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Visuospatial abilities in normal and pathological aging: cognitive processes and neuroimaging correlates

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...The future belongs to those who believe

in the beauty of their dreams…

(Eleanor Roosevelt)

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GENERAL INTRODUCTION

Spatial ability is defined as the ability to generate, retain, retrieve, and transform well-structured visual images. It is not a unitary construct but several spatial abilities have been described, each emphasizing different aspects of the process of image generation, storage, retrieval, and transformation (Linn & Petersen, 1985; Voyer, Voyer & Bryden, 1995).

Spatial abilities are implied in many cognitive tasks typically performed in every-day life: spatial reasoning (Bloch, 2006), navigation (Wolbers & Hegarty, 2010), spatial language comprehension and production (Meneghetti, De Beni, Pazzaglia & Gyselick, 2011) and performance of mathematical tasks. From here starts the importance to accurately define and assess spatial abilities in contexts of every-day life.

Recent studies also suggest that spatial abilities decline with normal aging, but so far, it is not yet clear what spatial components present a normal age-related decline, which ones are preserved and when and to what point a deficit is so severe to represent an index of Mild Cognitive Impairment (MCI) or a symptom of degenerative progression as in the early-stage of Alzheimer's disease (AD) or in Dementia with Lewy Body (DLB) (Iachini, Iavarone, Senese, Ruotolo & Ruggiero, 2009).

Definition and assessment of spatial ability

A number of difficulties in the study of spatial ability derives mainly from two order of factors: (i) definition of spatial ability and (ii) its assessment. Regarding the first point, from a simple review of the literature in the last decades, it emerges clearly that the term "spatial" is somewhat ambiguous as it has assumed different meanings and has been considered in various ways (Iachini, Iavarone, Senese, Ruotolo & Ruggiero, 2009).

Many interrelated concepts and different research dominions are involved in the investigation of spatial ability. On one side there are studies on spatial memory and, in particular, on spatial working memory. In this area much investigation has been devoted to the individuation of the architecture of visuo-spatial working memory (VSWM) with a first distinction between visual and spatial components (Logie, 1995). However, more recently other fragmentations have been proposed within spatial working memory based on the properties of the tasks used for its assessment. Hence it has been proposed a further distinction between sequential and simultaneous spatial memory (Cornoldi & Vecchi, 2003). These authors distinguished not only between different types of processes related to different types of content/format, but also between passive and active processes. The distinction between the sequential and simultaneous subcomponents might contribute to our understanding of VSWM (Mammarella et al., 2006) encouraging new cognitive approaches to its fractionation.

Several tasks are commonly used both in clinical and experimental contexts but a still open question is if these tasks can help to understand the real ability of subjects in their daily life, investigating also the role of different components of spatial abilities. A battery for the assessment of spatial ability in the elderly, which could also be used in patients affected by dementia, needs to also possess specific characteristics. It is known that unfamiliar and too abstract materials impair the performance in the elderly, with the consequent risk of an underestimation of the actual abilities. The battery should refer to theoretical models of spatial ability and spatial memory, in order to have a clear idea of the specific abilities that are assessed, and should also contain instruments potentially correlated with the orienting ability expressed in every-day life.

Spatial ability and navigation in normal and pathological aging

A long-standing literature has addressed the question of what deficits can be taken as early predictors of AD. So far, the greatest attention has been paid to verbally-mediated memory disorders, specifically episodic and semantic memory that are traditionally considered the earliest and deepest deficits (Fox, Warrington, Seiffer, Agnew & Rossor, 1998). Visuospatial deficits, even in early stages of AD, have long been recognized but have been studied much less closely (Mendez, Mendez, Martin, Smyth & Whitehouse, 1990).

Previous research has shown that older adults do not perform as well as younger adults on a variety of spatial tasks, including those requiring mental rotation and/or visualization abilities and memory for object locations (Cherry & Park 1993). Kirasic (2000) examined the relationships among age, spatial abilities, learning environmental layout, and wayfinding behavior: older adults acquired less information about a specific environmental layout than younger adults and there were also age-related decrements in wayfinding-related skills.

Changes in everyday visuospatial abilities can be observed in normal aging but especially in the preclinical stage of dementia (Mild Cognitive Impairment; MCI) (Farias et al., 2006). While the impact of spatial navigation decline in normal aging seems to be relatively small, patients suffering from AD are strongly impaired on this function as they manifest spatial disorientation in new environments and, later in the course of the disease, even in the domestic space (Hort et al., 2007). Navigational studies revealed declining performance in normal aging and MCI, but mostly in AD patients (Cushman, Stein & Duffy, 2008). The literature on healthy young and older people showed that a number of experimental tasks can predict performances in navigation and other spatial environmental tasks. An important distinction is between sequential memory spatial tasks, which predict performance on navigation, and objects location tasks, which predict the ability to use visual

landmark for orientation. Hence, the importance to focus both on spatial sequential abilities and memory for spatial location.

The effects of neurodegenerative diseases on different components of spatial cognition depend on the topographic patterns of brain pathology distribution, and for this reason the clinical assessment of these functions should be associated with neuroimaging investigations able to improve the diagnostic process and monitor the disease progression (Zhang et al., 2012; Hamalainen et al., 2007). Neurodegenerative diseases cause circumscribed atrophy in distinct neural networks, and accordingly, they impact visual spatial cognition in different and characteristic ways. Anatomically-focused visual spatial assessment can assist the clinicians in making an early and accurate diagnosis.

Spatial ability and differential diagnosis of Dementia

Numerous studies have focused on identifying neuropsychological variables that allow discrimination between Lewy body dementias and AD. These studies are important because compared to patients with AD, patients with Lewy body dementia may show greater response to cholinesterase inhibitors and abnormal sensitivity to neuroleptic drugs (Perry et al., 1994). The overall pattern emerging from these studies is that Lewy body dementia patients show more severe and pervasive visuospatial impairments than AD, whereas AD patients show more severe memory impairment. Visual spatial deficits are a particularly important component of differential diagnosis from AD (Aarsland et al., 2003; Johnson, Morris, & Galvin, 2005). Although patients with AD are frequently impaired on tests of visual spatial construction, patients with Lewy body dementia are usually more impaired on these tests early in the disease. For example, patients with DLB frequently fail to copy accurately the interlocking pentagons on the MMSE even when global cognitive impairment is mild (Tiraboschi et al., 2006). In literature, it is not well known if visual perceptual

organization ability, independent of constructional apraxia, could also be considered a prominent feature of dementia with Lewy bodies (DLB) that may help to clinically distinguish it from Alzheimer's disease (AD).

The general goal of this PhD thesis was to explore if the domain of "visuospatial abilities" should achieve a greater role in tracking cognitive decline in normal and pathological aging. First of all, a spatial battery was developed composed of new environmental and ecological spatial tests with the aim to understand the real ability of individuals in their daily life, investigating also the role of different components of spatial ability and their relation with self-rating dimensions. Secondly, it was explored whether this spatial battery could be able to discriminate between individuals with a normal age-related decline and those with MCI. Considering the strong relation between spatial deficits and specific neural networks, the assessment of the new spatial tests was also associated with a neuroimaging investigation, focalizing on the neuronal correlates of these deficits in normal aging and MCI patients. Finally, to give a more complete explanation about the role of visuospatial abilities in normal and pathological aging, it was explored if a specific component of visuospatial domain, specifically visuo-perceptual ability, could play an important role in the differential diagnosis between Alzheimer's Disease and Dementia with Lewy Body.

Chapter 1

Study 1: Spatial cognition in normal aging: neuropsychological evidence collected with three new visuospatial memory tests

1.1 Introduction

As shown in the previous chapter, spatial abilities are implied in many cognitive tasks typically performed in daily living: spatial reasoning, navigation, spatial language comprehension and production, performance of mathematical tasks.

Several studies (e.g. Allen, Kirasic, Dobson, Long, & Beck, 1996; Hegarty, Montello, Richardson, Ishikawa & Lovelace, 2006) showed that the definition of spatial ability has been an important topic within spatial cognition investigation; a relevant distinction was between spatial and environmental spatial ability. As stated by Hegarty et al. (2006), spatial ability can be defined as the ability "to encode, maintain and process visual configuration ". Paper and pencil tests are typically used for the assessment of spatial ability. These tasks require to mentally manipulate small objects, imagining the final product of mental activities, such as rotation or integration. Linn & Petersen (1985) and Voyer, Voyer & Bryden (1995) proposed a distinction between spatial perception, spatial visualization and mental rotation: spatial perception is the ability to individuate spatial relations, involving the disembedding or overcoming of distracting perceptual information; spatial visualization is the ability to perform multistep manipulation of complex spatial information; mental rotation requires management of spatial stimuli.

Environmental spatial abilities, such as finding one's way in the environment and learning the layout of a new environment, are examined by the use of environmental spatial tasks and self-report spatial questionnaires. A still open debate is the relationship between

basic spatial abilities and environmental spatial abilities. Previous research showed that older adults do not perform as well as younger adults on a variety of spatial tasks, including those requiring mental rotation or visualization abilities and memory for object location (Cherry & Park, 1993). Kirasic (2000) examined the relationships among age, spatial abilities, learning environmental layout and way-finding behavior: older adults acquired less information about a specific environmental layout than younger adults and there was also an age-related decline in way-finding skills. These evidences confirm the importance of having reliable instruments for the assessment of visuo-spatial abilities in healthy elderly.

A battery for the assessment of spatial ability in the elderly, which could also be administered to patients affected by dementia, needs to possess a number of characteristics: it should permit to collect a comprehensive assessment in a relatively short time in order to not fatigue the respondents; instructions should be short, in order to avoid attentive problems, and easy to comprehend; it should include ecological tasks (see Vecchi, Richardson & Cavallini, 2005), familiar to aged people. It is known that unfamiliar and excessively abstract/artificial materials impair the performance in the elderly, with the consequent risk of an underestimation of the actual abilities. Moreover, the spatial tests should refer to specific theoretical constructs of spatial abilities and spatial memory models, in order to have a clear understanding of what spatial processing component is evaluated. Finally, the cognitive battery should contain instruments potentially correlated with the spatial orientation ability expressed in daily living (environmental spatial abilities).

Several tests have been used for the assessment of spatial ability, mainly in the context of young people examination for experimental and job-selection purposes. Among the most frequently used there are the Minnesota Paper Form Board (MPFB) (Likert & Quasha, 1941) and the Paper Folding Test (Ekstrom, French & Harman, 1976), for the assessment of spatial visualisation; the Mental Rotations Test (Vandenberg & Kuse, 1978), the Card Rotation and

Cube Comparison Test (Ekstrom et al., 1976) for the assessment of the ability to mentally rotate 2- or 3-dimensional stimuli rapidly and accurately. In the field of visual and spatial memory few tests have been used, both in clinical and experimental context. For example, the Corsi's block test and the Visual Pattern Test are widely used for the assessment of spatial and visual short-term memory, respectively; whereas the Rey-Osterrieth Complex Figure (Caffarra, Vezzadini, Dieci & Zonato, 2002) gives a measure of visuospatial long term memory. These "non-ecological" tasks are not really specialized in the analysis of different components of spatial abilities important in every-day life orienting tasks, such as simultaneous vs sequential, and cannot reflect the daily-living spatial skills, particularly in the elderly.

The main purpose of Study 1 is to overcome this gap developing a cognitive battery of three new ecological tests that can help us to understand the real ability of individuals in daily living, investigating also the role of different components of spatial abilities: sequential memory for route and simultaneous memory for spatial patterns. This battery comprises of a number of objective tests on route and map learning, objects recognition and location, and pointing to unseen landmarks.

Another important part of this study is the use of self-rating questionnaires of spatial abilities. Self-reported spatial questionnaires are an important measure that gave us information on the individual's type of spatial representation and explored if the own perception of spatial self-efficacy corresponds to the objective performance obtained in the spatial tests. Many studies have found a significant correlation between environmental spatial abilities and self-rating spatial scales (Kozlowski & Bryant, 1977); we as well hypothesized to find this relationship between self-rating dimensions and these new more ecological spatial tasks.

1.2. Methods

1.*2.1 Participants*

A total of ninety healthy older adults (forty-one males; mean age 70.46, SD 7.19, range = 57 – 90; mean education 8.53, SD 3.45, range = 5 - 18) were enrolled in this study. All participants were selected among elderly attendees of the University of the Third Age of Verona. They had no history of neurological or psychiatric disorder and presented a cognitive performance in the normal range, such as a Mini Mental State Examination (MMSE) superior to 25 and preserved daily living functional activities.

1.2.2 Materials

Spatial visualization tests

***Minnesota Paper Form Board* (MPFB,** Likert & Quasha, 1970). The MPFB measures spatial visualization abilities (Linn & Peterson, 1985). It is composed of sixteen items, each comprising one 2D target and five alternative sets of separate elements. Participants have to choose the alternative sets which combined makes up the target. Time allowed for the task was five minutes. One point was assigned for each correct answer, 0 for the other.

***Embedded Figure Test* (EFT**, Oltman, Raskin & Witkin, 1971). Participants have to find simple shapes listed separately that were included (embedded) in a complex overall figure. There were twenty items and they were administered in two parts, with a time limit of 5 minutes for each part. One point was assigned for each correct answer, 0 for the other.

Working memory tests

***Corsi's Blocks Test* (CBT**, Mammarella, Toso, Pazzaglia & Cornoldi, 2008). The Corsi's Blocks Test consists of a series of nine blocks irregularly arranged on a board.

Participants have to reproduce sequences of blocks of increasing forward length. The sequence length varied from two to nine blocks and two sequences were used for each length. The final score corresponds to the maximum length of sequences correctly reproduced.

***Visual Pattern Test* (VPT**, Della Sala et al., 1997, in the version of Borella, Carretti & De Beni, 2007). The material is composed by matrix patterns of black and white squares in grids of different sizes. Participants are asked to memorize a series of black and white checkerboard-like patterns of increasing complexity for one minute each. Participants were then asked to reproduce the pattern by marking squares in an empty grid of the same size as the one bearing the pattern just presented. At each level of complexity three patterns were presented. The dependent variable was the number of filled cells in the most complex pattern correctly recalled two out of three probes. The final score was computed by summing up the score of the three highest levels of complexity correctly solved.

Environmental spatial ability tests

Objects recognition and location test. This test was developed to assesses the ability to recognize objects and to memorize their location. It is divided into three parts that require respectively to recognize, recall and locate a number of objects within a picture. In the recognition phase six cards with the picture of one object (elephant, lamp, slipper, guitar, bottle and hat) are presented and participants have 1 minute for each card to memorize the object's visual features. Then, for each object is presented three cards and s/he is required to recognize the target among three options (e.g. Figure 1.1). The final score is given by the sum of objects correctly recognized (1 point for each correct answer and 0 for the wrong one).

Figure 1.1 *Objects recognition and location test: target to recognize among three options (e.g. bottle*

The second phase consists in learning the picture of a room for 1 minute (Figure 1.2a) in which there are twelve objects (e.g. table, cat, chess, guitar, etc..). Then, the participant is required to recall verbally all the objects he/she is be able to remember from the picture. The final score is given by the sum of objects correctly recalled.

In the third phase the participant is required to locate the objects into an empty picture of the same room (Figure 1.2b). The final score is given by the sum of each object located in the correct position (1 object well located = 1 point).

Figure 1.2 . *Objects recognition and location test: a) image of a room with items to remember; b) image of the empty room where to locate the objects previously seen.*

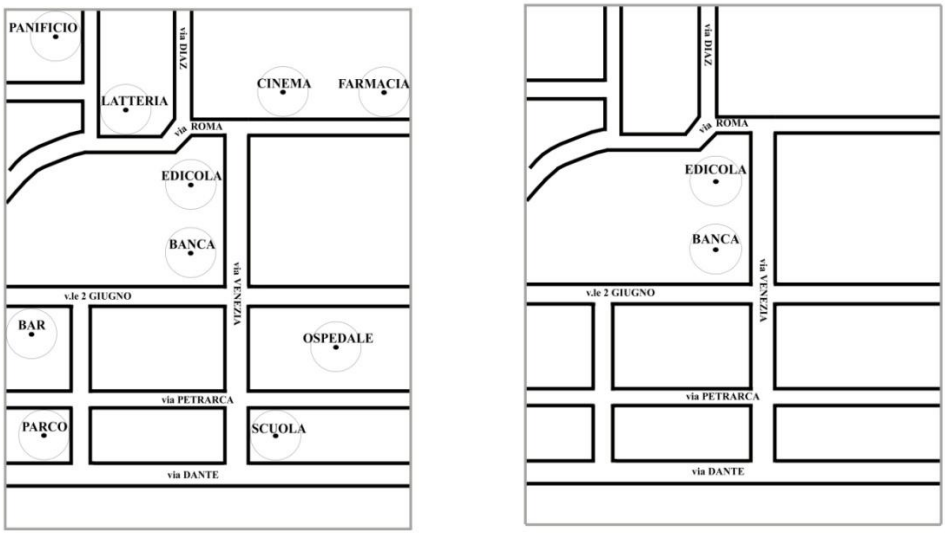
a) b)

Map Learning test. This test was developed to assess the ability to acquire spatial knowledge (memorization of landmarks and their location within a schematic map). The material consisted of two maps: one comprising eight landmarks and the other is a blank map (Figure 1.3a and 1.3b).

