a short form of the everyday cognition scales. Alzheimers Dement 2011; 7: 593–601.

Turriziani P, Serra L, Fadda L, Caltagirone C, Carlesimo G. A. Recollection and familiarity in hippocampal amnesia. *Hippocampus*. 2008;18(5):469-80.

Tversky, B. (1973) Coding processes in recognition and recall. *Cognitive psychology*, 5 (3), 275-287.

Valech N, Mollica MA, Olives J, et al. Informants' perception of subjective cognitive decline helps to discriminate preclinical Alzheimer's disease from normal aging. J Alzheimers Dis 2015; 48 (suppl 1): S87–98.

Valech N, Tort-Merino A, Coll-Padrós N, et al. Executive and language subjective cognitive decline complaints discriminate preclinical Alzheimer's disease from normal aging. J Alzheimers Dis 2018; 61: 689–703.

van Harten A.C, Mielke M.M, Swenson-Dravis DM, et al. Subjective cognitive decline and risk of MCI. Neurology 2018; 91: e300–12

Verfaillie SCJ, Timmers T, Slot RER, et al. Amyloid-β load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline: the SCIENCe project. Front Aging Neurosci 2019; 11: 7.

Verlinden VJA, Van Der Geest JN, De Bruijn RFAG, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of decline in cognition and daily functioning in preclinical dementia. Alzheimers Dement 2016; 12: 144–53.

Verma M., Howard RJ. Semantic memory and language dysfunction in early Alzheimer's disease: a review. *Int J Geriatr Psychiatry.* 2012; 27:1209–1217.

Whitwell, J. L., Shiung, M. M., Przybelski, S. A., Weigand, S. D., Knopman, D. S., Boeve, B. F. et al. (2008). MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. *Neurology,* 70 (7), 512-520.

Wimber, M., Bäuml, K. H., Bergström, Z., Markopoulos, G., Heinze, H. J., & Richardson-Klavehn, A. (2008). Neural markers of inhibition in human memory retrieval. *Journal of Neuroscience*, 28, 13419– 13427.

Wimber, M., Rutschmann, R. M., Greenlee, M. W., & Bäuml, K. H. (2009). Retrieval from episodic memory: Neural mechanisms of interference resolution. *Journal of Cognitive Neuroscience*, 21(3), 538– 549.

Wolfsgruber S, Kleineidam L, Wagner M, et al. Differential risk of incident Alzheimer's disease dementia in stable versus unstable patterns of subjective cognitive decline. *J Alzheimers Dis* 2016;54: 1135–46.

Wylie, S. A., Ridderinkhof, K. R., Eckerle, M. K., & Manning, C. A. (2007). Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia*, 45(7), 1408–1419.

Yonelinas A.P, Otten L.J, Shaw K.N, Rugg M.D. Separating the brain regions involved in recollection and familiarity in recognition memory. *J Neurosci.* 2005 Mar 16;25(11):3002-8.

Other publications

Neurobiology of Aging 94 (2020) 196–206

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Behavioral psychological symptoms of dementia and functional connectivity changes: a network-based study

Laura Serra[a,*], Michela Bruschini[a], Carlotta Di Domenico[a], Matteo Mancini[b], Giulia Bechi Gabrielli[a], Sabrina Bonarota[a], Carlo Caltagirone[c], Mara Cercignani[a,b], Camillo Marra[d], Marco Bozzali[b,e]

[a] Neuroimaging Laboratory, Fondazione Santa Lucia IRCCS, Rome, Italy
[b] Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brithon, UK
[c] Department of Clinical and Behavioural Neurology, Fondazione Santa Lucia IRCCS, Rome, Italy
[d] Institute of Neurology, Catholic University, Rome, Italy
[e] Department of Neuroscience "Rita Levi Montalcini", University of Torino, Turin, Italy

ARTICLE INFO

Article history:
Received 7 November 2019
Received in revised form 8 June 2020
Accepted 10 June 2020
Available online 16 June 2020

