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Verbal and Visuospatial Abilities in Alzheimer's Patients

Keywords: Alzheimer's disease; Ageing; Cognitive Performances; Verbal abilities; Visuospatial abilities

Abstract

Introduction: In normal ageing, cognitive performance changes according to the neuronal modifications that occur in the brain. The elderly, as compared to younger individuals, have better verbal than visuospatial performance. In Alzheimer's Disease (AD), neuropathological changes generally produce disorders of memory, language and semantic knowledge. However, recent studies have shown that early-stage AD may present visuospatial deficits. The aim of this research is to study the cognitive changes of verbal and visuospatial performance that occur during AD.

Method: Were recruited 30 subjects with mild and moderate AD and 30 healthy older-adult controls (NC). Both AD and NC participants were administered neuropsychological tasks in addition to the MMSE, a standardized cognitive screening test and experimental tasks. Neuropsychological tests have been divided according to ability and/or the brain areas involved, balancing them to access verbal and visuospatial. Data were analysed with the Statistic II software.

Results: The Mann-Whitney U Test, analysis of variance with repeated measures (ANOVA) and Bonferroni post hoc showed significant differences between the AD and NC group in verbal and visuospatial performance. The AD group was significantly worse than normal controls group both in verbal than visuospatial tasks. Our data indicate that the visuospatial ability appears to be less deteriorated than the verbal skill in AD.

Conclusion: The findings suggest that visuospatial access was more efficient than verbal access to detect patients who were at the early stage of cognitive decline. The progress of Alzheimer's disease cannot solely be considered as due to more rapid ageing: cognitive degeneration is a more elaborate process that affects different aspects of cognitive performance.

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Introduction

The concept of differential rates of maturation and decline for various cognitive functions has long been demonstrated. In recent years, researchers have hypothesized that functional reorganization in the brain is correlated with age [1]. Several studies have investigated the cognitive performances in healthy ageing [2,3], showing a more rapid loss of visual spatial than verbal skills [4], associate with a change on visual working memory [5], and a decline of divergent thinking [6]. The results of these studies suggest that functional reorganization of the brain occurs throughout the ageing process. Documented functional and structural neocortical hemispheric asymmetries in individuals with normal cognition [7-9], and a more rapid decline of the right than the left hemisphere corroborate this [10].

Alzheimer's Disease (AD) is one of the most common causes of cognitive decline [11]. Neuropathological alterations typical of the early stages of AD - cortical atrophy, neurofibrillary tangles, and a reduction in cerebral synapses connectivity - affect first the medial temporal regions of the cerebral cortex and then progress to the frontal lobes and finally to the parietal lobes [12]. Additionally, there is a progressive decrease in the degree of asymmetry, especially in the inferior parietal lobe [13]. Clinically, these pathological changes present as early deficit of attention, verbal learning, memory, working memory and executive functions, language, and semantic knowledge [14-25]. Changes of mood and affection often accompany the early stage of cognitive decline with the possibility of delusions and hallucinations in later stages [26].

Some reviews of studies about neuropsychological deficit of Mild Cognitive Impairment (MCI) and preclinical AD showed an onset characterized especially by verbal deficit [27,28]. Nevertheless, clear deficits in visuospatial abilities appear in the early stages of AD [29-31], particularly on tasks of elaboration and integration of visual information (e.g. copy of a complex picture, mental rotation exercises) [32,33]. Furthermore researchers have also found altered fMRI activity during visuospatial tasks among AD patients [34].

In a longitudinal study about the cognitive decline in preclinical AD, Johnson and his collaborators compared four cognitive factors, global, verbal and working memory, and visuospatial, and showed early change of visuospatial ability, which would seem to decrease fast [35]. These results are consistent with studies about normal cognitive abilities in aging [4], but it would seem contrary to the literature of the field [27,28]. Backman and collaborators realized a meta-analysis of studies about cognitive deficit in preclinical AD and, in addition to registering deficits in multiple cognitive domains, emphasized the difference of cognitive resources employed in verbal and visuospatial tasks [36].

Intrigued by this diversity of results, we decided to conduct a study about cognitive deficits in the early stages of disease, subdividing the tests on the basis neuropsychological abilities and cognitive resources used, balancing them to access verbal or visuospatial. Furthermore, because one of the abilities more and early compromised in AD is the memory [37,38], for not to influence the performance of the subjects, we excluded tests of short and long term memory, except tasks of semantic memory.

