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Beyond Episodic Memory: Semantic Processing as Independent Predictor of Hippocampal/Perirhinal Volume in Aging and Mild Cognitive Impairment due to Alzheimer's Disease

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Objective: Given that lexical-semantic decline precedes episodic memory deficits in the Alzheimer disease (AD) timeline, it is expected that performance on a lexical-semantic task would be associated with mediotemporal volumes independently of the association this region has with episodic memory in the early stage of AD. **Methods**: Fifty patients with MCI due to AD and fifty healthy adults completed tests of lexical-semantic skills (Category Fluency), episodic memory for semantically-relevant material (Prose Memory), episodic memory for non-semantically-relevant material (Rey-Osterrieth Figure) and lexical-executive abilities (Letter Fluency), and a neurostructural MRI. Hippocampal, perirhinal, entorhinal, temporopolar and orbitofrontal volumes were extracted. The association between test performance and volume of each region was tested using partial correlations (age-education corrected). The improvement (r-squared change) at predicting volumetric indices offered by episodic memory/lexical-semantic processing, once accounting for their counterpart was tested using hierarchical regressions. **Results**: There were no significant findings for control indices. Prose Memory accounted for independent portions of volumetric variability within almost all regions. Category Fluency accounted for independent portions of volumetric variability of left/right hippocampus and left perirhinal cortex additional to the predictive strength of the Rey-Osterrieth Figure, and for an independent portion of volumetric variability in the left hippocampus additional to the predictive strength of Prose Memory. **Conclusions**: There was an association between hippocampal and perirhinal volume and lexical-semantic processing, additional to the contribution given by episodic memory. This statistical separation supports the importance of lexical-semantic processing as independent indicator of AD.

Keywords: Category fluency, Mild cognitive impairment, Preclinical, Perirhinal cortex

Running Head: Category Fluency as independent predictor in early AD

Public Significance Statements

- It is well established that declining semantic skills precede memory symptoms in Alzheimer's disease (AD).
- Semantic skills are linked to the typical brain regions affected by AD.
- This link is still present after controlling for episodic memory.
- Semantic processing abilities can be used to detect preclinical AD.

It has been widely demonstrated that aspects of memory are dysfunctional in Alzheimer's disease (AD). The latest versions of diagnostic criteria for prodromal and preclinical AD, established by international consensus task forces, are moving towards a view of diagnostic algorithms for early stage AD in which episodic memory plays a central role (Albert et al., 2011; Dubois et al., 2016). Presence of episodic memory decline, however, is not unequivocally associated with the presence of AD. In fact, it is well known that normal, non-pathological ageing processes cause some degree of impoverishment of memory skills (Hanninen et al., 1996). Evidence of declining trajectories of memory functions in both types of ageing are sometimes not of easy clinical interpretation at an individual level. On this note, a cognitive measure which shows differences in its trajectory of change between the two diagnoses will be of more immediate clinical utility. This has been indicated to be the case for semantic processing. Although it is well established that semantic representations can be accessed via multiple routes, semantic content is often tested exploiting the linguistic modality. As a consequence, semantic processing is commonly (although not exclusively) tested via tests of language assessing lexical variables (Venneri, Jahn-Carta, De Marco, Quaranta, & Marra, 2018).

Although it is well established that deficits in episodic memory are major clinical evidence of the symptomatic stage of the diseases, decline of semantic processing and semantic memory occurs in parallel (Barbeau et al., 2012), and there is mounting evidence that it precedes the appearance of episodic memory decline. Subtle insidious changes may occur and might go undetected if not thoroughly assessed, given that for a long time they do not cause any major disruption to everyday cognitive performance. Evidence has repeatedly shown that lexical-semantic impoverishment appears insidiously decades before the onset of clinical symptoms (Amieva et al., 2008; Didic, Barbeau, Felician, Tramoni, Guedj, Poncet, & Ceccaldi, 2011; Le, Lancashire, Hirst, & Jokel, 2011; Snowdon, Kemper, Mortimer, Greiner, Wekstein, & Markesbery, 1996). This might represent an important cognitive aspect to be exploited in clinical settings for preclinical detection of AD, and

confers an advantage to lexical-semantic processing as central diagnostic domain of interest (Papp, Rentz, Orlovsky, Sperling & Mormino, 2017; Venneri, Mitolo, & De Marco, 2016).