The task requires to memorize the name and the location of eight landmarks located on the map (e.g. pharmacy, school, cinema, hospital, bakery, park, bar, dairy). Participants, immediately after having been exposed to the map for five minutes, have to write on the blank map all the landmarks in the correct position. The learning phase and the subsequent recall are repeated twice. Afterwards, four perspective taking tasks are presented: participants are required to imagine to be on the map, standing on one landmark (e.g. bank), facing another (e.g. newsstand) and to point to another one with their arm. Memory score is calculated by counting landmarks recalled and landmarks correctly-located (landmarks have to be located as in Figure 1.3a). In the perspective taking task, score is calculated by measuring the difference in degrees between the response of the individual and the correct response.

Figure 1 3. *Map Learning Test: a) image of a map with landmarks to remember; b) image of an empty map where to locate the landmarks previously seen.*

a) b)



Route learning test. The material consisted of 25 sheets of cardstock paper placed on the floor in order to reproduce a 5x5 matrix; each card was 15x15 cm, and they were placed with a gap of 15 cm between them. The task was divided into three different sub-tasks: 1. walking on the cards by following in the trainer's footsteps (route learning from action); 2. observing the trainer walking on the cards (route learning from visual input); 3. looking at the route on a map without seeing the trainer walk on the cards (route learning from a map). In each condition, participants were asked to remember the route and to reproduce it in the matrix. They began with a route involving 2 cards, then moved on to 3, 4, 5, 6 and 7 cards if they completed the previous difficulty levels correctly. In all the sub-tasks, the trials ended when a participant failed to reproduce two different routes of the same difficulty level. The final score corresponded to the highest level that participants were able to manage in each condition.

Self-rating environmental spatial ability questionnaires

Sense of Direction and Spatial Representation Scale **(SOD**, revised from Pazzaglia, Cornoldi & De Beni, 2000). The SDSR measures sense of direction, spatial representation and strategies to orient in the environment. It consists of eighteen items that require a response on a five points scale: 1 (nothing), 2 (little bit), 3 (enough), 4 (much), 5 (very much). The questionnaire identifies the management skills and strategies commonly used to travel in the space. The final score is calculated by adding the responses to each item. Example item: Think about the way you orient yourself in different environments around you. Would you describe yourself as a person who: a) orients themself by remembering routes connecting one place to another; b) orients themself by looking for well-known landmarks; c) tries to create a mental map of the environment.

Attitude towards Environmental Tasks **(AET**, adapted by Pazzaglia, Poli & De Beni, 2004). The AET investigates the general attitude in performing spatial tasks in every-day life. It consists of seven items based on a four points scale: 1 (nothing), 2 (little bit), 3 (enough), 4 (much); the scores of the items two and six are reversed from 4 (nothing) to 1 (much). The final score is calculated by adding scores to each item. Example item: I like exploring unfamiliar places to discover new and different places.

Spatial anxiety **(SA**, adapted by Lawton, 1994). The SA investigates the levels of anxiety experienced during the performance of every-day spatial tasks. It consists of eight items that require a response on a four points scale: 1 (nothing), 2 (little bit), 3 (enough), 4 (much). The final score is calculated by adding the responses to each item. Example item: Indicate the level of anxiety you experiment in the situations described (e.g. Reaching an appointment venue in an unfamiliar part of a town).

Spatial Self-Efficacy Questionnaire **(SSEQ,** adapted by Pazzaglia *et al*., 2004). The SSEQ investigates how much individuals feel confident to perform environmental spatial tasks correctly and what they think about their sense of direction. It consists of four items that require a response on a six points scale: 1 (nothing), 2 (little bit), 3 (little), 4 (enough), 5 (much), 6 (very much). Final score is calculated by adding the responses to each item. Indicate how well you think you would cope in the situations described (e.g. Locating your car in a large car park).

1.2.3 Experimental Procedure

All participants were tested in two separate sessions, both lasting about one hour. The first testing session was conducted collectively and the order of administration was the following: MPFB, EFT, SOD, AET, SA and SSEQ. During the second session, conducted individually, the MMSE, VPT, CBT, Objects recognition and location test, Map Learning test and Route Learning Test were administered.

It was hypothesized that the new environmental spatial ability tests explore different components of spatial abilities. Specifically it was assumed that the Map Learning Test (which requires to learn a spatial configuration with landmarks) and the Route Learning Test (that consists of a sequential presentation of spatial locations) measure the simultaneous and sequential components of spatial abilities, respectively. Whereas, it was assumed that the objects recognition and location test (which requires to recognize objects and memorize their locations) explores a spatial memory focused on objects. It was also expected to find a significant correlation between the self-rating scales and the environmental spatial tests.

1.3. Results

1.3.1 Confirmatory factorial analysis

Maximum likelihood structural equations were calculated for each of the four hypothetical models, using LISREL procedure. It was decided *a priori* that only models with values $\leq$ .08 for the root mean squared error of approximation (RMSEA), values $\geq$.60 for the parsimonious normed fit index (PNFI), and values $\geq$.90 for the comparative fit index (CFI) were acceptable. These criteria were selected on the basis of previous researches (Arnau & Thompson, 2000). Furthermore, lower values of the ratio of chi-square to degrees of freedom (X /df), lower values of the Akaike's information criterion (AIC), lower values of the expected cross validation index (ECVI) and higher levels of the adjusted goodness of fit index (AGFI) were also assumed to reflect better model fit (Hatcher, 1994).

Goodness of fit indexes for each of the four models are presented in Table 1.1. As the data in Table 1 indicated, Model 4 was the only model that met all the *a priori* criteria regarding acceptability (i.e., RMSEA $\leq$ .08, PNFI $\geq$ .60, and CFI $\geq$ .90). For these reasons, the four-factor model was considered to provide the best fit to the current data.

Table 1.1. *Goodness of Fit Indexes for Four Hypothetical Spatial components model*

Model	X	df	X/df	AGFI	AIC	RMSEA	ECVI	CFI	PNFI
1	368.81	90	4.09	.53	428.81	.19	4.82	.77	.60
2	242.36	89	2.72	.64	304.36	.14	3.42	.86	.67
3	148.26	87	1.7	.75	214.26	.09	2.41	.93	.71
4	131.69	84	1.57	.76	203.69	.08	2.29	.94	.69

Confirmatory factorial analysis (see Figure 1.4) showed that the spatial battery could be grouped in 4 factors that represent different components of spatial abilities. Specifically all sub-tests of the Map learning test are grouped in the first factor (simultaneous spatial memory); all sub-tests of the Object's recognition and Location test are grouped in the second factor (objects memory); Route learning test and CBT measure the sequential component of spatial memory (Factor 3) and finally EFT, VPT and MPFB measure spatial visualization (Factor 4). Each component is independent and reliable.

Figure 1.4. *Graph obtained by the Confirmatory Factorial Analysis with the four-factor model.*

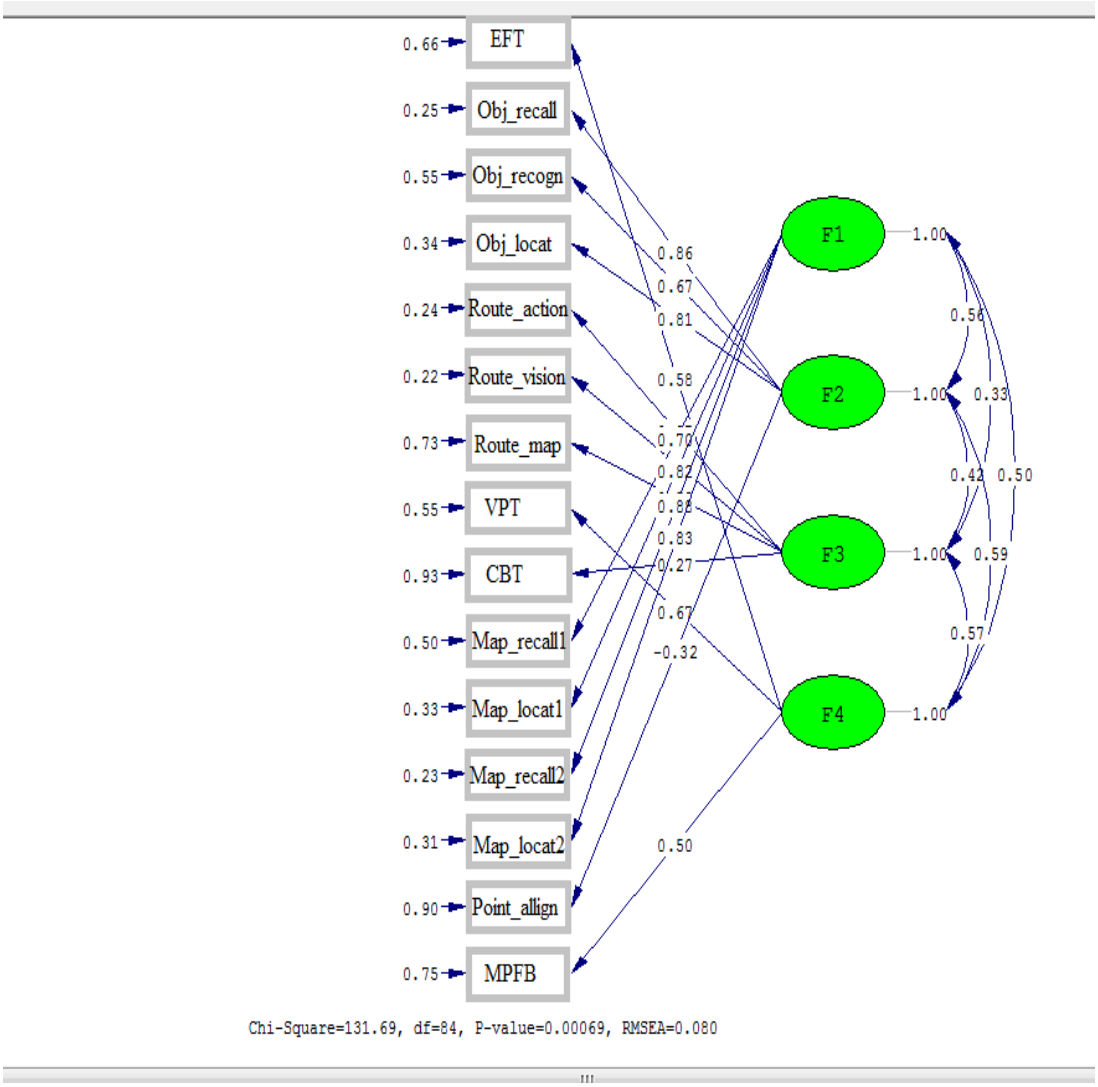


Table 1.2 contains the factor loadings for the four-factor model. Almost all factor loadings exceed .50, supporting the predicted relations between the subtests and the latent underlying factors (simultaneous spatial memory, sequental spatial memory, object memory and spatial visualizer).

Table 1.2. *Standardized structural Coefficients*

Variable	Simultaneous Spatial memory	Object memory	Sequential Spatial memory	Spatial visualizer
EFT	.00	.00	.00	.58
Object's recogn.	.00	.86	.00	.00
Object's recall	.00	.67	.00	.00
Object's location	.00	.81	.00	.00
Route action	.00	.00	.87	.00
Route vision	.00	.00	.88	.00
Route map	.00	.00	.52	.00
VPT	.00	.00	.00	.67
CBT	.00	.00	.27	.00
Map recall 1	.70	.00	.00	.00
Map location 1	.82	.00	.00	.00
Map recall 2	.88	.00	.00	.00
Map location 2	.83	.00	.00	.00
Pointing align.	.00	-.32	.00	.00
MPFB	.00	.00	.00	.50

The intercorrelations across factors are presented in Table 1.3. These data suggest acceptable amounts of shared variance.

Table 1.3. *Correlations between factors in Model 4*

Factor	Simultaneous Spatial memory	Object memory	Sequential Spatial memory	Spatial visualizer
1	-	.56	.33	.5
2		-	.42	.59
3			-	.57
4				-

1.*3.2 Relationship between Self-rating scales and spatial tests*

Correlations between the self-rating scales and spatial tests aimed to evaluate if emotional- motivational state is in relation with the spatial abilities performance. A bivariate analysis was computed. Results showed that self-rating scale on Sense of Direction was significantly correlated to Objects location, Visual Pattern Test and all components of Route Learning Test: Route Action, Route Vision, Route Map (see Table 1.4). The association of SOD with Map Learning Test was not significant. Instead, there was a significant correlation between Map Learning Test and Questionnaire on Self-Efficacy towards environmental spatial tasks, specifically with Map Recall 1, Map Location 1, Map Recall 2, Map Location 2 and aligned Pointing task. Self-Efficacy rating scale correlated also with Object's recognition and location test, Visual Pattern Test and with all components of Route Learning Test. These results showed that Self-efficacy might be considered a reliable measure of spatial performance.

There were not significant correlations between Questionnaire on Attitude Towards environmental Tasks and spatial tests, except in Route vision and Visual Pattern Test.

Finally, Questionnaire of Spatial Anxiety correlated negatively with Objects recall, Objects location, Route Action, Route vision and Corsi's Blocks Test. The correlations observed for this self-rating scale were negative meaning that a higher level of anxiety correspond to a lower performances in spatial tests.

Table 1.4 *Correlations between self-rating scales and spatial tests*

Variable	SOD	SA	AET	SSEQ
EFT	.091 (.391)	.012 (.908)	.166 (119)	.189 (.075)
Object's recogn.	.015 (.891)	-.093 (.382)	.150 (.159)	.351 (.001)*
Object's recall	.202 (.057)	-.209 (.048)*	.054 (.610)	.343 (.001)*
Object's location	.229 (.030)*	-.246 (.019)*	.082 (.443)	.277 (.008)*
Route action	.330 (.001)*	-.249 (.018)*	.202 (.057)	.306 (.003)*
Route vision	.257 (.014)*	-.303 (.004)*	.213 (.043)*	.281 (.007)*
Route map	.231 (.028)*	-.062 (.559)	.035 (.742)	.122 (.251)
VPT	.248 (.018)*	-.160 (.132)	.261 (.013)*	.222 (.036)*
CBT	.190 (.072)	-.231 (.029)*	.096 (.367)	-.005 (.960)
Map recall 1	.041 (.703)	-.033 (.758)	.009 (.933)	.208 (.049)*
Map location 1	.088 (.410)	-.072 (503)	.031 (.770)	.260 (.013)*
Map recall 2	.120 (.260)	-.116 (276)	-.005 (.959)	.347 (.001)*
Map location 2	.034 (.750)	-.086 (.419)	.058 (.587)	.362(<.001)*
Pointing align.	-.144 (.180)	.031 (.775)	-.142 (.187)	-.264 (.013)*
MPFB	.005 (.961)	.203 (.056)	.205 (.052)	.105 (.323)

1.4. Discussion

Spatial cognition is a crucial function in daily living that declines with aging, limiting older adults independent movements, and thereby affecting also their social activities. It is therefore essential to sustain their well-being and quality of life by monitoring the preservation of spatial abilities in daily living. The present study developed a cognitive battery of ecological tests exploring different components of spatial abilities, such as objects recognition and location, map and route learning. Furthermore it was investigated if the perception of own spatial self-efficacy correlated to the objective performance measured with the spatial tests.