The aim of this work was to model the cognitive decline in early stage of Alzheimer's Disease, verifying the difference between verbal

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Table 1: Demographic characteristics of AD patients and control group.

Groups	N°	Age *x (sd)*	Education *x (sd)*	MMSE *x (sd)*
AD	30 (M 10, F 20)	76.06 (6.66)	6.8 (2.88)	20.60 (3.29)
NC	30 (M 14, F 16)	70.16 (7.84)	8.06 (3.81)	28.90 (1.14)

Number of participant; age in years; years of education; Mini Mental State Examination; ***x*** = means; *sd* = standard deviation.

Table 2: Example of an Item of the Semantic Knowledge Task (SKT).

Guitar	Correct Answer
Is it man-made?	Y
Is it used to cook?	N
Does it have strings?	Y
Is it wooden-made?	Y
Can be used with one hand?	N

and visuospatial abilities in AD subjects. The hypothesis to be tested is that in the patients with mild-to-moderate AD, the visuospatial abilities are early affected like as verbal ones. The confirm of the existence of early deficit of both the verbal than the visuospatial abilities it's crucial for early detection of disease and opens the way to several interventions of prevention and treatment. Indeed, recently published guidelines suggest that the most opportune time to intervene in AD is during the preclinical phase of disease [39]. This is a stage in which individuals are defined as clinically normal but have accumulation of amyloid in their brains, neurodegeneration and subtle cognitive and behavioural impairments. The knowledge resulting from our research could be used for the construction of more sensitive non-invasive diagnostic tests for the early detection of dementia, and for the implementation of informatics applications of cognitive stimulation intended for subjects with subtle cognitive changes.

Methods and Materials

Subjects

Sixty subjects, all native Italian speakers, were recruited into two groups for this study. One group was composed of 30 mild-to-moderate AD patients (10 male, 20 female) with an average age of 76.06 years old (SD = 6.66). The normal control group (NC) was composed of 30 healthy seniors (14 male, 16 female), with an average age of 70.16 years old (SD = 7.84). To the extent possible, participants in the two groups were matched for age, gender and education (Table 1). AD patients were diagnosed by neurologists independent of the study, according to the NINCDS–ADRDA criteria [40]. Mini Mental State Examination (MMSE) scores ranged from 14 to 26 (moderate = 14 to 21; mild = 21 to 26) in the AD group and were greater than 27 for the NC group [41]. To confirm the presence of neurodegeneration, brain imaging (TAC or MRI) and laboratory tests were available for all patients. Exclusionary criteria for enrolment in this study (experimental and control subjects) included less 5 years of education, a history of alcohol or drug abuse, or a history of neurological or psychiatric disorders. Participants in the study provided written consent; when appropriate, caregivers for the patients with AD signed the consent form. The protocol was approved by the Ethics Review Committee of the University of L'Aquila (Italy) and was conducted in accordance with the Declaration of Helsinki (Table 1).

Materials

Both AD and NC participants were administered neuropsychological tasks in addition to the MMMSE [41], a standardized cognitive screening test.

Neuropsychological tests have been divided according to ability and/or the brain areas involved, balancing them to access verbal and visuospatial. The tests with verbal access were:

Token Test (TOK): It's a standardized test used to evaluate the level of verbal comprehension through the request for execution of simple verbal commands. In addition to the verbal comprehension, in the execution of the task is involved attention and working memory. Scores corrected for age and education [42,43], and the brain area activated is the portion of temporal lobe in the dominant hemisphere [44].

Boston Naming Test (BNT): Is a standardized test that provides a measure of the subject's ability to naming black and white drawings of common objects [45]. The left fronto-temporal lobe and the limbic system are involved in the naming tasks [46].

Verbal Fluency (FAS): It is a standardized test generally used to assess the frontal functions [47]. Evaluates the subject's ability to search the words in the personal lexicon through lexical and semantic access [48,49].