The most common approach to test lexical-semantic processing during neuropsychological assessment of patients is via the Category Fluency test. Engagement in this test depends upon the integrity of semantic associations, semantic memory, and language (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Rohrer, Salmon, Wixted, & Paulsen, 1999). The extent of its reliance on executive demands is, however, limited (Henry, Crawford, & Phillips, 2004), as it resembles cognitive operations involved in everyday tasks (e.g., creating a shopping list) normally carried out with little cognitive control (Shao, Janse, Visser, & Meyer, 2014). The mediotemporal involvement in this task has emerged from lesion mapping studies (Biesbroek, van Zandvoort, Kappelle, Velthuis, Biessels, & Postma, 2016), from measures of gray matter density (Venneri, Gorgoglione, Toraci, Nocetti, Panzetti, & Nichelli, 2011) and blood flow, which have highlighted the role of the hippocampus and subhippocampal areas (entorhinal and perirhinal cortex) for context-free semantic retrieval, typically requested in the Category Fluency test (Barbeau et al., 2012). This association has also been confirmed by studies that have measured semantic retrieval via the DMS48 visual recognition test (Barbeau et al., 2008; Didic et al., 2010), and via subtests of the CERAD battery (Hirni, Kivisaari, Monsch, & Taylor, 2013). The presence/absence of contextual information is a major feature of declarative memory traces, and is functionally related to the anatomical distinction between hippocampal and subhippocampal regions. In fact, episodic memories are characterized by a distinct set of contextual information (i.e., temporal, spatial, and other situational information), whereas semantic memories are not. The hippocampus, at the top of the computational hierarchy of the mediotemporal lobe, is necessary to retrieve context-rich episodic memories, whereas the subhippocampal region, at a secondary level of this hierarchy, is sufficient for the retrieval of context-free semantic memories. (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997).

The mediotemporal complex, heavily affected in AD (Braak & Braak, 1991), appears therefore to be implicated in the support of both episodic memory and semantic processing. Apart from a few investigations (Barbeau et al., 2012; Didic et al., 2011; Joubert, Felician, Barbeau, Didic, Poncet, & Ceccaldi, 2008), however, the distinction between the two types of declarative memory has not been studied in detail in patients who are at the early stage of AD. Seminal studies carried out on single patient cases, lesion-models or developmental conditions have indicated that major functional distinctions exist between the hippocampus and the subhippocampal regions (Barbeau et al., 2006; Jonin et al., 2018; Temple, & Richardson 2006; Vargha-Khadem, Gadian, Watkins, Connelly, Van Paesschen, & Mishkin, 1997). No study, however, has yet investigated this aspect in AD as a function of a test so widely used worldwide such as the Category Fluency test. If on one hand, the mediotemporal-episodic memory link is widely exploited as the main rationale of the criteria for preclinical and prodromal AD (Albert et al., 2011; Dubois et al., 2016), on the other hand the mediotemporal-semantic processing link has been relatively understudied. This is surprising, considering that lexical-semantic deficits have been shown to anticipate memory deficits and may thus become the core of novel criteria for preclinical AD (Amieva et al., 2008).

In this study we focused on the volumetric properties of mediotemporal regions. Since tests of memory are reliant on a multiplicity of cognitive processes, using models of linear statistics, we hypothesized that a measure that relies more on lexical-semantic processing than episodic memory will be a significant predictor of volumetric indices, independently of the predictive strength offered by a measure that relies instead more on episodic memory than lexical-semantic processing (please note that the word "prediction" refers to its statistical meaning). This hypothesis was tested in a cohort of healthy elderly adults and patients with mild cognitive impairment due to AD. The regions this study focused on were those affected significantly by AD pathology during the earliest stages, i.e., the mediotemporal complex, inclusive of hippocampus, entorhinal cortex and perirhinal cortex.