Confirmatory factorial analysis showed that the spatial battery scored four different components of spatial abilities such as simultaneous spatial memory, objects memory, sequential spatial memory and spatial visualization, and each component is independent and reliable. These results are in line with the distinction of Cornoldi & Vecchi (2003) between two different components of spatial memory: simultaneous and sequential. Specifically, these results showed that Map Learning Test, which requires to learn a spatial configuration containing landmarks, explores simultaneous spatial memory. Route Learning test, that consists of a sequential presentation of spatial locations to learn, measures abilities related to sequential spatial memory. Instead Objects recognition and location test, which requires to recognize objects and memorize their locations, is related to objects memory. All these tasks refer to a specific theoretical construct of spatial ability specifying which spatial process is taken under consideration. The distinction between the sequential and simultaneous subcomponents might also contribute to the understanding of visuospatial working memory (Mammarella et al., 2006) encouraging new cognitive approaches to its fractionation.

Recent studies suggest that environmental spatial abilities are mainly examined by the use of spatial tasks but can also be explored through the use of self-report spatial questionnaires. Consistently with the literature and *a priori* hypotheses, results of Study 1 showed a significant correlation between the environmental spatial tasks and self-rating dimensions. Self-rating scale on Sense of Direction and Questionnaire on Self-Efficacy towards environmental tasks were significantly related to Objects recognition and location test and Route Learning Test. Self-Efficacy rating scale correlated also with Map Learning Test. Questionnaire of Spatial Anxiety correlated negatively with Objects recognition and location test and with Route Learning Test. This indicates that at higher anxiety levels correspond lower performances in spatial tests. Many studies have already found significant correlations between environmental spatial abilities and self-rating spatial scales, but according to our knowledge, no one explored specifically the relationship with objects memory and the sequential and simultaneous component of spatial ability. Finally in this study the responses given by individuals on self-rating scales reflect the performance that they achieved in all three spatial tests confirming that emotional and motivational state are also related to these specific spatial performances.

Study 1 presented three new spatial tests and ascertained their reliability in measuring different components of spatial abilities and their relationship with self-rating spatial scales. Further studies are necessary in order to standardize these new spatial tests facilitating their use in the research and clinical setting.

Chapter 2

Study 2: Visuospatial memory and neuroimaging correlates in Mild Cognitive Impairment (MCI)

2.1 Introduction

Considering the strong relation between spatial deficits and specific neural networks, in Chapter 2 the assessment of spatial abilities by the use of the new spatial tests (examined in Chapter 1) was associated with a neuroimaging investigation, focalized on the neuronal correlates of spatial performances in normal and pathological aging (MCI).

A long-standing literature has focused on cognitive deficits traditionally considered particularly severe in AD, as episodic memory impairment supported by lesions in specific brain circuits (McKhann et al., 1984; Dubois et al., 2007; Dubois, Feldman, Jacova, Cummings & DeKosky 2010). Although visuospatial deficits have been described even in the early phases of AD, they are not fully investigated and assessed in clinical practice (Iachini et al., 2009). The literature shows that measures of visuospatial functions, semantic memory and attention are significantly correlated with functional measures of daily living in patients with AD, whereas episodic and verbal short-term memory are not (Perry & Hodges, 2000).

Changes in everyday visuospatial abilities can be observed very early in dementia and even in patients with MCI (Farias et al., 2006), such as a preclinical stage of AD characterized by one or more cognitive deficits that are not sufficiently severe to induce dementia or impair daily functional activities (Petersen, Doody, Kurz, Mohs & Morris, 2001). All together, these studies suggest that visuospatial impairments in AD are strongly related to deterioration in everyday activities.

Other studies investigated the decline of spatial navigation abilities in healthy aging and early AD. While the impact of spatial navigation decline in normal aging seems to be relatively small, patients suffering from AD are strongly impaired on this function as they manifest spatial disorientation in new environments and, later in the course of the disease, even in the domestic space (Hort et al., 2007). The spatial navigation is a complex process which is based on several underlying cognitive abilities. The learning of navigational landmarks is equivalent in real-world and virtual environments (Richardson, Montello & Hegarty, 1999), suggesting that cognitive mechanisms are similarly engaged under both conditions. Navigational studies revealed declining performance in normal aging and MCI, but mostly in AD patients (Cushman, Stein & Duffy, 2008). The literature on healthy young and older people showed that a number of experimental tasks can predict performances in navigation and other spatial environmental task. An important distinction is between sequential memory spatial tasks, which predict performance on navigation, and objects location tasks, which predict the ability to use visual landmark for orientation. Hence the importance to focus both on spatial sequential abilities and memory for spatial location.

Functional neuroimaging and clinical studies have identified a complex network of brain structures that are involved in spatial navigation. The proposed network includes the hippocampus, parahippocampus, medial and right inferior parietal cortex, regions within the prefrontal cortex, cerebellum, parts of the basal ganglia, posterior cingulate and retrosplenial cortex (Aguirre, Detre, Alsop & D'Esposito, 1996; Barrash, 1998; Ekstrom et al., 2003). Other sudies showed that visuospatial impairment was related to bilateral parietal hypometabolism and that visuoperceptual deficits were related to right temporo-parietal hypometabolism in patients with mild to moderate AD (Fujimori et al., 2000). Visuospatial cognition is composed of a multi-faceted set of functions mediated by a predominantly right-hemisphere network of widely-distributed brain regions including the parietal lobes, lateral

prefrontal cortex, medial temporal lobes, inferior temporal cortex, occipital cortex, basal ganglia and white matter tracts (Possin, 2010). The hippocampus plays a crucial role in spatial memory and in the recognition of items locations (Mcnaughton et al., 1996). The early medio-temporal damage in AD, including the hippocampus, might explain the visuospatial memory impairment in the first stages of the disease.

In the present chapter (Study 2) I associated a voxel-based morphometry (VBM) (Good et al., 2001) with a neuroimaging investigation with the assessment of the new spatial tests validated in Study 1. The effects of neurodegenerative diseases on visuospatial cognition depend on the topographic patterns of brain pathology distribution, and for this reason the clinical assessment of these functions should be associated with neuroimaging investigations able to improve the diagnostic process and monitoring the disease progression (Zhang et al., 2012; Hamalainen et al., 2007). In most cases, however, the evaluation of spatial cognition in dementia does not encompass comprehensive specific tasks integrated with neuroimaging examination.

The VBM technique may provide a general view of the disease- related brain morphological changes. VBM literature agrees to point out medio-temporal lobe and temporal cortices disease-related gray matter shrinkage in Alzheimer disease and amnestic MCI subtype. Also the insula, the cingulate gyri, the parietal and the frontal lobes were found to present some extent of atrophy in subject affected by MCI (Bell-McGinty et al., 2005; Chetelat et al., 2002; Pennanen et al 2005).

As described in the Methods section in details, we approached the VBM technique by using mainly two software. Firstly ANTS (http://picsl.upenn.edu/ANTS/) which has been recently recognized to be the best performing tool in achieving high-resolution brain volumes and best suited for the creation of a study population template to be used as reference image

for such a registration. Secondly we applied SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) which is the most commonly used tool, to perform parametric statistical tests to MR imaging 3D volumes dataset.

The main goal of Study 2 was to assess visuospatial abilities (measured with the environmental spatial tests described in Study 1) in MCI compared to healthy older adults in order to verify whether visuospatial evaluation increases the diagnostic power of MCI compared with other standard clinical tests. It was focused both on spatial sequential abilities measured through route learning tests and memory for spatial locations, assessed with a task of objects and location recognition and a map learning task. Moreover, it was aimed to investigate if these specific spatial abilities in MCI were associated with a different pattern of brain regions compared with controls. If this is the case, we might suppose that a diverse neurofunctional organization of visuospatial processes in MCI might express as a breakdown in these cognitive tasks.

It was also evaluated how participants self-rated their sense of direction, attitude towards environmental tasks, spatial anxiety and their self-efficacy towards environmental tasks. Studies on sense of direction show that self evaluation reflects performances in spatial tasks. Some authors demonstrated a relationship between self-evaluation of sense of direction, mental rotation, and performance in map learning and pointing tasks (De Beni, Pazzaglia & Gardini, 2006). Other studies showed that people who reported higher spatial anxiety were less efficient navigators (Lawton, 1994).

2.2 Methods

2.2.1.Participants

Twenty MCI patients (mean age 74.75, SD 6.93; mean education 7.85, SD 4.39; ten females and ten males) diagnosed according to the Petersen's criteria (Petersen et al., 2001)

and fourteen healthy controls (mean age 68.64, SD 4.53; mean education 8.57, SD 4.88; ten females and four males) took part in this study. MCI patients were recrutied at the Cognitive Disorders Unit, whereas healthy elderly controls were recruited among patient's caregivers and relatives of the Cognitive Disorders Unit staff.

All participants underwent the following standardized neuropsychological tests: Mini Mental State Examination (Folstein & McHugh, 1975), IQ (intelligence quotient) tests– Raven's Coloured Progressive Matrices (Raven, Court & Raven, 1990), TIB (Sartori, Colombo & Vallar, 1997), Vocabulary test (WAIS sub-test) (Wechsler, 1981), verbal memory tests - Prose Memory Test (Spinnler & Tognoni, 1987), Rey Auditory Verbal Learning Test (Rey, 1964), Verbal semantic encoding and recognition (Carlesimo et al., 1998), Digit Span forward (Spinnler & Tognoni, 1987), language test – Boston Naming Test (Kaplan, Goodglass & Weintraub, 1983), Verbal Associative Fluency Test (Spinnler & Tognoni, 1987), Category Words Fluency Test (Spinnler & Tognoni, 1987); executive function tests – Stroop test (Stroop, 1935), Wisconsin Card Sorting Test(WCST) (Bergh, 1948), Tower of London (Shallice, 1982), Dual task (Della Sala, Laiacona, Spinnler & Ubezio, 1992), Multiple feature target cancellation (Gainotti, Marra & Villa, 2001), Digit Span backward (Spinnler & Tognoni, 1987), visuospatial and visual perception test - Corsi Block Tapping test (Spinnler & Tognoni, 1987), Rey-Osterrieth Complex Figure (Caffarra et al., 2002), Visuospatial supra span (Hebb, 1961), VOSP (Warrington & James, 1991), Mental Rotation test (Vandenberg & Kuse, 1978).

The MCI patients presented a profile of cognitive deficits with spared daily functional activities, whereas healthy elderly controls performed all tasks in the normal range. In particular, control subjects were in good general physical and cognitive health and had a Mini-Mental State Examination (MMSE) (Folstein et al.1975) score higher than 24.

Participants with neurological or mood disorders were excluded. Groups did not differ in age ($t_{(1, 32)} = -1.346$, $p = 0.189$), education ($t_{(1, 32)} = 1.087$, $p = 0.450$) or gender (χ^2 test = 0.169, $p = 0.681$).

2.2.2 Procedure

All participants underwent to the spatial battery described in Study 1 composed by an Object's Recognition and location Test, a Map Learning test, Route Learning Tests and self-rating spatial questionnaires (Sense of Direction and Spatial Representation, Attitude toward Environmental task, Spatial Anxiety and Spatial Self-Efficacy Questionnaire) and 3D MRI brain scanning.

A series of multivariate ANOVAs were carried out: experimental visuo-spatial scores were entered as within subjects factors, group (MCI and healthy controls) as between subjects factor and age, gender, education and MMSE score as covariates. The scales accuracies were compared by means of their respective AUCs: for each pair of golden standard tests and new experimental visuo-spatial tasks, a Z-test was run, dividing the difference between the AUCs by their standard errors, weighted for the average Tau correlation coefficient in MCI and controls samples (Hanley & McNeil, 1982).

All participants underwent the same MRI protocol on a 3T GE MR750 scanner, equipped with 8-channel phased array receiver head coil. The protocol included a 3D high resolution T1-weighted sequence, IR-prepared FSPGR (0.9x0.9x0.9mm^3, TR/TE=9,7/4ms).

Image Processing: Data were transferred and processed on a work-station MAC-PRO 2x2.26GHz Quad-Core Intel Xeon, 8GB 1060MHz DDR3 RAM. The image processing was implemented within the ANTs software (http://picsl.upenn.edu/ANTS/), with the help of some tools included in FLS software (Woolrich et al., 2009; Smith et al., 2004) as described in (Fasano et al al., 2011). We removed the skull from each T1-weighted data volume by

using the ‘bet’ tool (Smith, 2002) included in the FSL software. Each ‘betted’ T1-weighted data volume was affine registered to MNI space with the ANTs software. A reference T1-weighted template was created by the betted and MNI registered T1-weighted data volumes of 20 subjects (10 healthy controls and 10 patients, matched for sex and age). The betted and MNI registered T1-weighted data volumes of all the subjects, and the template one, were segmented by using the Atropos tool, included in ATNs, and grey matter, white matter and CSF probability maps were extracted. The grey matter probability maps of all the subjects were non-linearly registered to the grey matter probability map of the template using the Symmetric Normalization (SyN) diffeomorphic algorithm (Avants, Epstein, Grossma & Gee, 2008). The vector deformation field for each subject was extracted by the transformation process, and the Jacobian map of the vector deformation field was calculated. Finally, for each subject, the modulated grey matter map was computed as the product of the grey matter probability map and the logarithm of the Jacobian map.

Image analysis: Image analysis was performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). A voxel based morphometry (VBM) statistical approach (Ashburner & Friston, 2000) was carried out on the modulated grey matter maps in two ways: 1) the patients group was compared with the healthy control group through a two-sample t-test analysis; 2) correlations between the modulated grey matter map values and the scores on the individual tests in the experimental spatial battery and self-rating spatial questionnaire, using a multiple regression analysis. Statistical significance level was set at false discovery rate (FDR) corrected $p < 0.05$ using SPM8. This method of correction for multiple comparisons was preferred to family-wise error (FWE) correction to avoid false rejection of true positives as well as false positives.

2.3 Results

2.3.1 Cognitive data

MCI had significant lower scores on objects and location recognition, map and route learning and on self-rating spatial questionnaires of attitude and self-efficacy, except for the questionnaire of spatial anxiety and sense of direction (see Table 2.1 for mean scores and statistical results).

Table 2.1. *Mean (and standard deviation) scores and p statistical value, of the MCI patients on the new visuo-spatial tasks and self-rating spatial questionnaires compared to a reference sample of healthy age matched elderly controls (* Significant differences between groups)*

	Mean (SD)		
	MCI	**Controls**	**P**
Objects recognition and location			
Objects recognition	3.45 (1.27)	4.71 (1.1)	0.005*
Objects recall	6.35 (2.91)	9.64 (1.28)	0.005*
Objects location	7.05 (2.46)	11.07 (1.1)	0.005*
Map Learning			
Map recall 1	2.75 (1.83)	6.5 (1.28)	0.002*
Map location 1	1.85 (1.75)	5.57 (2.24)	0.002*
Map recall 2	4.1 (2.44)	7.07 (1.33)	0.002*
Map location 2	3 (2.62)	6.79 (1.77)	0.002*
Route Learning			
Learning from action	3.75 (1.06)	5.21 (.58)	0.001*
Learning from vision	3.94 (1.06)	5.71 (.73)	0.001*
Learning from map	4.31 (1.49)	6.21 (.69)	0.001*
Spatial Questionnaire			
Questionnaire of Anxiety	16.3 (5.82)	13.21 (3.9)	0.185
Questionnaire of Attitute	19 (3.5)	22.21 (3.4)	0.019*
Questionnaire of Self-efficacy	13 (3.77)	18.5 (4.16)	0.013*
Questionnaire on Sense Of Direction	44.35 (10.68)	54.57 (7.48)	0.056

The objects recognition test demonstrated only the principal effect of the group [$F_{(1,28)}$ = 9.511, p= .005, η^2= .254]. The map learning task displayed a significant effect for the group [$F_{(1,28)}$ = 11.942, p= .002, η^2= .299] and for age [$F_{(1,26)}$ = 6.110, p= .02, η^2= .179]. Older patients obtained lower scores in the second recall (*r*= -.604, p= .005) and second

location (*r*= -.494, p= .027), whereas older controls showed lower scores in the first recall (*r*= -.759, p= .002) and first location (*r*= -.667, p= .009); it also showed a significat interaction between map learning subtests and MMSE scores [$F_{(3,28)}$ =3.187, p= .028, η^2= .102] and groups [$F_{(3,28)}$ = 3.069, p= .032, η^2= .099]. Only MCI revelead positive relationships between MMSE scores and map learning subtests (respectively: *r*= .576, p= .023; *r*= .353, p= .127; *r*= .619, p= .004; *r*= .553, p= .012). MCI and controls showed analogue and significant differences in the first recall [$t_{1,32}$= -6.593, p= .000, δ= -3.75], first location [$t_{1,32}$= -5.426, p= .000, δ= -3.72] and second location [$t_{1,32}$= -4.708, p= .000, δ= -3.79]; instead MCI evidenced a slightly higher improvement in the second recall than controls [$t_{1,32}$= -4.125, p= .000, δ= -2.97].