Semantic Knowledge Task (SKT): It is an experimental task composed of the 40 stimulus words used in the other experimental tasks (SAT). The task was composed of 43 items: 3 practice items and 40 test items. For each of the items, we created 5 yes = no semantic memory questions (e.g., is the object "natural"? see Table 2) according to the Giffard's Semantic Knowledge Question [50]. There were a total of 200 questions. Questions were printed sequentially for each word–stimulus. Each item was composed of 1 stimulus noun and 5 questions. The subjects were requested to answer yes or no to each question asked by the examiner. The order of the questions and the order of the stimulus word with respect to the NT and SAT were

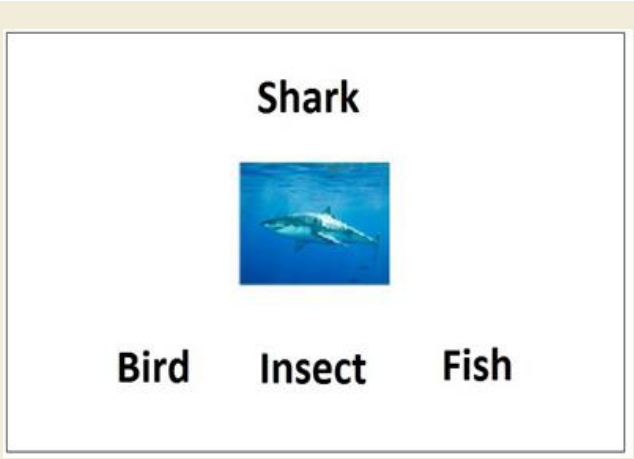

Figure 1: Example of an Item of experimental task SAT.

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Table 3: Means and Standard Deviations of Raw Scores of the Sample.

Test	AD	NC
	X (*sd*)	X (*sd*)
Token Test	10.40 (7.16)	32.48 (2.37)
Boston Naming Test	23.30 (9.05)	41.10 (9.54)
Verbal Fluency (FAS)	29.97 (12.65)	66.93 (16.45)
Semantic Knowledge Task (SKT)	160.50 (10.46)	179.06 (1.01)
Raven's Coloured Progressive Matrices	17.70 (6.39)	37.09 (2.35)
Visual Discrimination Test	10.93 (3.59)	18.30 (2.71)
Paper Folding test	6.43 (2.99)	14.93 (3.03)
Semantic Association Task (SAT)	142.50 (26.16)	177.93 (2.46)

randomized. There was an equal number of "yes" and "no" correct answers throughout the task. The score was based on pass = fail and ranged from 0 to 200 (Table 2).

To evaluate the ability with visuospatial access were administered the following tests:

Raven's Coloured Progressive Matrices (CPM): It is a standardized multiple-choice paper-and-pencil test and it consists of a series of visual pattern matching, gestalt completion and analogy problems pictured in non representational designs. The CPM is considered a test of logical-deductive reasoning based on visuospatial data, which involved the frontal lobe [51].

The Visual Discrimination Test (WEP): The Test of Visual Discrimination is a standardized multiple-choice test that involves the ability to discriminate among closely related versions of geometric designs. The brain area activated in this task is the temporo-parietal lobe [52].

Paper Folding test (P&F): It is a standardized construction tasks designed to assess the ability of the subject to realize the mentally manipulation of three-dimensional stimuli. The examiner cuts holes in folder paper so that the subject can see how the paper is cut but not how the unfolded paper looks. The parietal lobe and the frontal medial gyrus are involved in visuospatial tasks [53].

Semantic Association Task (SAT): The SAT test is developed to assess semantic association ability. This test is composed of 180 items, plus 3 item of initial training. Each item, presented in a booklet (A4; horizontal orientation), consisted of one of 40 words-target (20 for living and 20 for non-living), a picture (size: 5 x 6 cm) and three choice: only one is semantically associated to the stimulus-target, according to the semantic associative categories indicated by Goodglass [54]: superordinate, function, attribute, contiguity, part-hole. The other two words have the function of distracters that were similar to the target word in terms of length, frequency of use and concreteness (Figure 1). Each of the 40 targets was presented five times, one for associative categories. Only the category "function" has 20 representations because there were no appropriate and unanimously recognized specific functions for living things. Subjects were told the following: "I will show you a series of pictures and read words aloud to you. You must tell me what word goes best with the picture". The examiner pronounced the name of the pictures and the words. The subjects then had to say (or point to) the word that was semantically associated with the target picture. Respondents received one point for each correct response. The total score range was 0-180 and representing the sum of all correct answers. The test is extensively described in studies by De Federicis and Di Giacomo et al. [55,56]. The brain areas involved in semantic processing are the anterior temporal lobe region and the inferior prefrontal cortex (Figure 1) [57].