Keywords:
BPSD
AD
a-MCI
Brain functional connectivity
MRI

ABSTRACT

Behavioral and psychological symptoms of dementia (BPSD) are commonly observed since the early stage of Alzheimer's disease (AD) associated with structural brain changes. It is conceivable that they may also relate to functional brain changes. This resting-state functional MRI (RS-fMRI) study investigated the alterations within functional brain networks of a cohort of AD patients at different clinical stages who presented with BPSD. One hundred one AD patients and 56 patients with amnestic mild cognitive impairment underwent a neuropsychological evaluation including the Neuropsychiatry Inventory-12 (NPI-12). All patients and 35 healthy controls (HS) underwent 3T-MRI. Factor analysis was used to extract the principal factors from NPI-12, while RS-fMRI data were processed using graph theory to investigate functional connectivity. Five factors were extracted from NPI-12. Sixty-two percent of patients showed BPSD and functional brain connectivity changes in various networks compared to those without BPSD and HS. These changes contributed to account for patients' BPSD. This work opens new perspectives in terms of nonpharmacological interventions that might be designed to modulate brain connectivity and improve patients' BPSD.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder typically characterized by behavioral symptoms in addition to a progressive cognitive decline (Bessey and Walaszek, 2019; Chakraborty et al., 2019). Behavioral disorders and psychological symptoms (behavioral and psychological symptoms in dementia [BPSD]) (Tascone and Bottino, 2013), which are particularly distressing for patients' family members, are frequently observed in AD as well as in patients with amnestic cognitive impairment (a-MCI) (Köhler et al., 2016). BPSD may strongly contribute to patients' disability and typically result in an increased need of caregiving (Feast et al., 2016).

Observational studies report an estimated prevalence of BPSD in AD patients that ranges from 25% to 80% (Mega et al., 1996). The most frequently observed BPSD include agitation (Mega et al., 1996), apathy (Boccardi et al., 2017; Marin et al., 1993; Starkstein et al., 2006), depression (Boccardi et al., 2017; Burns et al., 1990a; Frisoni et al., 1999), anxiety (Boccardi et al., 2017), and delusions (Boccardi et al., 2017; Burns et al., 1990b), while disinhibition (Teri et al., 1992), hallucinations (Burns et al., 1990b; Hirono et al., 1998), aggression (Gilley et al., 1997), wandering, and disturbances in eating behavior (Burns et al., 1990c) are less frequent (Assal and Cummings, 2002; Ropacki and Jeste, 2005). When considering the clinical evolution of AD, depression, apathy, and irritability are commonly observed since the early stages of the disease (Craig et al., 2005). Conversely, psychotic symptoms and wandering are more typical of patients at a more advanced AD stage (Piccininni et al., 2005).

Specific gray (GM) and white matter (WM) abnormalities have been shown to account for the presence and severity of BPSD in patients with AD (Makovac et al., 2016). Consistent with the progression of symptoms, regional GM atrophy also spreads when moving from early (i.e., mild cognitive impairment) to more

* Corresponding author at: Neuroimaging Laboratory, Via Ardeatina 306, 00179 Rome, Italy. Tel.: 39-06-5150 1493; fax: 39-06-5150 1213.
E-mail address: l.serra@hsantalucia.it (L. Serra).

0197-4580/$ – see front matter © 2020 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2020.06.009

AIMS Neuroscience, 8(4): 496–509.
DOI: 10.3934/Neuroscience.2021026
Received: 12 May 2021
Accepted: 31 August 2021
Published: 02 September 2021

http://www.aimspress.com/journal/neuroscience

Research article

The beneficial effects of physical exercise on visuospatial working memory in preadolescent children

Laura Serra[1,*], Sara Raimondi[1], Carlotta di Domenico[1], Silvia Maffei[1], Anna Lardone[2], Marianna Liparoti[2], Pierpaolo Sorrentino[3], Carlo Caltagirone[4], Laura Petrosini[5] and Laura Mandolesi[6]

[1] Neuroimaging Laboratory, Fondazione Santa Lucia, IRCCS, Rome, Italy
[2] Department of Motor Sciences and Wellness, University "Parthenope", Naples, Italy
[3] Institute de Neurosciences Des Systèmes, Aix-Marseille University, Marseille, France Department of Engineering, University "Parthenope", Naples, Italy
[4] Department of Clinical and Behavioural Neurology, Fondazione Santa Lucia, IRCCS, Rome, Italy.
[5] Laboratory of Experimental and Behavioural Neurophysiology, Fondazione Santa Lucia, IRCCS, Rome, Italy
[6] Department of Humanities, University of Naples Federico II, Naples, Italy

* **Correspondence:** Email: l.serra@hsantalucia.it; Tel: +390651501493.

Abstract: The relationship between physical exercise and improvement in specific cognitive domains in children and adolescents who play sport has been recently reported, although the effects on visuospatial abilities have not yet been well explored. This study is aimed at evaluating in school-age children practicing artistic gymnastics the visuospatial memory by using a table version of the Radial Arm Maze (table-RAM) and comparing their performances with those ones who do not play any sport. The visuospatial performances of 14 preadolescent girls practicing artistic gymnastics aged between 7 and 10 years and those of 14 preadolescent girls not playing any sport were evaluated in the table-RAM forced-choice paradigm that allows disentangling short-term memory from working memory abilities. Data showed that the gymnasts obtained better performances than control group mainly in the parameters evaluating working memory abilities, such as within-phase errors and spatial span. Our findings emphasizing the role of physical activity on cognitive performances impel to promote physical exercise in educational and recreational contexts as well as to analyse the impact of other sports besides gymnastics on cognitive functioning.