Method

Participants

One hundred participants were included in these analyses. These were recruited from the outpatient memory service at [location not disclosed in compliance with the masked review guidelines], and included healthy controls (n = 50), and patients referred to their first neurological examination for suspected cognitive decline (n = 50) who then received a clinical diagnosis of mild cognitive impairment following widely established clinical criteria (Albert et al., 2011; Petersen, 2004) further corroborated by clinical follow ups. Each participant had been assessed with an extensive diagnostic protocol, as part of the clinical procedures led by a senior neurologist, including a brain MRI investigation and an extensive neuropsychological assessment. As part of clinical routine, patients received follow up assessments for confirmation of clinical diagnosis and conversion to AD was established clinically. Each individual case was assessed and discussed by a team of clinicians including a neuroradiologist, a senior neurologist and a neuropsychologist. Following consensus among these clinicians, conversion to AD was either confirmed or ruled out. Based on this, inclusion criteria were set as follows: a Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975) score of 24 or above, and a clinical profile compatible with the presence of potential underlying AD pathology, as determined by a clinical consensus during follow up examinations. Exclusion criteria were set up to identify and discard any case for whom the etiology was of non-neurodegenerative nature (i.e., vascular, traumatic, psychiatric, metabolic; see Winblad et al., 2004). More specifically, these were represented by: the presence of an established diagnostic entity of clinical importance (including cerebrovascular or cardiovascular disease at a moderate-severe stage, neuropathy presenting with conduction difficulties, peptic ulcer, sick sinus syndrome); a history of medical events of clinical concerns (e.g., system failure, transient ischemic attacks, brain seizures); the presence of major clinical traits which might represent confounding factors in the study of AD neurodegeneration (i.e., presence of severe neuropsychiatric

symptomatology, evidence of abnormal levels of thyroid-stimulating hormone, folates, and vitamin B12); or by specific treatment medication (i.e., memantine/cholinesterase inhibitors consumption at the time of recruitment, or medication for research purposes or with toxic effects to internal organs). Moreover, participants were not included in the study if the MRI images indicated or suggested a major non-neurodegenerative problem (e.g., normal-pressure hydrocephalus, previous stroke, brain tumor) which could be associated with the presence of cognitive impairment. Data from neuropsychological assessment at first referral and contemporary MRI scans were used for analyses in this study.

All demographic characteristics are reported in **Table 1**. Approval for this research was granted by the institutional ethics panel of the [name of panel not disclosed in compliance with the masked review guidelines] (reference number CE: 11.07). Written informed consent was requested and obtained from all recruited participants. The entire research protocol was executed in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

- Please insert **Table 1** about here –

Neurocognitive assessment

A team of experienced clinical neuropsychologists administered an extensive battery of cognitive tests to all study participants. The battery included measures of: verbal and non verbal short-term and working memory, visuoconstructive skills, visual long-term memory, verbal long-term memory and new learning, phonological and semantic fluency, visual search and speed of processing, executive functioning, comprehension and receptive language, and verbal and non-verbal measures of abstract reasoning. For a complete description of the instruments, please see De Marco,

Meneghello, Duzzi, Rigon, Pilosio, & Venneri (2016). The scores obtained on these tests were used as part of the clinical pipeline to establish diagnostic status. For the purpose of this study question, the performance on four tests was further considered.

- The Category Fluency test was chosen as measure of lexical-semantic processing with no primary reliance on mechanisms of episodic memory. The categories for access to lexicon were: car brands, animals and fruits (one minute per category), as originally chosen for the collection of the Italian normative data (Novelli, Papagno, Capitani, Laiacona, Vallar, & Cappa, 1986). Ample evidence indicates semantic processing is the central cognitive component addressed by this task (Venneri, Jahn-Carta, De Marco, Quaranta, & Marra, 2018).
- The delayed (ten minutes) recall of the Rey-Osterrieth Complex Figure test was selected as measure of "non-semantic" episodic memory. This test, in fact, consists of encoding and recall of an abstract figure which does not request any semantic processing (Pelati et al., 2011).
- The delayed (ten minutes) recall of the Prose Memory test was included as a measure of episodic memory of semantically-relevant material. It is well established that semantic processing is used as computational strategy in tests of memory based on verbal material which show a degree of semantic relatedness (e.g., Carlesimo et al., 1998). The trial chosen as part of the Prose Memory test was the Italian version of the Babcock story (De Renzi, Faglioni, & Ruggerini, 1977).
- The Letter Fluency test was also included, as a measure of linguistic-executive skills. This latter test was chosen as a methodological control because: a) it is methodologically reliant on a comparable set of technical characteristics as those of the Category Fluency test (one minute, three trials); b) a large proportion of patients with clinically-established AD dementia, albeit mostly of mild level, in fact, reach performance levels within normal limits

on the Letter Fluency task (Bizzozero, Scotti, Clerici, Pomati, Laiacona, & Capitani, 2013; De Marco, Duzzi, Meneghello, & Venneri, 2017; Herbert, Brookes, Markus, & Morris, 2014). In addition, the neural correlates of this test have been reported to be located mainly in the left frontal lobe, with no overt mediotemporal involvement (Biesbroek et al., 2016; Meizer et al., 2009). The letters for access to lexicon were: F, L and P (one minute per letter), as originally devised for the collection of the Italian norms (Novelli et al. 1986).