Procedure

AD patients were recruited from the San Salvatore Hospital, L'Aquila (Italy), and the Italian Hospital Group (Rome). Control subjects were recruited from the AD patients' families and from Elderly Associations, and were tested in the Department of Clinical Medicine, Public Health, Life and Environmental Science of University of L'Aquila. All subjects were tested individually by a technician who was unaware of the study goals and who recorded all responses. The order of the tasks was pseudo-random (counterbalanced across participants) to prevent fatigue from being a factor on the same test.

A summary of the neuropsychological assessment of the AD and NC participants is presented in Table 3.

Data analysis

To compare performances on tests from different functional domains and with different numbers of items, all results were converted to z scores. The z score of an individual was calculated as follows:

$$z\text{score} = \frac{\text{subject data} - mean\text{NC}}{ds\text{NC}}$$

Inspection of Multiple Regression revealed two extreme cases, one in the AD and one in NC group, and these were removed from the analysis. The data were examined for normality (tested with the Kolmogorov-Smirnov and Lilliefors test). In case of non-normal distributions, the analyses were carried out by the non-parametric Mann-Whitney U Test. For normally distributed data, parametric tests were used, specifically analysis of variance with repeated measures (ANOVA). The association between baseline cognitive performance and prospective cognitive decline was assessed similarly, using repeated measures ANOVA with covariance (ANCOVA), with MMSE score, age, and education as covariates. We calculated partial eta squared (η^2) as a measure of the effect size and characterized the effect sizes as small (η^2 = 0.04), medium (η^2 = 0.25), or large

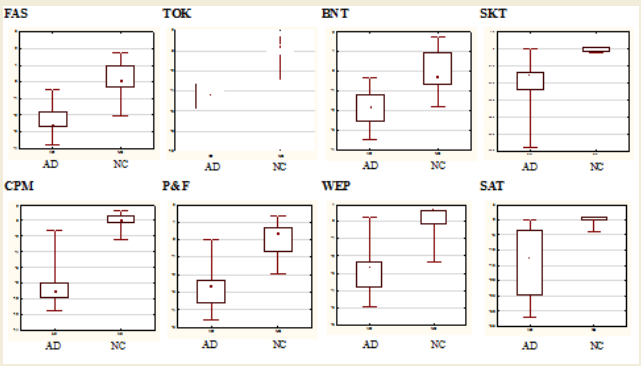

Figure 2: Box-plots illustrating distribution of cognitive test in AD and NC. FAS = Verbal Fluency; TOK = Token Test; BNT = Boston Naming Test; SKT = Semantic Knowledge Task; CPM = Raven's Coloured Progressive Matrices; P&F = Paper Folding Test; WEP = Visual discrimination test; SAT = Semantic Association task.

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Table 4: Analysis of Variance with repeated measures Groups (2) X composite scores of laterality (2) (ANOVA).

	F	gf	*p*	partial η^2
Groups	548.45	1	0.000	0.907
Composite scores of laterality	7023.08	1	0.000	0.992
Iteration	82.51	1	0.000	0.595

Groups = NC e AD; Composite scores of laterality = VERBAL and SPATIAL.

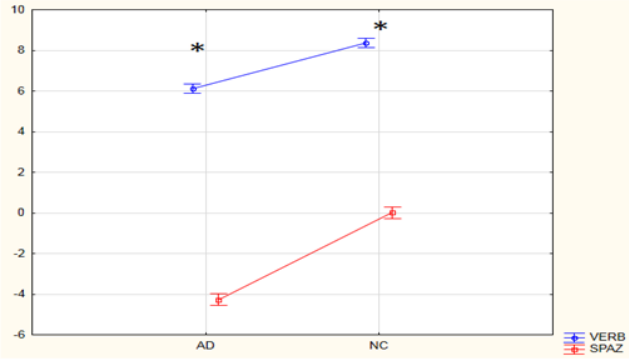

Figure 3: Trends of AD and NC on the basis composite scores of laterality. * = significant difference between verbal and visuospatial composite scores (Bonferroni Post-hoc).

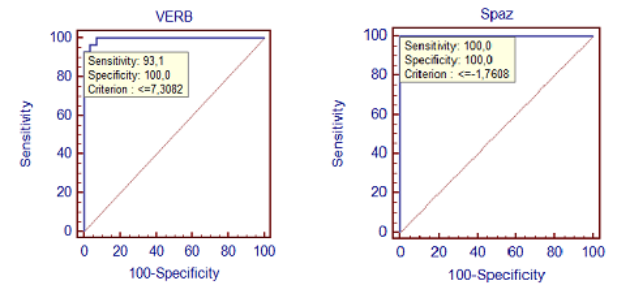

Figure 4: ROC curve of verbal and visuospatial coefficients.