The route learning test revealed a significant effect for the group [$F_{(1,24)}$ = 23.993, p= .0001, η^2= .500], for education [$F_{(1,24)}$ = 15.048, p= .001, η^2= .385] and for MMSE score [$F_{(1,24)}$ = 4.845, p= .038, η^2= .168]. More educated patients obtained higher performance in all subtests, such as learning from action (*r*= .700, p= .003), learning from vision (*r*= .617, p= .011) and learning from map (*r*= .621, p= .010); whereas in controls higher levels of education correlated with a better performance only in learning from action (*r*= .634, p= .015) and learning from map (*r*= .548, p= .043). Only in the MCI patients, the MMSE scores significantly correlated with an increased performance in the route learning from map.

The questionnarie of spatial anxiety did not show a significant difference between groups [$F_{(1,28)}$ = 1.844, p= .185, η^2= .062], whereas it showed a significant effect for age [$F_{(1,28)}$ = 9.360, p= .005, η^2= .251] and for MMSE score [$F_{(1,24)}$ = 5.245, p= .03, η^2= .158]. Older controls showed lower level of spatial anxiety (*r*= -.742, p= .002).

The questionnaire of attitude demonstrated a significant effect for the group [$F_{(1,28)}$ = 6.215, p= .019, η^2= .182], and for gender [$F_{(1,24)}$ = 5.115, p= .032, η^2= .154], where only in the patients groups, males obtained higher scores than females [$t_{1,18}$= -4.543, p= .000].

The self-efficacy questionnaire showed only a significant effect for the group [$F_{(1,28)}$ = 7.006, p= .013, η^2= .200].

The questionnaire on sense of direction did not reach the significant level for the group [$F_{(1,28)}$ = 3.978, p= .056, η^2= .124].

The ROC curve analysis revealed an elevated between-groups discriminative power of the experimental visuo-spatial tests: in particular, objects location, map first recall, learning from action and from vision showed AUC values ≥.900, analogue to other neuropsychological tests commonly used in clinical testing (i.e. Tower of London, Rey – delayed Osterrieth Complex Figure, VOSP-object 3; See Table 2.2).

Table 2.2. *Discriminative power of cognitive tests obtained by ROC curve analysis.*

Cognitive Tasks		
Experimental visuo-spatial tests	**AUC**	Confidence Interval
Objects recognition and location		
Objects recognition	.768	.609-.926
Objects recall	.845	.700-.989
Objects location	.936	.860-1.000
Map learning		
Map - first recall	.946	.879-1.000
Map – first location	.884	.751-1.000
Map – second recall	.857	.732-.982
Map – second location	.880	.768-.993
Route learning		
Learning from action	.900	.768-1.000
Learning from vision	.906	.800-1.000
Learning from map	.862	.727-.996
Standard tests*		
Tower of London	.932	.850-1.000
Rey-Osterrieth Complex Figure – delayed	.942	.865-1.000
VOSP – object 3	.910	.803-1.000

** Only standard tests with AUC>.900 are reported*

Moreover, their AUCs risulted significantly higher than the AUCs of other several standard tests, showing an higher discriminant power compared with other standard neuropsychological tests, such as Stroop test, Wisconsin Card Sorting Test and semantic fluency test (see Table 2.3).

Table 2.3. *AUCs comparisons proving an higher discriminant power of new spatial tasks compared to other standard tests. Only significant (p<.05) Z-tests are shown.*

	VOSP						MRT	Supra span imm.	Stroop		WCST persev	Fluency		TIB - QIV	Memory prose imm.	Rey words –imm.	Verbal memory	
	Screening	Obj. - 4	Space -5	Space -6	Space -7	Space -8			Time	Error		Verbal	Semantic				Delayed	Recognition
Objects recognition	--	3.88	--	--	--	--	--	--	4.11	2.34	5.14	--	--	--	--	--	--	--
Objects recall	--	3.86	--	--	--	--	--	--	4.53	2.78	5.65	--	--	--	--	--	--	--
Objects location	2.51	6.32	3.03	2.02	2.17	2.44	3.64	--	5.86	3.72	7.62	--	2.33	2.19	2.04			2.82
Map- first recall	2.75	6.68	3.53	2.40	2.56	3.03	3.80	1.97	6.37	4.03	9.19	2.06	2.73	2.49	2.42	2.00	2.05	2.51
Map- first location	2.78	6.73	3.48	2.46	2.61	3.09	3.94	2.03	5.03	2.77	6.84	--	2.07	--	--	--	--	--
Map- second recall	--	4.67	2.12	--	--	--	3.00	--	5.22	3.30	7.10	--	--	--	--	--	--	2.51
Map- second location	--	5.55	2.50	--	--	2.42	3.07	--	5.27	3.34	6.20	--	--	--	--	--	--	2.01
Learning- from action	2.69	6.50	3.41	--	2.42	3.04	4.08	--	5.76	3.47	2.42	--	2.15	2.15	--	--	--	--
Learning- from vision	2.54	6.29	3.07	--	2.22	2.92	3.70	--	7.14	3.62	7.41	--	2.36	2.36	--	--	--	--
Learning- from map	--	5.02	2.62	--	--	--	3.18	--	4.98	2.95	7.85	--		2.02	--	--	--	--

2.3.2 Neuroimaging data

Voxel-based morphometry analyses

MCI patients showed more atrophy than control group in middle and superior frontal gyrus (usually involved in spatial working memory tasks) and in cerebellum and uncus, the anterior extremity of the parahippocampal gyrus (see Figure 2.1 and Table 2.4).

Figure 2.1. *Areas of significant decrease of grey matter values in MCI patients compared to healthy elderly controls*

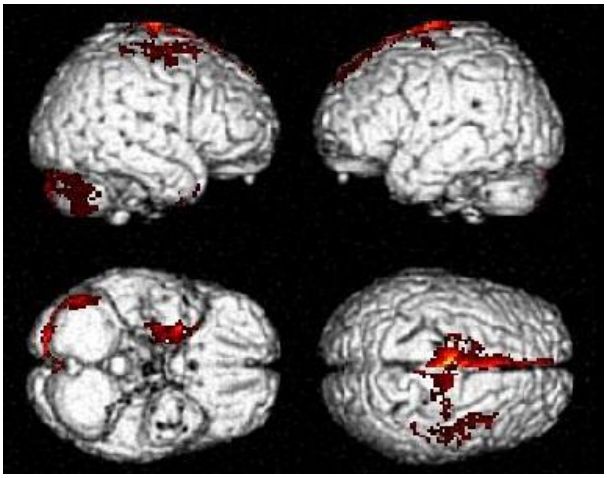


Table 2.4. *T-Test: Areas of significant decrease of grey matter values in MCI patients compared to healthy elderly controls*

Brain area	**Left/Right**	**Brodmann area (BA)**	**Z value at local maximum**	**Talairach coordinates**		
				x	**y**	**z**
Superior Frontal Gyrus	L	6	5.13	-2	2	76
	R	8	5.13	42	16	60
Middle Frontal Gyrus	R	6	4.30	42	-4	66
Uncus	R	36	4.72	28	4	-36
	R	20	4.47	30	4	-44
Cerebellum	R		4.35	24	-90	-40

Voxel-based regression analyses

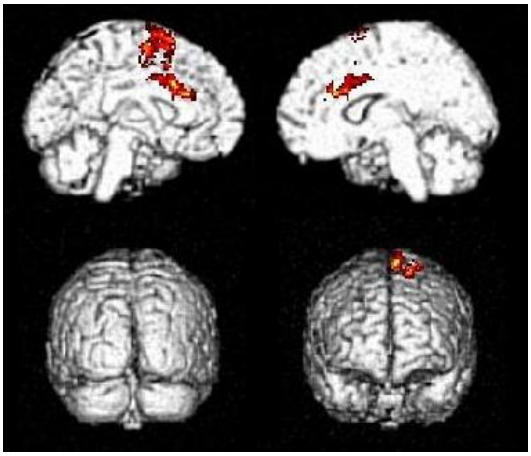
MCI patient and healthy elderly controls group

Objects location test

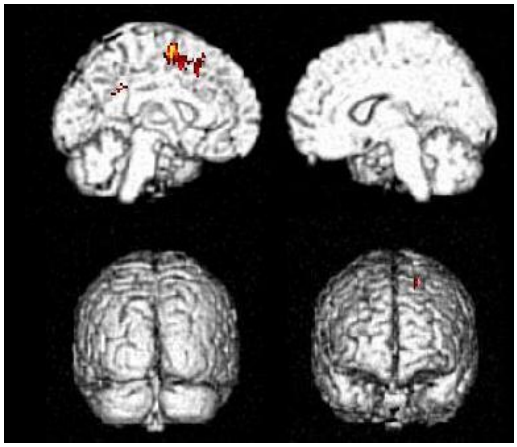
For the object's location task in the MCI group, significant correlations were found in left cingulate gyrus, superior and medialfrontal gyrus, left and right anterior cingulate (see Figure 2.2a). Healthy elderly, instead, showed significant correlations in medial frontal gyrus, left cingulate gyrus and insula (see Figure 2.2b).

Figure 2.2. *Areas of significant correlation between matter volume and objects location test in a) MCI; b) healthy elderly controls*

a) MCI



b) Healthy elderly controls

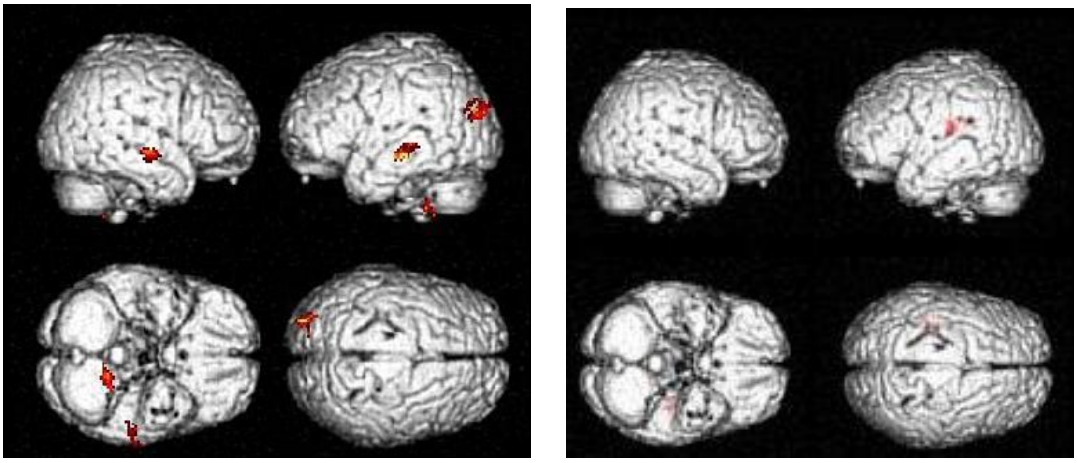


Map learning test

Map learning test in the MCI group showed significant correlations in left cuneus, middle and superior temporal gyrus, insula and cerebellar tonsil (see Figure 2.3a). Instead, the healthy elderly group showed correlation with insula and lentiform nucleus (see Figure 2.3b).

Figure 2.3 *Areas of significant correlation between grey matter volume and map learning test in a) MCI; b) healthy elderly controls*

a) MCI b) Healthy elderly controls

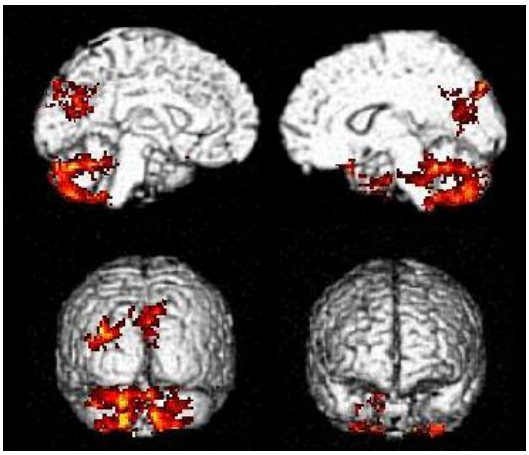


Route learning test

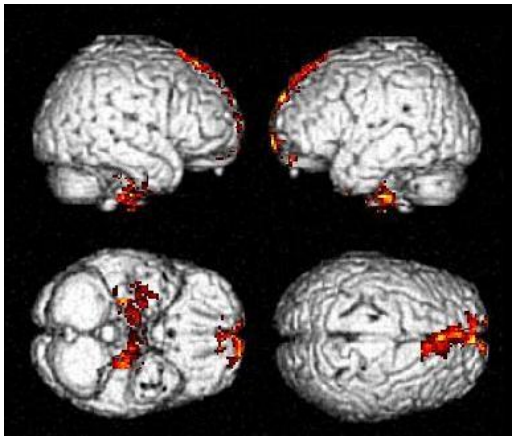
For the action route learning test, MCI showed significant correlations with the inferior, middle and superior temporal gyrus, cuneus, precuneus, uvula, fusiform gyrus and rectal gyrus (Figure 2.4a). In the healthy elderly group significant correlations were found in left and right superior frontal gyrus, right uncus and inferior temporal gyrus (Figure 2.4b).

Figure 2.4. *Areas of significant correlation of grey matter volume and route learning test (action) in a) MCI; b) healthy elderly controls*

a) MCI



b) Healthy elderly controls

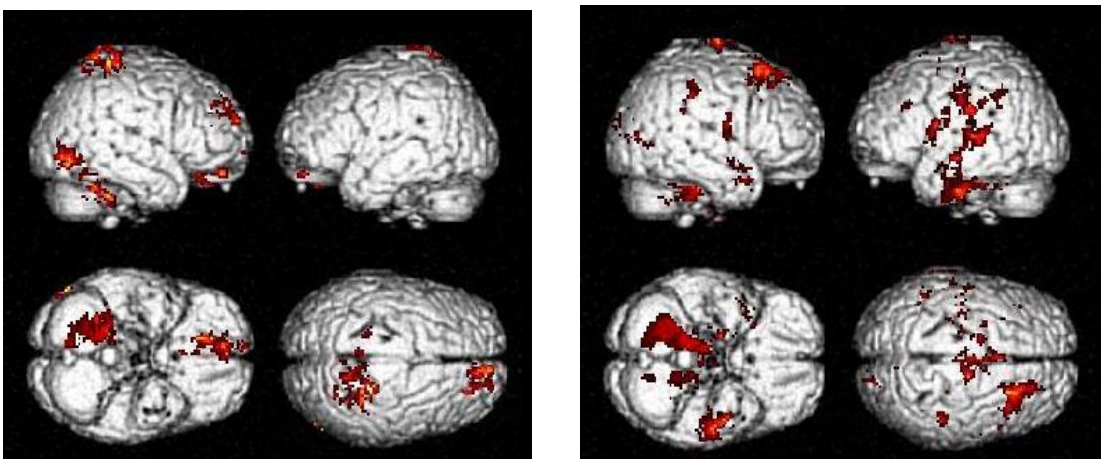


Spatial questionnaires

Questionnaire of sense of direction presented significant correlations in the MCI group in postcentral gyrus, inferior temporal gyrus, middle occipital gyrus and medial frontal gyrus (see Figure 2.5a). In the healthy elderly group there were significant correlations in precentral gyrus, cingulate gyrus, culmen and superior frontal gyrus (see Figure 2.5b).

Figure 2.5. *Areas of significant correlation between grey matter volume and sense of direction in a) MCI; b) healthy elderly controls*

a) MCI b) Healthy elderly controls



Finally for the questionnaire of spatial anxiety in MCI significant correlations were found only in the inferior frontal gyrus, superior temporal gyrus and left claustrum. In the healthy group correlations were found in left precuneus, cingulate gyrus, left caudate and posterior cingulate (see Figure 2.6a and 2.6b).