Ventral Tegmental Area Disconnection Contributes Two Years Early to Correctly Classify Patients Converted to Alzheimer's Disease: Implications for Treatment

Article type: Research Article

Authors: Serra, Laura[a,*] | D'Amelio, Marcello[b,c] | Esposito, Sharon[a] | Di Domenico, Carlotta[a] | Koch, Giacomo[d,e] | Marra, Camillo[f] | Mercuri, Nicola Biagio[g,h] | Caltagirone, Carlo[i] | Artusi, Carlo Alberto[j] | Lopiano, Leonardo[j] | Cercignani, Mara[a,k] | Bozzali, Marco[j,l]

Affiliations: [a] Neuroimaging Laboratory, Fondazione Santa Lucia, IRCCS, Rome, Italy | [b] Laboratory Molecular Neurosciences, Fondazione Santa Lucia, IRCCS, Rome, Italy | [c] Unit of Molecular Neurosciences, Department of Medicine, University Campus-Biomedico, Rome, Italy | [d] Non Invasive Brain Stimulation Unit/Department of Behavioral and Clinical Neurology, Fondazione Santa Lucia, IRCCS, Rome, Italy | [e] Section of Human Physiology, University of Ferrara, Ferrara, Italy | [f] Institute of Neurology, Catholic University, Rome, Italy | [g] Laboratory of Experimental Neurology, Fondazione Santa Lucia, IRCCS, Rome, Italy | [h] Department of Systems Medicine, University of Rome 'Tor Vergata', Rome, Italy | [i] Department of Clinical and Behavioural Neurology, Fondazione Santa Lucia, IRCCS, Rome, Italy | [j] 'Rita Levi Montalcini' Department of Neuroscience University of Torino, Turin, Italy | [k] Cardiff University Brain Imaging Centre, School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom | [l] Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brighton, East Sussex, United Kingdom

Correspondence: [*] Correspondence to: Laura Serra, PhD, Via Ardeatina 306, 00179 Rome, Italy. Tel.: +39 06 5150 1493; Fax: +39 06 5150 1213; E-mail: l.serra@hsantalucia.it.

Abstract: Background:Recent cross-sectional studies highlighted the loss of dopaminergic neurons in the ventral tegmental area (VTA) as an early pathophysiological event in Alzheimer's disease (AD). Objective:In this study, we longitudinally investigated by resting-state fMRI (rs-fMRI) a cohort of patients with mild cognitive impairment (MCI) due to AD to evaluate the impact of VTA disconnection in predicting the conversion to AD. Methods:A cohort of 35 patients with MCI due to AD were recruited and followed-up for 24 months. They underwent cognitive evaluation and rs-fMRI to assess VTA connectivity at baseline and at follow-up. Results:At 24-month follow-up, 16 out of 35 patients converted to AD. Although converters and non-converters to AD did not differ in demographic and behavioral characteristics at baseline, the first group showed a significant reduction of VTA-driven connectivity in the posterior cingulate and precentral cortex. This pattern of additional disconnection in MCI-Converters compared to non-converters remained substantially unchanged at 24-month follow-up. Conclusion:This study reinforces the hypothesis of an early contribution of dopaminergic dysfunction to AD evolution by targeting the default-mode network. These results have potential implications for AD staging and prognosis and support new opportunities for therapeutic interventions to slow down disease progression.

Keywords: Alzheimer's disease, amnestic mild cognitive impairment, dopaminergic system, functional connectivity, restingstate MRI, ventral tegmental area

DOI: 10.3233/JAD-210171

Journal: Journal of Alzheimer's Disease, vol. 82, no. 3, pp. 985-1000, 2021

Accepted 10 May 2021 | **Published:** 03 August 2021

Cognitive Reserve Modulates Brain Structure and Cortical Architecture in the Alzheimer's Disease

Article type: Research Article

Authors: Serra, Laura[a,*] | Giancaterino, Giulia[a] | Giulietti, Giovanni[a] | Petrosini, Laura[b] | Di Domenico, Carlotta[a] | Marra, Camillo[c] | Caltagirone, Carlo[d] | Bassi, Andrea[d] | Cercignani, Mara[e] | Bozzali, Marco[f,g]

Affiliations: [a] Neuroimaging Laboratory, Fondazione Santa Lucia, IRCCS, Rome, Italy | [b] Laboratory of Experimental and Behavioural Neurophysiology, Fondazione Santa Lucia, IRCCS, Rome, Italy | [c] Institute of Neurology, Catholic University, Rome, Italy | [d] Department of Clinical and Behavioural Neurology, Fondazione Santa Lucia, IRCCS, Rome, Italy | [e] Cardiff University Brain Imaging Centre, School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom | [f] Brighton & Sussex Medical School, University of Sussex – Brighton, United Kingdom | [g] Rita Levi Montalcini' Department of Neuroscience University of Torino, Turin, Italy

Correspondence: [*] Correspondence to: Dr. Laura Serra, Via Ardeatina 306, 00179 Rome, Italy. Tel.: +39 06 5150 1493; Fax: +39 06 5150 1213; E-mail:l.serra@hsantalucia.it.