(η^2 = 0.64) [58]. A Bonferroni post hoc analysis was conducted to determinate the level of interaction. To gauge the impairment of verbal and visuospatial ability, two composite scores were developed: "verbal composite score" (VERB), calculating the mean z scores of the verbal tasks (FAS, Token Test, SKT), and a "spatial composite score" (SPAZ), resulting by the mean of z scores of the visuospatial tests (CPM, Visual Discrimination Test, SAT). The Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the accuracy of the variables to discriminate normal from pathological cases [59].

Data were analysed with the Statistic II software [60]. We adopted α level of 0.05 for each analysis.

Results

The NC group was statistically younger ($p < 0.05$) than the AD sample, although the age ranges and frequency distributions were similar, and the actual differences were quite small. There was no statistically significant difference between the levels of education of the two groups ($p = 0.148$). The gender distribution was studied by frequency table, and the distribution was not statistically significant within the two groups (p = 0.287). Subjects with AD performed significantly worse than the controls on all tests ($p = 0.000$, Mann-Whitney U Test) (Figure 2).

To evaluate the presence of differences between verbal and visuospatial performance in the two groups, we obtained a "verbal composite score" (VERB) and a "spatial composite score" (SPAZ), calculating the mean z scores of the only tests that involve the same brain areas. Therefore, the coefficient "VERB" is the result of the average of z scores of FAS, Token Test, and SKT, and "SPAZ" coefficient is the mean z scores of CPM, Visual Discrimination Test, and SAT. The assumption of normality of the samples was confirmed by Kolmogorov-Smirnov test: VERB $p = 0.20$; SPAZ $p = 0.05$.

The 2 x 2 ANOVA (groups x VERB and SPAZ composite scores) was conducted to compare the performances of the AD and NC groups. The analysis demonstrated a main effect for the groups, $F(1) = 548.45$, p = 0.000, partial $\eta^2 = 0.90$, and of the composite scores, $F(1) = 7023.08$, $p = 0.000$, partial $\eta^2 = 0.99$, and a significant interaction between the groups and the composite scores, $F(1) = 82.51$, $p = 0.000$, partial $\eta^2 = 0.59$ (Table 4).

Bonferroni's *post-hoc* analysis revealed that the AD group's VERB and SPAZ composite scores were both lower than the NC composite indexes. In both groups (AD and NC) there was a significant difference between the verbal and visuospatial indexes ($p = 0.000$), with the lowest spatial index than the verbal. Figure 3 shows the cognitive-performance trends of the two groups (Figure 3).

The ROC curve analysis was used to evaluate the accuracy of the new variables (VERB and SPAZ) to discriminate normal from pathological cases. For the VERB coefficient, the results showed high accuracy: AUC = 0.996, with 100% specificity and 93.1% sensitivity; similar results were obtained for the SPAZ coefficient: AUC = 1.000, with 100% specificity and 100% sensitivity, confirming the high accuracy of two variables to discriminate normal from pathological subjects. The Figure 4 shows the ROC curve of VERB and SPAZ coefficients (Figure 4).

To determine whether the interaction between groups and verbal and visuospatial performances was due to the confounding influence of the MMSE score, we conducted an analysis of covariance with the MMSE as a covariate. The analysis showed the significant interaction effect of groups x composite scores (VERB, SPAZ), $F(1) = 17.87$, $p < 0.000$, partial $\eta^2 = 0.245$.

To determine whether the interaction between groups and verbal and visuospatial abilities was due to the confounding influence of age, we conducted an analysis of covariance with age as the covariate. Analysis showed an interaction between groups and composite scores, $F(1) = 65.30$, $p < 0.000$, partial $\eta^2 = 0.542$.

To determine whether the interaction between groups and verbal and visuospatial performances was due to the confounding influence of education, we conducted an analysis of covariance with the level of education as a covariate. The analysis again showed a significant interaction effect between groups and composite scores, $F(1) = 77.52$, $p < 0.000$, partial $\eta^2 = 0.584$.