All cognitive features are summarized in **Table 1**.

MRI acquisition and processing

A three-dimensional Turbo Field Echo T1-weighted image was acquired on a 1.5 T Philips Achieva scanner as part of a brain MRI protocol (1.1 × 1.1 × 0.6 mm^3 (gap 0.6 mm) voxel resolution, 256 × 256 × 124 matrix size, 250 mm field of view, 7.4 ms repetition time, 3.4 ms echo delay time, and 8° flip angle). This image modality, together with T2-weighted and FLAIR sequences served to comply with clinical procedures and exclusion criteria. Furthermore, 3D T1-weighted images were also used for modelling and statistical inference. Each image was processed to extract a series of volumetric indices. For this purpose, the standard cortical and subcortical probabilistic segmentation and parcellation procedures of the FreeSurfer Image Analysis Suite (http://surfer.nmr.mgh.harvard.edu/) were implemented. Of the entire output, the volume of the mediotemporal complex was extracted for each participant, maintaining the two hemispheres separated. The perirhinal cortex was defined as the cytoarchitectural-defined Brodmann Area 35 (Augustinack et al., 2013), while the entorhinal cortex was defined as the the cytoarchitectural-defined Brodmann Area 28 (Fischl et al., 2009). Both regions are accurately and reliably defined by FreeSurfer, as detailed in their respective publications. The hippocampus was instead extracted from the atlas of subcortical regions (Fischl et al., 2002). Additionally, the volumes of the left and

right temporal poles were extracted from the Destrieux atlas (Fischl et al., 2004), since this region is considered an important "amodal" hub that processes similarities among semantic representations (Patterson, Nestor, & Rogers, 2007). Each measure was divided by the total volume of gray matter. By doing so, fractional indices were obtained (**Table 1**). This was carried out for two reasons: to allow for immediate inter-individual comparability, and to allow for a simpler interpretation of the hierarchical regression models (see the statistical modelling section for details). As a control region not as profoundly affected by AD pathology as the mediotemporal areas, the volume of the lateral orbitofrontal complex was extracted by conjoining a number of left and right symmetrical orbitofrontal patches (Fischl et al., 2004), and calculating a fractional value. All regions included in this investigation are illustrated in **Figure 1**.

- Insert **Figure 1** about here -

Statistical modelling

Analyses were run in the entire cohort and, separately, in each diagnostic group. To test our experimental hypothesis, three sets of analyses were designed.

First, a number of group-comparisons between patients and controls were run. This served to characterize our sample of patients and verify that the pattern of differences was as expected from a cohort of individuals with a diagnosis of MCI due to AD (Albert et al., 2011).

Second, correlation models were created to test the simple association between the four cognitive tests and volumes of interest. Pearson's r correlations were run between each cognitive index and each regional fraction. Control variables added to these models were age and education levels. Age was included because MCI patients were older than healthy controls, and also because of its effects

on both cognitive performance and brain volumes (Tarroun, Bonnefoy, Bouffard-Vercelli, Gedeon, Vallee, & Cotton, F, 2007). Years of education served as control for cognitive reserve (Stern, 2009).

Third, to test our study hypothesis, statistical models were devised to compare the predictive power of the Category Fluency test as a measure of lexical-semantic processing with that of the Rey-Osterrieth Complex Figure test as a measure of episodic memory, and that of the Prose Memory test as a measure relying on both episodic memory and semantic processing. The exclusivity with which the performance on each of these three tasks predicted the degree of mediotemporal integrity was modelled with hierarchical multiple regression models, set up for the entire cohort. The scores obtained on two of the three tasks were inserted in a first and second block, respectively, to establish to what degree each test could account for an independent amount of anatomical variability. The r-squared statistics associated with the combined predictive strength of the pair of tests were extracted for descriptive purposes. r-squared change statistics were instead inferred to establish the block-to-block predictive improvement. All combinations were inferred for each regional fraction (six regression models, in total). Since fractional indices (and not raw volumes) were used as dependent variables, there was no need to covariate further for a global measure of brain or intracranial volume. In this way, the interpretability of the r-squared change statistic was maximized.