Abstract: Background:Cognitive reserve (CR) explains the individual resilience to neurodegeneration. Objective:The present study investigated the effect of CR in modulating brain cortical architecture. Methods:278 individuals [110 Alzheimer's disease (AD), 104 amnestic mild cognitive impairment (aMCI) due to AD, 64 healthy subjects (HS)] underwent a neuropsychological evaluation and 3T-MRI. Cortical thickness (CTh) and fractal dimension (FD) were assessed. Years of formal education were used as an index of CR by which participants were divided into high and low CR (HCR and LCR). Within-group differences in cortical architecture were assessed as a function of CR. Associations between cognitive scores and cortical measures were also evaluated. Results:aMCI-HCR compared to aMCI-LCR patients showed significant decrease of CTh in the right temporal and in the left prefrontal lobe. Moreover, they showed increased FD in the right temporal and in the left temporo-parietal lobes. Patients with AD-HCR showed reduced CTh in several brain areas and reduced FD in the left temporal cortices when compared with AD-LCR subjects. HS-HCR showed a significant increase of CTh in prefrontal areas bilaterally, and in the right parieto-occipital cortices. Finally, aMCI-HCR showed significant positive associations between brain measures and memory and executive performance. Conclusion:CR modulates the cortical architecture at pre-dementia stage only. Indeed, only patients with aMCI showed both atrophy (likely due to neurodegeneration) alongside richer brain folding (likely due to reserve mechanisms) in temporo-parietal areas. This opposite trend was not observed in AD and HS. Our data confirm the existence of a limited time-window for CR modulation at the aMCI stage.

Keywords: Alzheimer's disease, cognitive reserve, cortical thickness, fractal dimension, mild cognitive impairment

DOI: 10.3233/JAD-220377

Journal: Journal of Alzheimer's Disease, vol. 89, no. 3, pp. 811-824, 2022

Accepted 8 July 2022 | **Published:** 27 September 2022

Received: 31 August 2021 | Accepted: 20 July 2022

DOI: 10.1111/jnp.12286

RESEARCH ARTICLE

Are the inhibitory and faciliatory effects during retrieval of semantically related items present in amnestic mild cognitive impairment?

Laura Serra[1] | Giulia Bechi Gabrielli[1] | Carlotta Di Domenico[1] | Chiara Del Bono[1] | Camillo Marra[2] | Leonardo Lopiano[3] | Carlo Caltagirone[4] | Marco Bozzali[3,5]

[1]Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy

[2]Institute of Neurology, Catholic University, Rome, Italy

[3]Department of Neuroscience 'Rita Levi Montalcini', University of Torino, Turin, Italy

[4]Laboratory of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation, Rome, Italy

[5]Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brighton, UK

Correspondence
Laura Serra, Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Via Ardeatina 306, 00179 Rome, Italy.
Email: l.serra@hsantalucia.it

Funding information
Consiglio Nazionale delle Ricerche; Ministero della Salute (Italian Ministry of Health) (Linea di Ricerca Corrente: Neuroriabilitazione Cognitiva, Motoria e Neuroimmagini)

Abstract

Prefrontal functions subserve inhibition control for retrieval of semantically related items inducing forgetting 19 a-MCI patients and 29 controls underwent neuropsychological evaluation and retrieval-practice paradigm (RPP) to estimate baseline remember (BR), retrieval-induced facilitation (FAC) and retrieval-induced forgetting (RIF). A-MCI patients underwent also 3 T-MRI to assess relationship between regional grey matter (rGM) volumes and RPP indexes Behaviourally, RIF and FAC were both observed controls, while RIF only was observed in a-MCI patients. In patients but not in controls, RIF was associated with cognitive efficiency and FAC with memory performance. Patients showed also associations between BR and rGM volumes in the precuneus, no association was found between rGM volumes and RIF and FAC. A-MCI patients did not benefit from repeated practice during retrieval of studied items, which is likely due to their memory disorder. In contrast, patient cognitive efficiency would drive retrieval suppression of interfering stimuli.

KEYWORDS

forgetting, hippocampus, mild cognitive impairment, prefrontal cortex, retrieval-practice paradigm