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To evaluate the difference in verbal and visuospatial performance in mild and moderate dementia, we divided the pathological group on the basis of value of MMSE: mild deterioration, between 21-26; moderate, 14 to 20. The result is a group of n. 13 subjects with mild deterioration [age X = 75.15 (*sd* 6.17), education X = 6.61 (*sd* 3.37), MMSE X = 23.35 (*sd* 1.44)], and a group of n. 16 subjects with moderate deterioration [age X = 76.93 (*sd* 7.32), education X = 7.06 (*sd* 2.56), MMSE X = 18.02 (*sd* 1.92)]. The 2 x 2 ANOVA (mild and moderate groups x VERB and SPAZ composite scores) was conducted to compare the performances of two pathological groups. The analysis demonstrated a main effect for the groups, $F(1) = 9.59$, p = .004, partial $\eta^2 = .26$, and of the composite scores, $F(1) = 3157.36$, p = 0.000, partial $\eta^2 = 0.99$, but not a significant interaction between the groups and the composite scores, $F(1) = 0.101$, p = 0.752, partial $\eta^2 = 0.003$, confirming the presence of a severe visuospatial deficits in the mild stage of disease.

Discussion

The aim of this work was to model the cognitive decline in early stage of Alzheimer's Disease, verifying the difference between verbal and visuospatial abilities in AD subjects. Two samples of subjects-one composed of subjects with mild-to-moderate AD and one of NC subjects free from neurological pathology-were compared on MMSE, standardized cognitive screening test, and two experimental tasks. Neuropsychological tests have been divided according to ability and/or the brain areas involved, balancing them to access verbal and visuospatial, and, for not to influence the performance of the subjects, we excluded tests of short and long term memory, except tasks of semantic memory.

In line with our hypothesis, the findings indicate that AD, compared to controls, affects both verbal than visuospatial abilities in early stage of disease. Moreover, the cognitive impairment does not to follow a homogeneous trend: the visuospatial abilities seem to suffer a more rapid deterioration. The findings suggested that visuospatial input was more efficient than verbal input to detect patients who were at the early stage of cognitive decline. This finding is consistent with the studies of Johnson [35], which suggested that visuospatial deficit may occur early, even in preclinical stages. However, a large number of studies have found verbal performance deficits in the early stages of dementia [27]. An explanation for this trend could be derived from the analysis of the studies considered in a review by Collie & Maruff [28]. The authors highlight the widespread use in the early diagnosis of tests that involve verbal abilities. Our analysis, however, showed high accuracy to discriminate normal from pathological subjects both verbal tasks than visuospatial ones. Greater detection of verbal deficit in the early stages of disease may indeed depend on large use, in clinical practice, the verbal tasks that usually require most and simple administration. Furthermore, since not supported by the language and verbal reasoning, visuospatial tasks may be more difficult to resolve.

A growing body of research suggests that subtle cognitive changes during the clinical and preclinical phase of AD can be detected as brain asymmetry on cognitive tasks [61]. Jacobson and collaborators, in accordance with this theory, studies 20 cognitively normal elderly adults who were in a preclinical phase of AD and compared them to 20 age- and education-matched normal control subjects through a series of cognitive tests. They found a statistically difference between verbal (Boston Naming Test) and spatial (Test Block Design) standardized scores, supporting the thesis of cognitive asymmetry and highlighting the utility of asymmetric cognitive profiles in identifying individuals at risk for AD [62]. On the other hand, some studies have shown that there is not always a correspondence between brain asymmetry in AD and cognitive performance. A recent study by Balasubramanian and collaborators [63], conducted on subjects with AD neuropathology and on the very elderly (over 90 years old) with no dementia, reported that AD neuropathology at autopsy was not associated with the trajectory of cognitive performance. The authors found no significant difference in cognitive performance over time, based on plaque or tangle staging, and suggested searching for causes other than AD neuropathology that may affect cognition in the very elderly. However, several researches documented a reduction of brain asymmetry in AD subjects [64]. Studies about the lateralization of cognitive deficits in subgroups of AD patients with mild dementia showed that discrepancies between language and visuospatial deficits in patients with early AD are related to asymmetrical reductions in cerebral cortical [65], especially in the inferior parietal lobule [66]. Similar results were obtained by studies on healthy elderly show a reduction of cerebral asymmetry [1,67]. By comparing regional brain activation of young adults and elderly subjects during tasks of episodic and semantic memory, it was shown that the young adults had activation of the left prefrontal cortex, while the elderly individuals experienced bilateral activation of prefrontal cortex [1]. Similar results were obtained by Stebbins [67], who demonstrated that young people, on both abstract and concrete-language tasks, had almost double the activation in the left prefrontal cortex than in the right, in comparison, the asymmetry of activation disappeared among the elderly participants. In healthy seniors, therefore, there is a reduction of cerebral asymmetry, meaning that, during cognitive tasks, there is activation in both the left and right hemispheres. Based on the above, in the current state of the art, it is not possible for us to declare with certainty that the early impairment of verbal and/or visuospatial abilities depend on the reduction of brain asymmetry, this thesis needs more confirmations.