Figure 2.6 *Areas of significant correlation between grey matter volume and spatial anxiety in a) MCI; b) healthy elderly controls*

a) MCI b) Healthy elderly controls

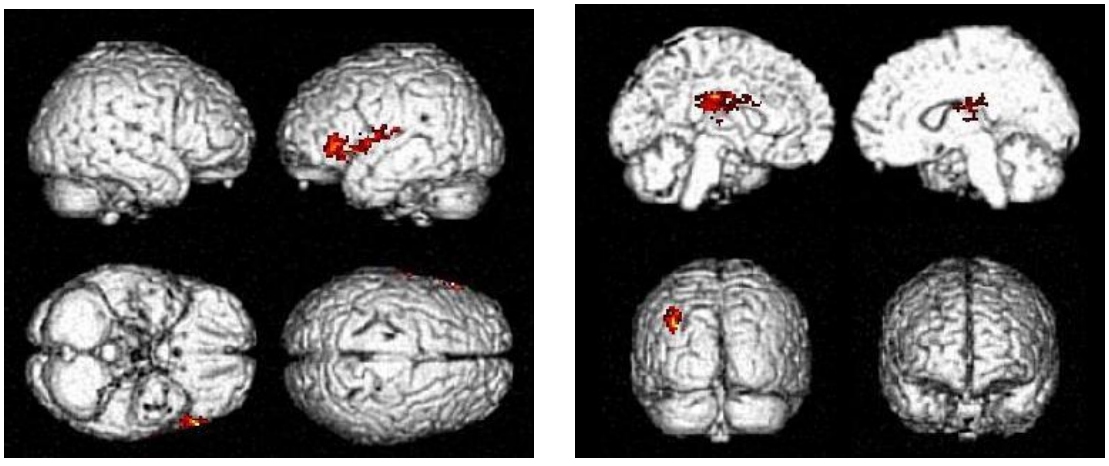


Table 2.6. *Areas of significant correlation between grey matter density and spatial performance in controls.*

Brain area	**Left/Right**	**Brodmann area (BA)**	**Z value at local**	**Talairach coordinates**		
				x	**y**	**z**
a) Objects location test						
Cingulate Gyrus	L	24	5.14	-6	19	28
Anterior Cingulate	L	24	3.95	-4	28	21
	R	24	3.64	6	21	25
Superior Frontal Gyrus	L	6	4.09	-4	5	66
Medial Frontal Gyrus	L	6	3.45	-10	6	53
b) Map Learning test						
Cuneus	L	18	4.27	-18	-78	24
	L	19	4.40	-26	-88	30
Superior Temporal Gyrus	R	22	4.42	53	-14	-4
	L	21	3.87	-49	-23	-4
Insula	R		3.34	42	-10	-1
Cerebellar Tonsil	L		4.32	-14	-47	-38
Middle Temporal Gyrus	L	21	3.33	-53	-28	-9
c) Route learning test (action)						
Cuneus	R	19	5.16	6	-76	31
Precuneus	L	31	4.01	-18	-63	22

Middle Temporal Gyrus	L	19	4.00	-40	-81	19
Uvula	L		4.48	-34	-61	-24
Fusiform Gyrus	R	37	4.25	34	-39	-13
Superior Temporal Gyrus	R	22	3.78	45	-16	-8
	R	38	3.73	22	16	-26
Inferior Temporal Gyrus	R	20	3.53	63	-13	-23
Rectal Gyrus	R	11	3.73	10	16	-24
d) Questionnaire SOD						
Postcentral Gyrus	R	5	4.11	32	-43	68
	R	3	3.69	24	-30	64
	R	7	3.60	16	-47	70
Inferior Temporal Gyrus	R	19	3.63	55	-72	-1
Middle occipital Gyrus	R	19	3.09	53	-70	-8
Medial Frontal Gyrus	R	10	3.14	12	52	-8
	R	11	3.12	8	50	-16
e) Spatial Anxiety						
Inferior Frontal Gyrus	L	47	3.50	-55	30	0
Superior Temporal Gyrus	L	38	3.27	-54	17	-9
Claustrum	L		3.16	-36	1	6

2.4 Discussion

Visuospatial data showed that MCI patients had significant lower performances in comparison with healthy elderly controls in objects recognition and location, map learning and route learning. Self-rating spatial questionnaires showed a significant difference between groups. The discriminant analyses revealed an elevated discriminative power of the new spatial battery in identifying MCI, analogue to other neuropsychological tests commonly used in clinical testing (i.e. Tower of London, Rey – delayed Osterrieth Complex Figure, VOSP-object 3), but also higher than other several standard tests, such as Stroop test, Wisconsin Card Sorting Test and semantic fluency test. The self-rating spatial questionnaires reported a less good discriminative capacity of MCI. Neuroimaging findings showed that MCI patients presents a higher level of cortical atrophy in memory-related regions (such as medio-temporal and frontal regions) and a different pattern of brain correlation between visuospatial abilities and grey matter values compared with healthy elderly controls.

The present cognitive data showed that MCI patients present a visuospatial deficit, mainly in landmarks recognition and location. It was found that both spatial sequential abilities measured through a route learning test and memory for spatial locations, assessed with a task of objects and location recognition were impaired in MCI. These findings confirmed previous evidence that visuospatial impairment may develop as an independent sign of neurodegenerative disease, possibly preceding the clinical onset of AD (Mapstone, Steffenella & Duffy, 2003), and it might manifest with a deficit in landmarks recognition in AD (Cherrier, Mendez & Perryman, 2001). These results might depend on the overloading effect of the attentional resources generating from landmarks in comparison to non-landmarks reference points. Furthermore object-location binding requires elevated cognitive resources and does not occur automatically in

AD patients (Kilb & Naveh-Benjiamin, 2007) whereas the processing of single spatial information should be automatic and cognitively less demanding (Hasher & Zacks, 1979). To support object-location binding in AD, some data showed that patients with AD are unable to represent in visual long-term memory the association between patterns and their spatial locations (Parra et al., 2010). Conversely, in healthy older adults, attentional resources can be effectively allocated to both object processing and object-space binding, hence showing better performance. Based on these suggestions, our data recollected on MCI patients, seems to suggest that the decline of visuospatial memory in the preclinical phase of dementia might be related to difficulties in object-location binding and in landmark memory.

Voxel-based morphometry analysis showed that MCI had higher level of atrophy in frontal and medio-temporal regions in comparison with healthy elderly controls. This result agreed with a recent study showing that medio-temporal regions are involved in topographical memory, not only hippocampus, and deficits in this neural network represent a marker of neurodegeneration (Pengas et al., 2012). These data are in agreement with previous results showing a damage of these memory-related circuit in MCI (Chetelat et al., 2002).

Moreover MCI presented a different pattern of correlation between grey matter density and visuospatial performance.

In the objects location task, both groups showed a positive correlation with anterior cingular regions, although MCI showed a more extensive cluster. Controls showed a significant involvement of medio-frontal and insular areas in comparison with MCIs in which there is also an involment of superior and medial frontal areas. Recent studies (Vetere et al., 2011) suggest the role of anterior cingulate cortex (ACC) for objects memory. The results of Study 2 supported the involvement of this network not only in objects recall but also in objects location. The

involvement of more extensive brain areas in MCI to support objects location performance might represent an altered neurobiological substrate responsible for the failure in this task.

It was also found a different cerebral involvement in the map learning score, indicated by the number of landmark recalled, between the two groups. Specifically, patients showed a more significant association with temporal and occipital areas (cuneus) whereas only insula and putamen were associated with map learning in healthy older group. In this task, which requires to remember and retrieve the name and the location of eight landmarks written on a map, the two groups engaged two different brain networks suggesting the use of different strategies: MCI patients seem to use a visual encoding strategy supported by temporo-occipital pathway (Cho & Kesner, 1996) whereas control group seems to engage structures related to subcortical area (putamen and insula) partially related to spatial working memory performance and spatial planning (Bor, Cumming, Scott & Owen, 2004). These differences might indicate a different neural organization of visuospatial functions in MCI compared to healthy elderly.

The performance of the route learning test from action, i.e. to learn the route from its execution following the examiner, in healthy controls was positively associated with grey matter values in medio-temporal lobe (uncus) and superior frontal gyrus, whereas in MCI it was associated with temporal and occipital structures (cuneus and precuneus). These data agree with the literature, showing in controls the involvement of medio-temporal and frontal areas in this task, which requires to memorize, image and recall sequential spatial information. Other authors evidenced that memorizing a route is a very complex task, which can be accomplished by different systems: sequences of learned responses, such as repeating a fixed route, depending on the striatum (Iaria et al., 2003), and mental representations permitting new routes, for example finding new shortcuts, depending on the hippocampus (Voermans et al., 2004). These data on

MCI showed that this visuo-spatial sequential memory task needs a widespread neural set of regions engaged in visuospatial and imagery processing (such as cuneus, precuneus and fusiform gyrus) to be accomplished.

Furthermore, spatial anxiety trait in healthy controls was negatively correlated with grey matter values in cingulate gyrus and parietal areas, such as precuneus, whereas MCI showed a significant correlation mostly with fronto-temporal areas. In healthy elderly group the level of spatial anxiety was related to structural variance of areas implicated in visuospatial processes, such as precuneus, confirming that the degree of spatial anxiety dimension can reflect the level of performance on spatial abilities (Gron et al., 2000). Additionally in healthy controls, spatial anxiety was correlated with the cingulate gyrus, involved in anxiety disorder (Holzschneider & Mulert, 2011). In MCI patients significant correlations were present in orbito-frontal cortex which is involved as well in anxiety modulation.

Finally, patients showed a significant correlation between the scores obtained in the questionnaire of sense of direction and grey matter values in fronto-temporal and occipital areas, whereas in the healthy elderly controls there was a positive correlation only with frontal areas, implicated in metacognition processes (Cosentino & Stern, 2005). These results suggested that in MCI patients the judgement of sense of direction is related to widely distributed regions, whereas in healthy controls mainly frontal structures, implicated in self-referential processes and judgement capacity, had a greater role. These different pattern might reflect an impairment of MCI patients in judgement abilities and self-referential decision making, which involves also the estimation of their own sense of direction.

The different pattern of correlation between regional grey matter values and visuospatial memory abilities in MCI patients compared with healthy elderly controls, suggested that the

visuospatial impairment in MCI is underpinned by a neurofunctional reorganization of spatial processes.

In conclusion, these findings support previous evidence that visuospatial memory decline exists in the preclinical phase of dementia (Bird et al., 2010) and provide empirical strength of the discriminant power of this new spatial battery in the early diagnosis of MCI. This evidence support that visuospatial evaluation should achieve a greater role in completing the diagnostic process of MCI.

Chapter 3

Study 3: Visual perceptual organization abilities in autopsy-verified dementia with Lewy bodies and Alzheimer's disease

3.1 Introduction

To give a more complete explanation about the role of spatial abilities in normal and pathological aging in this Chapter 3 it was also explored if a specific component of visuospatial domain, specifically visuo-perceptual ability (measure with the Hooper task), could play an important role in the differential diagnosis between Alzheimer's Disease and Dementia with Lewy Body.

Dementia with Lewy bodies (DLB) is now recognized as the second most common cause of dementia in older adults, exceeded only by Alzheimer's disease (AD; McKeith et al., 2005). DLB shares many clinical features with AD, including the insidious onset of cognitive deficits that gradually worsen over time and ultimately result in complete functional dependence.

Comparisons of the rate of cognitive decline in patients with autopsy-confirmed DLB or AD have yielded mixed results with some showing equal rates of cognitive decline (Helmes, Bowler, Merskey, Munoz, & Hachinski, 2003; Heyman et al., 1999; Johnson, Morris, & Galvin, 2005; Stern et al., 2001) and others showing more rapid decline in DLB than in AD (Galasko, Gould, Abramson, & Salmon, 2000; Kraybill et al., 2005; Olichney et al., 1998). Both disorders are marked by substantial individual variation in the progression rate (Helmes et al., 2003; Olichney et al., 1998), but this variability may be more pronounced in patients with DLB than in those with AD (Olichney et al., 1998).

Visuospatial deficits may be a particularly salient marker of DLB (Tiraboschi et al., 2006). The level of visuospatial impairment found in patients with DLB is disproportionately severe relative to the deficits that they exhibit in other cognitive domains (Aarsland et al., 2003; Hansen et al., 1990; Johnson et al., 2005). Prominent loss of visuospatial abilities is listed among the deficits that compose the cognitive syndrome of DLB (McKeith et al., 2005), and DLB patients consistently exhibit disproportionately severe deficits in visuospatial, visuoperceptual, and construction abilities relative to patients with "pure" AD (Aarsland et al., 2003; Ala, Hughes, Kyrouac, Ghobrial, & Elble, 2001; Galasko, Katzman, Salmon, & Hansen, 1996; Hamilton et al., 2004; Hansen et al., 1990; Johnson et al., 2005; Mori et al., 2000; Salmon et al., 1996).

Performance on construction tasks in Lewy body dementias is affected by impairments in visual perception and pre-attentive visual processing. These early aspects of bottom-up visual cognition are typically more impaired in Lewy Body dementias than AD, and likely play an important role in their more severe construction deficits (Possin, 2010). Calderon et al. (Calderon et al., 2001) compared patients with DLB to patients with AD on the Visual Object and Space Perception Battery (Warrington & James, 1991), a set of tasks that emphasize bottom-up aspects of visual cognition. DLB patients showed more severe impairments than AD patients on tests tapping both ventral stream (Fragmented Letters and Object Decision) and dorsal stream (Cube Analysis) aspects of visual perception. Similarly, Mosimann et al. (Mosimann et al., 2004) found that DLB patients showed more severe impairments than AD patients on tests tapping both ventral stream (tests of object and form perception) and dorsal stream function (tests of dot position and motion perception). Based on these and similar results, visual constructional apraxia is considered a prominent feature of DLB that may help clinically distinguish it from AD (Ala et

al 2001; Tiraboschi et al., 2006). It is less clear, however, whether this extends to pure visuoperceptual processes that do not involve construction or motor manipulation.

A widely-used visual information processing task that might be particularly sensitive to the presence and progression of DLB is the Hooper Visual Organization Test (VOT; Hooper, 1983). The VOT requires the perceptual and conceptual reorganization of the parts of a dissected visual object into a coherent whole so that the object can be identified and named. In its standard form, the VOT requires the integration of spatial and object identity information separately processed by dorsal and ventral visual neural circuits or "streams" that analyze different aspects of the visual scene (Lennie, 1998; Livingstone and Hubel, 1988; Merigan and Maunsel, 1993; Ungerleider and Mishkin, 1982). While the VOT does not appear to place heavy demands upon attention or executive functions, and does not involve construction or motor manipulation common to many visuospatial tasks, it does require confrontation naming ability that may be compromised in patients with AD (Bayles and Tomoeda, 1983; Hodges et al., 1991; Huff et al., 1986) but also in DLB with concomitant Alzheimer's disease pathology [i.e. the Lewy body variant of AD (Hansen et al., 1990)]. It is possible that these patients can effectively perform the perceptual integration aspect of the task, but score poorly because they are unable to correctly name the perceived objects.

Evidence for an important role of confrontation naming in VOT performance is mixed. Several studies have shown that the VOT performance of normal individuals (Paolo et al., 1996; Paul et al., 2001; Ricker and Axelrod, 1995) or patients with a variety of neurological disorders (Merten, 2005) is more strongly related to performance on visuospatial or visual-perceptual tasks than on tests of confrontation naming. It should be noted, however, that the VOT comprises common, easily-named objects and the impact of naming might only be observed in individuals

with some degree of anomia. This possibility is supported by a study of stroke patients with anomia that showed they were impaired on the standard version of the VOT, but significantly improved their performance on a multiple choice version that did not require naming (Schultheis et al., 2000). Further evidence for a role of naming in VOT performance is provided by a recent functional magnetic resonance imaging (fMRI) study in normal individuals (Moritz et al., 2005). When performing a version of the VOT that did not require overt naming, task-related activation was evident in cortical regions involved in visuospatial processing (i.e., bilateral superior occipital and posterior superior parietal cortex), object identification and semantic retrieval (i.e., lateral occipital and posterior inferomedial temporal cortex), and covert naming (i.e., left inferior/middle prefrontal gyrus). These latter studies indicate that semantic processes contribute to VOT performance, and suggest that performance on the standard version of the test needs to be corrected for anomia when used as a measure of higher-order visual information processing.