Results

Group comparisons between patients and controls

Between-group differences were found for the left and right hippocampal fractions and the left perirhinal fraction, with healthy adults having larger structures. No differences were found for the right perirhinal fraction or the entorhinal fractions, nor for the temporal poles (**Table 1**). Controlling for age did not alter these results. Patients scored significantly worse than healthy controls on the Prose Memory test, the Rey-Osterrieth Complex Figure test, and on the Category Fluency test. No difference was found for the Letter Fluency test (**Table 1**). These findings confirmed that the studied sample had the typical characteristics of prodromal AD.

Association between each ability and volume of mediotemporal structures

In the group of healthy controls, the sole significant association was that between the Prose Memory test performance and the left perirhinal fraction.

In the group of patients, scores on the Category Fluency test and Prose Memory test were both associated with hippocampal size (left and right). In addition, Prose Memory test scores were also associated in this group with the perirhinal fraction bilaterally, and the left entorhinal fraction. No association was found between any mediotemporal fraction and the performance on the Rey-Osterrieth Complex Figure test.

In the whole cohort, the Rey-Osterrieth Complex Figure test was associated with the left hippocampal and perirhinal fraction, and with the entorhinal fraction bilaterally. The Prose Memory test was instead associated with the hippocampal and perirhinal fraction bilaterally, and with the left entorhinal fraction. The Category Fluency test, finally, was associated with the hippocampal fraction bilaterally and with the left perirhinal fraction.

Scores on the Letter Fluency test did not correlate with any fractional measure, neither in one of the diagnostic groups, nor across the entire cohort. Similarly, no significant correlation was found in association with the lateral orbitofrontal fraction or with the temporal pole. All r scores and p values are reported in **Table 2**.

- Insert **Table 2** about here -

Semantic skills vs. episodic memory skills as predictor of volume of mediotemporal structures

Hierarchical regression models indicated that the scores obtained on the Prose Memory test accounted for a significant portion of variability of all mediotemporal areas but the right entorhinal cortex, after accounting for the predictive power of the Category Fluency test or Rey-Osterrieth Complex Figure test. The maximal significant exclusive contribution of the Prose Memory test ranged between 5.8% and 11.6% of additional variability after accounting for that explained by the Category Fluency test, and between 4.6% and 13.5% of additional variability after accounting for that explained by the recall of the Rey-Osterrieth Complex Figure.

When the exclusive contribution of the Category Fluency test was modelled after accounting for the predictive strength of the Prose Memory test score, a significant block-to-block improvement was found only for the left hippocampus, where Prose Memory test scores accounted for 23% of the variability, and category fluency scores contributed with an additional 3%. When the exclusive contribution of the Category Fluency test was instead modelled after accounting for the predictive strength of the recall of the Rey-Osterrieth Complex Figure, a significant block-to-block improvement was found for the left hippocampal fraction (+10% variability), the right hippocampal fraction (+8.6%), and the left perirhinal fraction (+4.5%).

The exclusive contribution of the performance on the Rey-Osterrieth Complex Figure test was not associated with any improvement in the prediction of the volume of mediotemporal structures. The lateral orbital and temporopolar fractions were not associated with any cognitive test. All results are illustrated in **Table 3**.

- Insert **Table 3** about here –

Discussion

In this study, the association between neuropsychological tests commonly used to diagnose cognitive changes induced by early AD and the volume of key mediotemporal regions was investigated in a cohort of healthy controls and patients with MCI due to AD. First and foremost, the Prose Memory test was confirmed as the task most strongly associated with the entire mediotemporal complex in all models. A second test of episodic memory, the recall of the Rey-Osterrieth Complex Figure, showed instead more modest associations with mediotemporal fractions, and these were limited to the analyses of the entire cohort. Finally, the Category Fluency test was found to be a significant independent predictor of hippocampal and perirhinal volume even when controlling for measures of episodic memory.