Another aspect that should be further investigated is the role of the APOE genotype in the evolution of brain atrophy [68,69]. Some authors claim that the heterogeneity of symptoms could be explained by apolipoprotein E (APOE): the 3 APOE genotype modifies the clinical phenotype in terms of cognitive impairment and is predictive of progression to disease [70,71]. Wolk & Dickerson studied APOE carriers and non-carriers and report a strong relationship between performances in specific cognitive domains and neuroanatomical changes in the regions that support those functions, while Donix and his collaborators have shown that the APOE-4 allele modulates hemispheric asymmetry in entorhinal cortical thickness [72,73]. Additionally, Hashimoto and colleagues reported different patterns of regional brain atrophy among patients with different APOE genotypes, meaning that the effect of APOE epsilon 4 gene may have regionally specific effects on the brains of AD patients [74]. The results of these studies are very encouraging and we believe that they represent one of the ways to follow for clarifying the nature and extent of cognitive deficits in AD.

In a study of 2011 about verbal and visuospatial performances

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in healthy subjects, the authors showed that with increasing age there was a different use of cognitive skills, characterized by early development of visuospatial skills compared to a slower specialization of verbal abilities, which reach full maturity in adulthood. This trend is also preserved in old age, albeit with less accurate performance than are possible in adulthood [4]. Even though it is difficult to make a strong conclusion based on the small number of AD patients studied in the current investigation, our findings indicate that the trends of cognitive impairment in AD follow cognitive trends seen in healthy-aging subjects. Based on this assumption, and the data we obtained, it could be argued that the ability to mature and specialize before, it is also the one that deteriorates earlier. This is in accordance with some researches that showed a more rapid greater age-related decline of the right than the left hemisphere [10]. Verify this hypothesis means to clarify one of the fundamental questions of neuroscience: how the architecture of the brain supports the complexities of cognitive functions. Several studies using modern neuroimaging techniques and neurocognitive test batteries to observe simultaneously changes in neuroanatomy and cognitive function as children mature into adults. Among them, we find a study of 2013 by Denninson and collaborators. The authors have shown that the left hemisphere was consistently larger than the right in subjects 12 to 16 years of age, and their results suggest that subcortical brain development from early to middle adolescence is characterized by striking hemispheric specialization [75]. Further researches are needed to identify the role of maturation and specialization of cerebral hemispheres in cognitive performance in lifespan.

Numerous studies have found a connection between age, education, gender, and cognitive performance in both healthy subjects and those with AD [3,76-78]. However, our analysis does not suggest this correlation, though this result could have been affected by a small sample size.

Finally, we did not take into consideration the role of cognitive reserve. In the literature there are several studies which have shown a correlation between level of cognitive deterioration and cognitive reserve and the role of cognitive reserve in the evolution of dementia [79,80]. Further development of this research could help clarify if levels of cognitive reserve differentially influence the execution of verbal and visuospatial tasks.

In conclusion, our results suggest that, in AD, both the verbal than visuospatial skills deteriorate in early stage of disease, and visuospatial abilities seem to have a more rapid impairment. The findings suggest that visuospatial access was more efficient than verbal access to detect patients who were at the early stage of cognitive decline. These results are not in line with a large part of research in the field which considers the verbal deficits as early signs of dementia. This difference in results may be due to a large use of test with verbal access in clinical practice, which is of faster and easier administration. It is still necessary to deepen the role of maturation and specialization of the cerebral hemispheres and of modification of the brain asymmetry, which seems to reduce with age. Further research needs to identify more sensitive instruments to detection visuospatial abilities in the early phases of dementia. The confirm of the early impairment is crucial for early detection of the disease and opens the way to several interventions of prevention and treatment. The knowledge resulting from these researches could be used for the construction of more sensitive non-invasive diagnostic tests for the early detection of dementia, and for the implementation of informatics applications of cognitive stimulation intended for subjects with subtle cognitive changes.

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