The present study was designed to evaluate the utility of the VOT in clinically differentiating between DLB and AD dementia. While other tests such as Clock Drawing test or block construction may be more specific in measuring visual constructional apraxia, the VOT was chosen because it requires visuoperceptual and mental reorganization, without requiring a physical manipulation. Although it is known that patients with AD are often impaired on the VOT (Paxton et al 2006), no studies have been done with autopsy-confirmed cases and little is known about how effective this measure of visual-perceptual ability might clinically differentiate between AD and DLB patients.

Furthermore, since our patients are autopsy-confirmed, we also examined the influence of concomitant AD pathology on VOT performance and on the other cognitive domains: high and low Braak stage DLB subgroups were compared. Neuropathologically, Lewy bodies are

requisite for a diagnosis of Lewy body disease, but most brains of patients with autopsy-proven DLB (i.e. cases with dementia during life and Lewy body disease at autopsy) also display concomitant AD pathology in the form of diffuse plaques, neuritic plaques and neurofibrillary tangles [i.e. the Lewy body variant of Alzheimer's disease (Hansen et al., 1990)]. If the visuoperceptual deficit in patients with DLB primarily reflects Lewy body pathology, there should be little difference in VOT performance of DLB patients with high or low AD-Braak stages. If, on the other hand, the visuoperceptual deficit is related to AD pathology, then those DLB patients with high AD-Braak stages should performance worse on the VOT than those with low AD-Braak stages.

3.2 Methods

3.2.1 Participants

Patients with dementia who were eventually confirmed at autopsy to have DLB (n=28) or AD (n=115) were included in the present study. All patients had been participants in the University of California, San Diego (UCSD) Alzheimer's Disease Research Center (ADRC), through which they received yearly physical, neurologic, and neuropsychological assessments. Eligible participants met the following inclusion criteria: 1) autopsy revealed no significant pathological process (e.g., hippocampal sclerosis, metabolic encephalopathy, or infarct with a clinical history of stroke) other than DLB or AD, 2) a comprehensive behavioral, motor, and neuropsychological battery, including the Hooper Visual Organization Test (VOT), had been completed at one of the annual evaluations, and 3) they scored at least 14 on the Mini-Mental State Examination (MMSE) at the year of the VOT evaluation. It should be noted, however, that many of these patients were tested before DLB clinical criteria (McKeith et al., 1996) had been

developed. A group of cognitively-healthy elderly individuals (n=85) who served as normal controls (NC) in the UCSD ADRC and completed the VOT at one of the annual evaluations was included in the present study for comparison to the patient groups.

The mean age, years of education and scores on the Mini-Mental State Examination (MMSE) and Mattis Dementia Rating Scale (DRS) for the three groups are shown in Table 3.1. The groups did not differ significantly in age [$F(2,228)=2.22$; $p=.11$, $_p\eta^2=.02$] or education [$F(2,228)=0.39$; $p=.68$, $_p\eta^2=.003$]. The three groups differed on the MMSE [$F(2,228)=58.76$; $p<.001$, $_p\eta^2=.34$] and DRS [$F(2,228)=66.48$; $p<.001$, $_p\eta^2=.37$]. Post-hoc group comparisons with Tukey's Least Significant Difference (LSD) test ($p<.05$) showed that AD and DLB patients performed significantly worse than NC participants on each of these tests, but did not differ significantly from each other.

Informed consent to participate in the present investigation was obtained at the point of entry into the longitudinal study from all patients or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

Table 3.1 *The mean (and standard deviation) age, years of education, Mini-Mental State Examination (MMSE) score, and Mattis Dementia Rating Scale (DRS) score of normal control (NC) participants and patients with autopsy-verified Alzheimer's disease (AD) or Dementia with Lewy Bodies (DLB).*

	NC (n = 85)	**AD (n = 115)**	**DLB (n = 28)**
Age (years)	71.58 (8.7)	74.06 (8.8)	74.18 (8.2)
Years of Education	14.85 (3.0)	14.46 (3.3)	14.80 (3.3)
MMSE Score	29.47 (0.8)	24.43 (4.3)	24.04 (4.6)
Mattis DRS Score	139.19 (4.0)	122.37 (13.6)	118.96 (14.4)

Neuropathologic examination and Diagnosis

Autopsy was performed within 12 hours of death using a protocol described by Terry et al. (1981). Briefly, the left hemibrain was fixed by immersion in 10% formalin for 5–7 days. Paraffin-embedded blocks from midfrontal, rostral superior temporal and inferior parietal neocortex, anterior cingulate gyrus, posterior cingulate gyrus, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons were cut at 7-μm thickness for hematoxylineosin (H & E) and thioflavin-S counts. Total plaques, neuritic plaques, neurofibrillary tangle (NFT), and Lewy body counts were determined by the same examiner (LAH) using the same criteria. A modified Braak stage was obtained for each case using methods described by Hansen et al. (1990). Briefly, the modified Braak stage for AD pathology involves counting the number of NFT in at least five neuron clusters in layer two of the entorhinal cortex and then averaging the results. Cases with modified Braak Stage I to IV have fewer than 18 tangles on average in layer two of the entorhinal cortex and sparse neocortical tangles. Modified Braak Stage V cases have moderate numbers of tangles in at least two

neocortical sections. In modified Braak Stage VI, all neocortical areas assessed have at least moderate numbers of tangles. Lewy bodies were absent in cases of "pure" AD.

The DLB cases met consensus criteria for the pathologic diagnosis of DLB based on H & E staining and antiubiquitin immunostaining, and anti-α-synuclein immunostaining. Cases were only construed as DLB if Lewy bodies were found in the locus coeruleus, substantia nigra, and/or nucleus basalis of Meynert, as well as in the neocortex. Because all cases categorized as DLB had neocortical as well as brainstem Lewy bodies, they would all fall into either the limbic (transitional) or neocortical categories proposed in the 1996 consensus guidelines for the pathologic diagnosis of DLB (McKeith et al., 1996). Furthermore, all DLB cases were neocortical Stage V or VI according to the proposed Lewy body–based staging of brain pathology related to sporadic Parkinson disease. Cases were not classified as DLB if Lewy bodies were only found in the amygdala. Of the 28 DLB, 15 achieved a high Braak stage of V or VI, indicative of notable cortical neurofibrillary tangle formation, and 13 achieved a low Braak stage (i.e., I-IV).

3.2.2 Procedure

Participants were tested with the Hooper VOT and an extensive battery of neuropsychological tests in a single session at the UCSD ADRC. The test battery has been described in detail (Salmon & Butters, 1992). It included measures of memory, language, executive function, attention, and visuospatial abilities. Participants were tested individually in a quiet, well-lit room.

Hooper Visual Organization Test. The Hooper VOT (Hooper, 1983) is a neuropsychological instrument designed to measure an individual's ability to visually organize

perceptually fragmented stimuli. The test consists of line drawings of 30 relatively common objects that are fragmented into two or three pieces. The fragments for each object are arranged randomly on a stimulus card. The fragmented object drawings were presented, one at a time, to the participant who was asked to mentally reassemble the pieces and verbally identify each object. The participant was allowed one minute to respond for each item and was encouraged to guess if no response was provided within the time limit. Correct responses were awarded one point and responses that correctly identified, but did not name, the object were awarded a half point. A standard VOT score was calculated as the sum of points awarded for all 30 items. The standard administration of the VOT was immediately followed by a non-standard naming task in which participants were asked to name those objects that they did not correctly identify in the fragmented condition when the whole (i.e., non-fragmented) object was presented in a line drawing. The participant was allowed 20 seconds to respond for each item and was encouraged to guess if no response was provided within the time limit. Correct responses were awarded one point and responses that correctly identified, but did not name, the object were awarded a half point. A VOT naming score was calculated by summing the point values for items receiving full or partial credit in the fragmented and whole-object depictions. This VOT naming score was then used to generate a derived VOT score [(VOT score / VOT naming score) * 100)] that controls for the contribution of naming ability to VOT performance. Both the standard and derived VOT scores were used in analyses that follow.

Data Analysis

Statistical analyses were completed using SPSSv20. Group differences in demographic and neuropsychological data, including VOT scores, were compared using one-way analysis of

variance (ANOVA). Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. Post-hoc pair-wise group comparisons were made with Tukey's Least Significant Difference (LSD) test ($p<.05$) when the one-way ANOVA was significant. The influence of concomitant AD pathology in patients with DLB on the performance of the VOT and other cognitive tests was examined by comparing DLB subgroups with high or low AD-Braak stages using Student's t-tests. Cohen's *d* was used to measure effects sizes for these analyses.

3.3 Results

3.3.1 Hooper Visual Organization Test (VOT)

The mean VOT, VOT-naming, and derived VOT scores are shown for the three participant groups in Table 3.2. The groups differed on each of these measures [VOT: $F(2,228)=37.01$; $p<.001$, $_p\eta^2=.25$; VOT-naming: [$F(2,228)=23.69$; $p<.001$, $_p\eta^2=.17$; derived VOT: [$F(2,228)=31.78$; $p<.001$, $_p\eta^2=.22$]. Post hoc comparisons with LSD tests showed that DLB patients scored significantly lower than both AD patients ($p<.05$) and NC participants ($p<.05$) on all three VOT measures. In addition, AD patients scored significantly lower than NC participants on all three measures (all p's$<.05$).

Table 3.2 *The mean (and standard deviation) scores achieved by normal control (NC) participants and patients with autopsy-verified Alzheimer's disease (AD) or Dementia with Lewy Bodies (DLB) on the standard Hooper Visual Organization Test (VOT) and the naming component of the VOT. The mean (and standard deviation) derived VOT score that corrects for naming performance is also shown.*

	NC (n=85)	**AD (n=115)**	**DLB (n=28)**
VOT score	24.19 (3.2)	19.13 (5.6)	16.73 (6.96)
VOT naming	29.79 (0.5)	28.78 (1.7)	27.52 (2.8)
VOT derived	81.18 (10.4)	66.03 (17.7)	59.60 (18.4)

Exploratory analyses were carried out to compare the VOT performance of DLB patients with high or low levels of concomitant AD pathology (i.e., DLB-High Braak versus DLB-Low Braak). The two DLB groups did not differ significantly in age (DLB-High Braak: mean=73.80, sd=9.8; DLB-Low Braak: mean=74.62, sd=6.2; t(26)=0.26; p=.80, *d*=.10), education (DLB-High Braak: mean=14.47, sd=2.9; DLB-Low Braak: mean=15.15, sd=3.8; t(26)=0.54; p=.59, *d*=.20), or MMSE scores (DLB-High Braak: mean=22.73, sd=4.5; DLB-Low Braak: mean=25.54, sd=4.3; t(26)=1.67; p=.11, *d*=.61). However, the DLB-High Braak group (mean=113.20, sd=13.8) scored significantly lower than the DLB-Low Braak group (mean=125.62, sd=12.5) on the Mattis DRS (t(26)=2.48; p=.02, *d*=.86).

There were no significant differences in the VOT [t(26)=0.46; p=.65, *d*=.32], VOT-naming [t(26)=0.70; p=.49, *d*=.27], and derived VOT [t(26)=0.44; p=.66, *d*=.17] scores of DLB patients with high or low AD-Braak stages (see Table 3.3). This remained the case when DRS scores were used as a covariate to adjust for group differences in level of global cognitive impairment [all F's<1; all ${}_p\eta^2$<.04].

Table 3.3. *The mean (and standard deviation) standard Hooper Visual Organization Test (VOT) score, VOT naming score, and derived VOT score corrected for naming performance are shown for subgroups of patients with DLB with high or low Braak stage for Alzheimer's disease pathology.*

	DLB-Low Braak stage 0-IV (n = 13)	**DLB-High Braak stage V-VI (n = 15)**
VOT score	17.31 (5.9)	16.25 (6.1)
VOT naming	27.92 (2.5)	27.17 (3.1)
VOT derived	61.27 (17.8)	58.15 (19.5)

3.3.2. Neuropsychological Assessment

The mean scores achieved on the additional neuropsychological tests by NC participants and patients with DLB or AD are shown in Table 3.4. One-way ANOVAs showed that the three groups differed significantly on all cognitive measures (all p's<.001). Post-hoc comparisons showed that DLB and AD patients performed worse than NC participants on all tests. The DLB and AD patients differed significantly only on tests of visuospatial ability: the DRS construction subscale and the copy condition of the Clock Drawing Test.

Comparison of DLB subgroups showed that DLB-High Braak patients scored significantly worse than DLB-Low Braak patients on tests of language (Boston Naming Test and semantic category verbal fluency) and memory (CVLT and Logical Memory Test) (see Table 3.5). Notably, the DLB-High Braak and DLB-Low Braak groups did not differ significantly on tests of visuospatial ability.

Table 3.4 *Mean (and standard deviation) neuropsychological test scores achieved by normal control (NC),patients with Alzheimer's disease (AD), and patients with DLB. DRS=Dementia Rating Scale; CVLT= California Verbal Learning Test.*

Cognitive Test	NC (n=85)	AD (n=115)	DLB (n=28)	Significance Test	Post-hoc
Attention/WM					
Trail-Making Test A	42.26 (15.0)	76.09 (38.9)	84.15 (47.9)	F(2,222)=29.23; p<.001, $_p\eta^2$=.21	NC > AD, DLB
DRS Attention	36.29 (0.9)	35.46 (1.5)	35.15 (1.5)	F(2,224)=13.01; p<.001, $_p\eta^2$=.11	NC > AD, DLB
Executive Functions					
Wisconsin Card Sort Test	5.48 (1.0)	3.45 (2.1)	2.73 (2.1)	F(2,219)=39.40; p<.001, $_p\eta^2$=.27	NC > AD, DLB
Phonemic Fluency (FAS)	41.94 (13.3)	30.40 (13.4)	26.26 (15.2)	F(2,224)=22.33; p<.001, $_p\eta^2$=.17	NC > AD, DLB
Trail-Making Test B	92.35 (36.1)	198.18 (88.9)	215.58 (105.4)	F(2,214)=53.01; p<.001, $_p\eta^2$=.33	NC > AD, DLB
Language					
Boston Naming Test	28.02 (1.8)	22.88 (6.0)	21.85 (6.5)	F(2,224)=30.22; p<.001, $_p\eta^2$=.22	NC > AD, DLB
Category Fluency	48.55 (11.8)	28.97 (12.6)	24.78 (11.4)	F(2,222)=72.52; p<.001, $_p\eta^2$=.40	NC > AD, DLB
Visuospatial Function					
Clock Drawing	2.83 (0.4)	2.14 (0.8)	1.85 (0.9)	F(2,224)=28.99; p<.001, $_p\eta^2$=.21	NC > AD, DLB
Clock Copy	2.91 (0.3)	2.66 (0.6)	2.19 (1.0)	F(2,222)=15.09; p<.001, $_p\eta^2$=.12	NC > **AD > DLB**
DRS Construction	5.59 (0.7)	5.11 (1.1)	4.52 (1.1)	F(2,224)=13.96; p<.001, $_p\eta^2$=.11	NC > **AD > DLB**
Block Design Test	43.08 (10.1)	29.11 (14.9)	25.22 (17.6)	F(2,224)=31.02; p<.001, $_p\eta^2$=.22	NC > AD, DLB
Memory					
CVLT Learning 1-5	49.59 (12.2)	24.66 (13.9)	22.24(14.5)	F(2,216)=92.11; p<.001, $_p\eta^2$=.46	NC > AD, DLB
CVLT Short Delay	10.06 (3.4)	2.76 (3.7)	3.20 (3.4)	F(2,216)=105.21; p<.001, $_p\eta^2$=.50	NC > AD, DLB
CVLT Long Delay	9.99 (3.6)	2.59 (4.0)	3.00 (3.7)	F(2,214)=93.87; p<.001, $_p\eta^2$=.47	NC > AD, DLB
CVLT Discriminability	92.16 (5.9)	70.78 (17.0)	73.42 (14.9)	F(2,212)=60.13; p<.001, $_p\eta^2$=.37	NC > AD, DLB
Logical Memory Immed.	27.41 (6.7)	12.44 (9.3)	11.16 (9.6)	F(2,218)=82.55; p<.001, $_p\eta^2$=.43	NC > AD, DLB
Logical Memory Delay	22.73 (8.2)	6.95 (9.7)	6.08 (7.8)	F(2,217)=81.11; p<.001, $_p\eta^2$=.43	NC > AD, DLB

Table 3.5 *Mean (and standard deviation) neuropsychological test scores achieved by patients with DLB with High or Low Braak stages for concomitant Alzheimer's disease pathology. DRS=Dementia Rating Scale; CVLT= California Verbal Learning Test.*

Cognitive Test	DLB Low Braak (n=13)	DLB High Braak (n=15)	Significance Test
Attention/WM			
Trail-Making Test A	78.54 (49.9)	89.77 (47.2)	t(24)=0.59; p=.56, *d*=.23
DRS Attention	35.54 (1.5)	34.78 (1.4)	t(25)=1.34; p=.19, *d*=.51
Executive Functions			
Wisconsin Card Sort Test	3.08 (2.5)	2.38 (1.4)	t(24)=0.86; p=.40, *d*=.34
Phonemic Fluency (FAS)	30.38 (16.8)	22.42 (12.9)	t(25)=1.38; p=.18, *d*=.52
Trail-Making Test B	196.50 (114.0)	234.67 (97.1)	t(22)=0.88; p=.39, *d*=.36
Language			
Boston Naming Test	25.69 (4.6)	18.29 (6.1)*	t(25)=3.56; p=.002, *d*=1.14
Category Fluency	30.23 (12.1)	19.71 (8.3)*	t(25)=2.65; p=.014, *d*=.92
Visuospatial Function			
Clock Drawing	1.92 (1.0)	1.79 (0.9)	t(25)=0.39; p=.70, *d*=.14
Clock Copy	2.38 (1.0)	2.00 (1.0)	t(25)=0.96; p=.35, *d*=.37
DRS Construction	4.61 (1.0)	4.42 (1.2)	t(25)=0.45; p=.65, *d*=.18
Block Design Test	27.84 (20.6)	22.79 (14.7)	t(25)=0.74; p=.47, *d*=.29
Memory			
CVLT Learning 1-5	27.69 (15.1)	16.33 (11.7)*	t(23)=2.09; p=.05, *d*=.78
CVLT Short Delay	4.08 (3.3)	2.25 (3.3)	t(23)=1.39; p=.18, *d*=.55
CVLT Long Delay	4.15 (4.0)	1.75 (3.0)	t(23)=1.69; p=.10, *d*=.65
CVLT Discriminability	77.25 (14.6)	69.58 (14.9)	t(22)=1.28; p=.22, *d*=.51
Logical Memory Imm.	14.84 (11.0)	7.17 (5.9)*	t(23)=2.15; p=.04, *d*=.80
Logical Memory Delay	10.15 (8.8)	1.67 (2.5)*	t(23)=3.23; p=.004, *d*=1.09

3.4 Discussion

The results of the present study indicate that visual perceptual organization ability, independent of constructional apraxia, is more impaired in DLB than AD. This deficit was evident when the test was administered and scored in its standard form, and when performance was adjusted for a deficit in the ability to name visually intact objects. The naming adjustment was warranted given that patients with DLB were significantly worse than AD in naming items, even when the items were presented in an intact form. The two groups were well-matched in terms of demographics and disease course so these factors are not likely to contribute to the observed differences.

The visual-perceptual organization deficit exhibited by patients with DLB is in accord with previous studies that show that these patients are more impaired on visuospatial, visuoperceptual, and construction tasks than patients with "pure" AD (Aarsland et al., 2003; Ala et al., 2001). Retrospective studies of patients with DLB have also demonstrated that these patients have greater impairment on visuoconstructive tests than patients with AD (Hansen et al., 1990: Salmon et al., 1996; Hamilton et al., 2004).Walker et al. (1997) demonstrated that patients with DLB performed worse than those with AD who were similar in overall degree of cognitive impairment on the praxis subtest of the Cambridge Cognitive Examination, including visuoconstructive tasks. Futhermore, Gnanalingham et al., (1996) pointed out the usefulness of the clock face test that assesses executive and visuospatial functioning in differentiating DLB from AD: patients with AD do well on the "copy" part of the test despite doing poorly on the "draw" part, while patients with DLB do equally poorly on both parts of the test. However, it is not clear if this disproportionate visuoperceptual deficit in DLB patients is limited to tasks that involve construction or motor manipulation or could be extended

to all visuoperceptual processes. Our results suggest that the disproportionate visuospatial deficits found in DLB patients extend to abilities that do not involve construction or motor manipulation; the VOT, in contrast to other visuospatial tasks used in previous studies, does not require physical manipulation.

We found that DLB subgroups divided according to their Braak Stage did not differ in VOT performance. This finding suggests that the severity of this deficit is not related to degree of concomitant AD pathology but might primarily reflect Lewy body pathology. Further studies are needed to determine if the severity of DLB pathology is related to the severity of these disproportionately visuoperceptual deficits.

In summary, the present results of Study 3 demonstrate that visual perceptual organization ability, independent of constructional apraxia, is more impaired in patients with autopsy-confirmed DLB than in patients with autopsy-confirmed pure" AD. The severity of this deficit is not related to stage of concomitant AD pathology, suggesting that it is primarily driven by more posterior cortical Lewy body pathology.

SUMMARY AND CONCLUSION

The field of spatial cognition has been evolving rapidly over the last few years, driven by convergence of results from both basic and clinical research. Spatial ability is involved in many cognitive tasks typically performed in everyday life, so it is important to accurately define and assess spatial ability in the context of everyday life. Recent studies also suggest that spatial abilities decline with normal aging, but it is not yet clear which spatial components decline during normal age-related cognitive decline, which are preserved, and at what point the spatial deficits become severe enough to suggest MCI or another degenerative disease.

The main goal of my research projects, developed in three studies, was to investigate different components of spatial ability in a population of healthy older people, in individuals affected by mild cognitive impairment, and in autopsy-verified patients with dementia, in order to (a) develop new, more ecological instruments for the assessment of spatial abilities, (b) verify whether the assessment of spatial abilities may help in discriminating between MCI and controls and be used as a marker of the onset of AD, and (c) be used in differential diagnosis between Alzheimer's Disease and Dementia with Lewy bodies.

In Study 1 I developed a spatial battery composed of new environmental spatial tests, (object recognition and location test, map learning test, and route learning test) with the aim of understanding the real spatial ability of individuals in their daily life, and also investigating the role of different components of spatial ability and their relationship with self-rating dimensions. Results confirm the *a priori* hypothesis, ascertaining the reliability of these new spatial tests in measuring different components

of spatial abilities: object memory, simultaneous spatial memory and sequential spatial memory. In addition these tests showed a relationship with self-rating spatial scales.

In the second study, to verify the efficacy of this new spatial battery in a clinical setting, it was explored its power to discriminate between individiuals with normal age-related decline and those with MCI. Indeed, considering the strong relationship between spatial deficits and specific neural networks, the assessment of the new spatial tests was also associated with a neuroimaging investigation, focusing on the neuronal correlates of these deficits in the two groups. The discriminant analyses revealed an elevated discriminative power of the new spatial battery in identifying MCI. Neuroimaging findings showed that MCI patients present a higher level of cortical atrophy in memory-related regions (such as medio-temporal and frontal regions) and a different pattern of brain correlation between visuospatial abilities and grey matter values compared with healthy elderly controls. This different pattern of correlation suggested that the visuospatial impairment in MCI is underpinned by a neurofunctional reorganization of spatial processes. In conclusion, the findings of the Study 2 support previous evidence that visuospatial memory decline exists in the preclinical phase of dementia, providing empirical strength of the discriminant power of the new spatial battery in the early diagnosis of MCI. After a 2 year follow-up period, further analysis will explore how many MCI will become demented, as well as the role of this spatial battery in predicting their degeneration.

Finally, to give a more complete explanation about the role of visuospatial abilities in pathological aging, Study 3 explored whether a specific component of the visuospatial domain (visuoperceptual ability) could play an important role in the differential diagnosis of Alzheimer's Disease and Dementia with Lewy bodies. Results

suggest that disproportionately severe visuospatial deficits, which are known to be prevalent in DLB patients, also extend to visuoperceptual abilities that do not involve construction or motor manipulation. This deficit reflects primarily Lewy Body pathology and is not related to the degree of concomitant AD pathology.

All of this evidence supports the main idea that visuospatial evaluation should have a greater role in normal and pathological aging, in understanding the daily life abilities of healthy older people, in completing the diagnostic process of MCI, and also helping in the differential diagnosis between different types of dementia.

RIASSUNTO

Le abilità spaziali sono coinvolte in molte attività della vita quotidiana, pertanto risulta importante valutarle e comprendere le sue ripercussioni nella vita di tutti i giorni. Recenti studi suggeriscono che le abilità spaziali peggiorano nell'invecchiamento normale, ma non è chiaro quali specifiche componenti declinano all'aumentare dell'età, quali sono preservate e quando il deficit spaziale diventa così severo da suggerire la presenza di un disturbo cognitivo lieve o di patologia degenerativa.

L'obiettivo principale della mia tesi di dottorato, sviluppata in tre diversi studi, è quello di esplorare lo sviluppo di deficit nelle abilità spaziali in una popolazione di anziani con invecchiamento normale, anziani con lieve compromissione cognitiva e pazienti con demenza degenerativa. Lo scopo della presente ricerca è dunque quello di a) sviluppare nuovi strumenti ecologici che ci consentano di valutare diverse componenti delle abilità spaziali, b) verificare se la valutazione delle abilità spaziali può aiutare nel discriminare tra compromissione cognitiva lieve e invecchiamento normale e se può essere considerata “marker” di demenza, c) valutare se le abilità spaziali possono giocare un ruolo e aiutare nella diagnosi differenziale tra Demenza di Alzheimer e Demenza a corpi di Lewy.

I risultati dello Studio 1 confermano le ipotesi *a priori*, sottolineando l’efficacia di questi nuovi test spaziali nel misurare diverse componenti delle abilità spaziali: memoria di oggetti, memoria spaziale simultanea e memoria spaziale sequenziale.

I risultati dello Studio 2 mostrano un elevato potere discriminativo delle nuove prove spaziali nel distinguere tra invecchiamento normale e compromissione cognitiva

lieve. Inoltre, i dati di neuroimaging mostrano un diverso pattern di correlazioni tra deficit spaziali e materia grigia nei due gruppi.

Infine, i risultati dello studio 3 mostrano deficit quantitativamente diversi tra il gruppo di pazienti con Demenza a corpi di Lewy e il gruppo di pazienti con Alzheimer in un test che valuta l'abilità visuopercettiva e che non richiede una manipolazione motoria. Si è dunque dimostrato che questo specifico deficit riflette un quadro di Demenza a corpi di Lewy ed è, invece, meno correlato con la patologia di Alzheimer.

Tutte queste evidenze supportano l'idea che la valutazione delle abilità spaziali giochi un ruolo fondamentale nell'invecchiamento sia normale che patologico.

REFERENCES

Aarsland, D., Litvan, I., Salmon, D., Galasko, D., Wentzel-Larsen, T., Larsen, J.P. (2003). Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 74(9)*, 1215–1220.

Aguirre GK, Detre JA, Alsop,DC, D'Esposito M (1996) The parahippocampus subserves topographical learning in man. *Cereb Cortex* 6, 823-829.

Ala, T.A., Hughes, L.F., Kyrouac, G.A., Ghobrial, M.W., Elble, R.J. (2001). Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 70*, 483–488.

Allen, G. L., Kirasic, K. C., Dobson, S. H., Long, R. G., & Beck, S. (1996) Predicting environmental learning from spatial abilities: An indirect route. *Intelligence, 22,* 327-355.

Arnou, R.C., & Thompson, B. (2000). Second order confirmatory factor analysis of the WAIS-III. Assessment, 7(3), 237–246.

Ashburner J, Friston KJ (2000) Voxel-Based Morphometry - The Methods. *Neuroimage* 11, 805-821.

Avants BB, Epstein CL, Grossman M, Gee JC (2008) Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 12, 26–41.

Barrash J (1998) A historical review of topographical disorientation and its neuroanatomical correlates. *Clin.Exp.Neuropsychol.* 20, 807-827.

Bayles, K.A., Tomoeda, C.K. (1983). Confrontation naming impairment in dementia. *Brain and Language, 19*, 98-114.

Bell-McGinty S, Lopez OL, Meltzer CC, Scanlon JM, Whyte EM, Dekosky ST, becker JT (2005) Differential cortical atrophy in subgroups of mild cognitive impairment. *Arch Neurol* 62, 1393–1397.

Bergh EA, 1948 A simple objective technique for measuring flexibility in thinking. *Journal of General Psychology.* 39, 15–22.

Bird CM, Chan D, Hartley T, Pijnenburg YA, Rossor MN, Burgess N. (2010) Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus* 20, 1154-1169.

Bloch I (2006) Spatial reasoning under imprecision using fuzzy set theory, formal logics and mathematical morphology. *International Journal of Approximate Reasoning* 41, 77–95.

Borella, E., Carretti, B., & De Beni, R. (2007). *Accertamento della Memoria negli Adulti [The evaluation of memory in adulthood]*. Firenze: Organizzazioni Speciali.

Bor D, Cumming N, Scott EL, Owen AM (2004) Prefrontal cortical involvement in verbal encoding strategies. *European Journal of Neuroscience* 19, 3365-3370.

Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A (2002) Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol Sci* 22, 443–447.

Calderon, J., Perry, R.J., Erzinclioglu, S.W., Berrios, G.E., Dening, T.R., Hodges, J.R. (2001). Perception, attention, andworking memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 70*, 157–164.

Carlesimo GA, Mauri M, Graceffa AM, Fadda L, Loasses A, Lorusso S, Caltagirone C (1998) Memory Performances in Young, Elderly, and Very Old Healthy Individuals versus Patients with Alzheimer's Disease: Evidence for Discontinuity Between Normal and Pathological Aging. *Journal of Clinical and Experimental Neuropsychology*. 20, 14-29.

Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC (2002) Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. *Neuroreport* 13, 1939–1943.

Cherry, K. E., & Park, D. C. (1993). Individual difference and contextual variables influence spatial memory in younger and older adults. *Psychology and Aging, 10,* 379–394.

Cherrier MM, Mendez M, Perryman K (2001) Route Learning Performance in Alzheimer Disease Patients. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology* 14, 159-168.

Cho YH, Kesner RP (1996) Involvement of entorhinal cortex or parietal cortex in long-term spatial discrimination memory in rats: Retrograde amnesia. *Behavioral Neuroscience* 110, 436-442.

Cornoldi, C., & Vecchi, T. (2003). *Visuo-spatial Working Memory and Individual Differences.* Hove: Psychology Press, UK

Cosentino S, Stern Y (2005) Metacognitive theory and assessment in dementia: Do we recognize our areas of weakness? *Journal of the International Neuropsychological Society* 11, 910–919.

Cushman LA, Stein K ,Duffy CJ (2008) Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology* 71, 888-895.

De Beni R, Pazzaglia F, Gardini S (2006) The role of mental rotation and age in spatial perspective-taking tasks: when age does not impair perspective-taking performance. *Applied Cognitive Psychology* 20, 807–821.

Della Sala S, Laiacona M, Spinnler H, Ubezio C (1992) A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. *Psychological Medicine* 22, 885-901.

Dubois B, Feldman H, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteri. *Lancet Neurol* 6, 734–746.

Dubois B, Feldman H, Jacova C, Cummings JL, DeKosky ST (2010) Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 9, 1118–1127.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003) Cellular networks underlying human spatial navigation. *Nature*, 425, 184-188.

Ekstrom, R. B., French, J. W., & Harman, H. H. (1976). *Manual for kit of factor-referenced cognitive tests.* Princeton: Educational Testing Service.

Farias ST, Mungas D, Reed BR, Harvey D, Cahn-Weiner D, De Carli C (2006) MCI is associated with deficts in everyday functioning. *Alzheimer Dis Assoc Disord* 20, 217-223.

Fasano F, Ganazzoli C, Gardini S, Sambataro F, Concari L, Caffarra P(2011) SyN based multimodal investigation on a small cohort of patients affected with Amnesic Mild Cognitive Impairment. *Proc. Intl. Soc. Mag. Reson. Med* 933.

Folstein MF, McHugh PR (1975) Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12, 189-198.

Fox, N.C., Warrington, E.K., Seiffer, A.L., Agnew, S.K. & Rossor, M.N. (1998). Presymptomatic cognitive defitits in individual at risk of familiar Alzheimer's disease. A longitudinal prospective study. *Brain, 121,* 1631-1639.

Fujimori M, Imamura T, Hirono N, Ishii K, Sasaki M , Mori E (2000) Disturbances of spatial vision and object vision correlate differently with regional cerebral glucose metabolism in Alzheimer's disease. *Neuropsychologia* 38, 135-1361.

Gainotti G, Marra C, Villa G (2001) A double dissociation between accuracy and time of execution on attentional tasks in Alzheimer's disease and multi-infarct dementia. *Brain* 124, 731-738.

Galasko, D.R., Gould, R.L., Abramson, I.S., Salmon, D.P. (2000). Measuring cognitive change in a cohort of patients with Alzheimer's disease. *Statistics in Medicine, 19,* 1421–1432.

Galasko, D., Katzman, R., Salmon, D.P., Hansen, L. (1996). Clinical and neuropathological findings in Lewy body dementias. *Brain and Cognition, 31*, 166–175.

Gnanalingham, K.K., Byrne, E.J., Thornton, A. (1996). Clock-face drawing to differentiate Lewy body and Alzheimer type dementia syndromes. *Lancet, 347,* 696–697.

Grön G, Wunderlich AP, Spitzer M, Tomczak R, Riepe MW (2000) Brain activation during human navigation: gender-different neural networks as substrate of performance. *Nature Neuroscience* 3, 404 – 408.

Hamalainen A, Tervo S, Grau-Olivares M, Niskanen E, Pennanen C, Huuskonen J, Kivipelto M, Hänninen T, Tapiola M, Vanhanen M, Hallikainen M, Helkala EL,

Nissinen A, Vanninen R, Soininen H (2007) Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *Neuroimage* 37, 1122–31.

Hamilton, J.M., Salmon, D.P., Galasko, D., Delis, D.C., Hansen, L.A., Masliah, E., et al. (2004). A comparison of episodic memory deficits in neuropathologically-confirmed Dementia with Lewy bodies and Alzheimer's disease. *Journal of the International Neuropsychological Society, 10*, 689–697.

Hansen, L., Salmon, D., Galasko, D.R., Masliah, E., Katzman, R., DeTeresa, R., et al. (1990). The Lewy body variant of Alzheimer's disease: A clinical and pathologic entity. *Neurology, 40*, 1–8.

Hasher L, Zacks RT (1979) Automatic and effortful processes in memory. *Journal of Experimental Psychology* 108, 356-388.

Hatcher, L .(1994), *A Step-by-Step Approach to Using the SAS System for Factor Analysis and Structural Equation Modeling*, Cary, NC: The SAS Institute, 325-339

Hebb DO (1961) Distinctive features of learning in the higher animal. In J. F. Delafresnaye (Ed.), *Brain mechanisms and learning* 37–46. Oxford, UK

Hegarty, M., Montello, D. R., Richardson, A. E., Ishikawa, T. and Lovelace, K. (2006) Spatial Abilities at Different Scales: Individual Differences in Aptitude-Test Performance and Spatial-Layout Learning. *Intelligence, 34*, 151-176).

Helmes, E., Bowler, J.V., Merskey, H., Munoz, D.G., Hachinski, V.C. (2033). Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. *Dementia and Geriatric Cognitive Disorders, 15*, 67–71.

Heyman, A., Fillenbaum, G.G., Gearing, M., Mirra, S.S., Welsh-Bohmer, K.A., Peterson, B., et al. (1999). Comparison of Lewy body variant of Alzheimer's disease

with pure Alzheimer's disease: Consortium to establish a registry for Alzheimer's disease, part XIX. *Neurology, 52,* 1839–1844.

Hodges, J.R., Salmon, D.P., Butters, N. (1991). The nature of the naming deficit in Alzheimer's and Huntington's disease. *Brain, 114,* 1547-1558.

Holzschneider K, Mulert C (2011) Neuroimaging in anxiety disorders. *Dialogues in Clinical Neuroscience* 13, 453-461.

Hooper, H.E. (1983). *Hooper Visual Organization Test (VOT) Manual.* Los Angeles, CA: Western Psychological Services.

Hort J, Laczo J, Vyhnalek M, Bojar M, Bures J, Vlcek C (2007) Spatial navigation deficit in amnestic mild cognitive impairment. *PNAS.* 104, 4042-4047.

Huff, F.J., Corkin, S., Growdon, J.H. (1986). Semantic impairment and anomia in Alzheimer's disease. *Brain and Language, 28,* 235-249.

Iachini I, Iavarone A, Senese VP, Ruotolo F, Ruggiero G (2009) Visuospatial memory in healthy elderly, AD and MCI: a review. *Curr Aging Sci*. 2, 43-59.

Iaria G, Petrides M, Dagher A, Pike B, Bohbot VD (2003) Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *J. Neurosci.* 23, 5945–5952.

Johnson, D.K., Morris, J.C., Galvin, J.E. (2005). Verbal and visuospatial deficits in dementia with Lewy bodies. *Neurology, 65,* 1232–1238.

Kaplan E, Goodglass H, Weintraub S (1983). *Boston Naming Test.* Philadelphia: Lee & Febiger.

Kilb A, Naveh-Benjamin M (2007) Paying attention to binding: Further studies assessing the role of reduced attentional resources in the associative deficit of older adults. *Memory & Cognition* 35, 1162-1174.

Kirasic, K. C. (2000). Age differences in adults' spatial abilities, learning environmental layout, and wayfinding behaviour. *Spatial Cognition and Computation, 2*, 117–134.

Kozlowski, L. T., & Bryant, K. J. (1977). Sense of direction, spatial orientation, and cognitive maps. *Journal of Experimental Psychology: Human Perception and Performance, 3,* 590-598.

Kraybill, M.L., Larson, E.B., Tsuang, D.W., Teri, L., McCormick, W.C., Bowen, J.D., et al. (2005). Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology, 64*, 2069–2073.

Lawton, C. A. (1994). Gender differences in way-finding strategies: Relationship to spatial ability and spatial anxiety. *Sex Roles, 30,* 765-779.

Lennie, P. (1998). Single units and visual cortical organization. *Perception, 27*, 889-935.

Likert, R., & Quasha, W. H. (1941). *Revised Minnesota Paper Form Board*. New York, NY: Psychological Corporation.

Linn, M.C., & Petersen, A.C. (1985). Emergence and characterization of sex differences in spatial ability: A meta-analysis. *Child Development, 56,* 1479-1498.

Livingstone, M.S., Hubel, D.H. (1988). Segregation of form, color, movement and depth: anatomy, physiology and perception. *Science, 240,* 740-749

Logie, R.H. (1995). *Visuo-spatial working memory*. Hove, UK: Erlbaum.

Mammarella, I. C., Cornoldi, C., Pazzaglia, F., Toso, C., Grimoldi, M., & Vio, C. (2006). Evidence for a double dissociation between spatial-simultaneous and spatial-

sequential working memory in visuospatial learning disabled children. *Brain & Cognition, 62,* 58-67.

Mammarella I.C., Toso C., Pazzaglia F. e Cornoldi C. (2008), *BVS-Corsi: Batteria per la valutazione della memoria visiva e spaziale*, Trento, Erickson.

Mapstone M, Steffenella TM, Duffy CJ (2003) A visuospatial variant of mild cognitive impairment. *Neurology* 60, 802-808.

McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., et al. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology, 65*, 1863–1872.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease. *Neurology* 34, 939.

McNaughton BL, Barnes CA, Gerrard JL, Gothard K, Jung MW, Knierim J, Kudrimoti H, Qin Y, Skagss WE, Suster K, Weaver KL (1996) Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *The Journal of Experimental Biology* 199, 173–185.

Mendez, M.F., Mendez, M.A., Martin, R., Smyth, K.A. & Whitehouse, P.J. (1990). Complex visual disturbances in Alzheimer's disease. *Neurology, 40*, 439-443.

Meneghetti C, De Beni R, Pazzaglia F, Gyselinck V (2011) The role of visuo-spatial abilities in recall of spatial descriptions: A mediation model. *Learning and Individual Differences* 21, 719–723.

Merigan, W.H., Maunsel, J.H.R. (1993). How parallel are the primate visual pathways? *Annual Review of Neuroscience, 16,* 369-402.

Merten ,T. (2005). Factor structure of the Hooper Visual Organization Test: A cross-cultural replication and extension. *Archives of Clinical Neuropsychology, 20,* 123-128.

Mori, E., Shimomura, T., Fujimori, M., Hirono, N., Imamura, T., Hashimoto, M., et al. (2000). Visuoperceptual impairment in dementia with Lewy bodies. *Archives of Neurology, 57,* 489–493.

Moritz, C.H., Johnson, S.C., McMillan, K.M., Haughton, V.M., Meyerand, M.E. (2004). Functional MRI neuroanatomic correlates of the Hooper Visual Organization Test. *Journal of the International Neuropsychological Society, 10,* 939-947.

Mosimann, U.P., Mather, G., Wesnes, K.A., O'Brien, J.T., Burn, D.J., McKeith, I.G. (2004). Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology, 63,* 2091–2096.

Olichney, J.M., Galasko, D., Salmon, D.P., Hofstetter, C.R., Hansen, L.A., Katzman, R., et al. (1998). Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology, 51,* 351–357.

Oltman, P., Raskin, E., & Witkin, H. A. (1971). *Embedded Figures Tests.* Palo Alto, CA: Consulting Psychologists.

Paolo, A.M., Cluff, R.B., Ryan, J.J. (1996). Influence of perceptual organization and naming abilities on the Hooper Visual Organization Test, A replication and extension *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 9,* 254-257.

Parra MA, Abraham S, Logie RH, Mendez LG, Lopera F, Della Sala S (2010) Visual short-term memory binding deficits in familiar Alzheimer's disease. *Brain* 133, 2702-2713.

Paul, R., Cohen, R., Moser, D., Ott, B., Zawacki, T., Gordon, N. (2001). Performance on the Hooper Visual Organization Test in patients diagnosed with subcortical vascular dementia: Relation to naming performance. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 14*, 93-97.

Paxton, J.L., Peavy, G.M., Jenkins, C., Rice, V.A., Heindel, W.C., Salmon, D.P. (2007). Deterioration of visual-perceptual organization ability in Alzheimer's disease. *Cortex, 43*, 967-975.

Pazzaglia, F., Cornoldi, C., & De Beni, R. (2000). Differenze individuali nella rappresentazione dello spazio: presentazione di un questionario autovalutativo [Individual differences in representation of space: presentation of questionnaire]. *Giornale Italiano di Psicologia, 3*, 627−650.

Pazzaglia, F., Poli, M., De Beni, R. *Orientamento e Rappresentazione dello Spazio. Attività per migliorare il Senso dell'Orientamento: leggere le mappe, memorizzare percorsi, organizzare viaggi.* Trento: Edizioni Erickson 2004.

Pengas G, Williams GB, Acosta-Cabronero J, Ash WJ, Hong JT, Izquierdo-Garcia D, Fryer TD, Hodges JR, Nestor PJ (2012) The relationship of topographical memory performance to regional neurodegeneration in Alzheimer's disease. *Frontiers in aging Neuroscience* 4, 1-10.

Pennanen C, Testa C, Laakso MP, Hallikainen M, Helkala EL, Hanninen T, Kivipelto M, Könönen M, Nissinen A, Tervo S, Vanhanen M, Vanninen R, Frisoni GB, Soininen H (2005) A voxel based morphometry study on mild cognitive impairment. *J Neurol Neuro- surg Psychiatry* 76, 11–4.

Perry RJ & Hodges JR (2000) Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. *Neurology* 54, 2277–2284.

Perry, E.K., McKeith, I., Thompson, P., Marshall, E., Kerwin, J., Jabeen, S., et al. (1991). Topography, extent, and clinical relevance of neurochemical deficits in dementia of Lewy body type, Parkinson's disease, and Alzheimer's disease. *Annals of the New York Academy of Science, 640*, 197–202.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC (2001) Current concepts in Mild Cognitive Impairment. *Arch Neurol*, 58, 1985-1992.

Possin, K.L. (2010). Visual spatial cognition in neurodegenerative disease. *Neurocase,16*, 466-487.

Raven JC, Court JH, Raven JH (1990) *Manual for Raven's Progressive Matrices and Vocabulary Scales - Section 2: Coloured Progressive Matrices.* Oxford: Oxford Psychologists Press.

Rey A (1964) *L 'examen clinique en psychologie [Clinical tests in psychology]*. Paris: Presses Universitaires de France.

Richardson AE, Montello DR, Hegarty M (1999) Spatial knowledge acquisition from maps and from navigation in real and virtual environments. *Mem Cognit* 27, 741–750.

Ricker, J.H., Axelrod, B.N. (1995). Hooper Visual Organization Test: Effects of object naming ability. *The Clinical Neuropsychologist, 9*, 57-62.

Salmon, D.P., Galasko, D., Hansen, L.A., Masliah, E., Butters, N., Thal, L.J., et al. (1996). Neuropsychological deficits associated with diffuse Lewy body disease. *Brain and Cognition, 31*, 148–165.

Sartori G, Colombo L, Vallar G, (1997) T.I.B.: Test di Intelligenza Breve per la valutazione del quoziente intellettivo attuale e pre-morboso. *La Professione di Psicologo*, 1, 2-24.

Schulteis, M.T., Caplan, B., Ricker, J.H., Woessner, R. (2000). Fractioning the Hooper: A multiple-choice response format. *The Clinical Neuropsychologist, 14*, 196-201.

Shallice T, 1982. Specific impairments of planning. *Philosophical Transactions of the Royal Society B: Biological Sciences* 298, 199–209.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H (2004) Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 23, 208-219.

Smith SM (2002) Fast robust automated brain extraction. *Hum Brain Mapp* 17, 143-155.

Spinnler H, Tognoni G (1987) *Gruppo Italiano per lo Studio Neuropsicologico dell'Invecchiamento: Standardizzazione e taratura italiana di test neuropsicologici.* Ital J Neurol Sci.

Stern, Y., Jacobs, D., Goldman, J., Gomez-Tortosa, E., Hyman, B.T., Liu, Y., et al. (2001). An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer disease. *Archives of Neurology,58*, 460–465.

Stroop, JR(1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18 (6), 643–662.

Tiraboschi, P., Salmon, D.P., Hansen, L.A., Hofstetter, R.C., Thal, L.J., Corey-Bloom, J. (2006). What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain, 129*, 729–735.

Ungerleider, L.G., Mishkin, M. (1982). Two cortical visual systems. In Ingle, D.J., Mansfield, R.J.W., Goodale, M.S. (Eds), *The Analysis of Visual Behavior.* Cambridge: MIT.

Vetere G, Restivo L, Cole CJ, Ross PJ, Ammassari-Teule M, Josselyn SA, Frankland PW (2011) Spine growth in the anterior cingulate cortex is necessary for the consolidation of contextual fear memory. *Proc Natl Acad Sci U S A* 108, 8456–8460.

Vandenberg, S.G. & Kuse, A.R. (1978). *Mental rotations, a group test of three-dimensional spatial visualization.* Perceptual and Motor Skills, 47, 599-604.

Vecchi, T., Richardson, J. T. E., & Cavallini, E. (2005). Passive storage versus active processing in working memory: Evidence from age-related variations in performance. *European Journal of Cognitive Psychology, 17,* 52-539.

Voermans NC, Petersson KM, Daudey L, Weber B, Van Spaendonck KP, Kremer HP, Fernandez G (2004) Interaction between the human hippocampus and the caudate nucleus during route recognition, *Neuron* 43, 427–435.

Voyer, D., Voyer, S., & Bryden, M. (1995). Magnitude of sex differences in spatial abilities: A meta-analysis and consideration of critical variables. *Psychological Bulletin,117,* 250-270.

Zhang, H, Sachdev P S, Wen W, Kochan NA, Crawford JD, Brodaty H, Slavin MJ, Reppermund S, Draper B, Zhu W, Kang K, Trollor JN (2012). Gray matter atrophy patterns of mild cognitive impairment subtypes. *Journal of the neurological sciences* 315, 26–32.

Walker, Z., Allen, R.L., Shergill, S., Katona, C.L. (1997). Neuropsychological performance in Lewy body dementia and Alzheimer's disease. *British Journal of Psychiatry, 170,* 156–158.

Warrington, E. K., James, M. (1991). *The Visual Object and Space Perception Battery (VOSP).* Bury St. Edmunds, England: Thames Valley Test Co.

Wechsler D (1981) Manual for the Wechsler Adult Intelligence Scale—Revised. *Psychological Corporation, New York.*

Wolbers T, Hegarty M (2010) What determines our navigational abilities? *Trends in Cognitive Sciences* 14, 3.

Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T (2009) Bayesian analysis of neuroimaging data in FSL. *NeuroImage* 45, 173-186.