At a first glance these findings may suggest that episodic memory would be the domain most suitable for the study of mediotemporal volumetric properties in healthy elderly adults and patients in the prodromal stages of AD. This is only partially confirmed by our findings. In fact, the performance on the Rey-Osterrieth Complex Figure (a prominent test of episodic memory) was poorly predictive of mediotemporal volumes. An important issue is clarifying why this was the case. Although the procedures of administration of the Prose Memory test and the Rey Osterrieth

Complex Figure are, overall, very similar, two major differences exist between these two tests. First, the modality channel (verbal vs. visuospatial) is different. It is well established that visuospatial and verbal-auditory materials are processed via distinct neurophysiological pathways of encoding. Two tests that exploit the same modality may in part share a common portion of variability. Vice versa, two tests that exploit different modalities may account for divergent (and complementary) portions of variability. The performance on the Category Fluency test is commonly aided by visuospatial strategies (Biesbroek et al., 2016; Pakhomov, Eberly, & Knopman, 2016). Yielding information on visuospatial processing, the variability on this task would mitigate the statistical effect outlined by a second visuospatial task, while it would not influence the statistical effect outlined by a verbal task. Second, the performance on the Prose Memory test is known to be influenced by the semantic relatedness of the elements included in the learning material (Carlesimo et al., 1998). The semantic nature of the material the Prose Memory test depends on is likely to be a crucial factor. This material, in fact, is particularly salient, as it is based on the description of a plot characterized by "the presentation of [a] character, a conflict, an aggravation / complements to the main plot, and a resolution" (Bolognani et al., 2015, page 138). We argue that the predictive strength shown by the Prose Memory test and the level by which scores on this task outperformed the level of statistical prediction achieved by the recall of the Rey-Osterrieth Complex Figure might in part be due to the interplay of episodic memory and semantic processing requested by the Prose Memory task, which is more strongly associated with the integrity of multiple mediotemporal regions. This is also postulated by the model by Mishkin and colleagues (1997), who highlight the hierarchical role of the hippocampal and subhippocampal regions, the former being crucial for the retrieval of the contextual information normally associated with episodic mnemonic traces, the latter being sufficient for the retrieval of context-free semantic memory. In summary, both differences in modality and semantic content (or, a combination of the two) between the recall of the Rey-Osterrieth Complex Figure and the recall of the Prose Memory test might underlie the pattern of findings described above.

The sole measurement of episodic memory levels for the clinical characterization of patients leads to major methodological limitations in a clinical setting. In fact, tests of this function allow clinicians to make a diagnosis only after episodic memory deficits are present. On the other hand, there is ample evidence indicating that a lexical-semantic decline is present, although subtle, during the preclinical stage of AD, when episodic memory deficits are still absent. This highlights a clinical interval along the disease timeline in which lexical-semantic skills are the only measurable symptom. Considering this as an assumption, and since it has been widely demonstrated that integrity of the mediotemporal lobe is responsible for sustaining lexical-semantic skills (Barbeau et al., 2012; Biesbroek et al., 2016; Didic et al., 2011; Hirni et al., 2013), it derives that there must be some degree of independence in the way mediotemporal integrity affects episodic memory and lexical-semantic processing. This provides the rationale whereby mediotemporal regions must be associated with lexical-semantic competence additional to episodic memory competence. As hypothesized, not only did this study produce empirical evidence of an association between performance on the Category Fluency test and structures of the mediotemporal complex (specifically, hippocampus bilaterally and left perirhinal cortex), Category Fluency test scores could explain a portion of AD-related neurostructural variability in the left and right hippocampus and, above all, in the left perirhinal cortex independently of that explained by the recall of the Rey-Osterrieth Complex Figure. Moreover, this test improved significantly the predictive strength of Prose Memory test scores in accounting for the variability of the left hippocampal fraction. Importantly, the absence of any associations between fractional values in mediotemporal complex structures and Letter Fluency test scores indicates that it is semantic processing and not any generic lexical processing which is associated with the mediotemporal lobe.

Experimental findings indicate that, across the lifespan, lexical-semantic skills remain stable (Park, Lautenschlager, Hedden, Davidson, Smith, & Smith, 2002; Verhaeghen, 2003) or show only limited decline (Ferguson, Spencer, Craig, & Colyvas, 2014; Lövdén, Rönnlund, Wahlin, Bäckman,

Nyberg, & Nilsson, 2014), of minimal magnitude as opposed to the concurrent decline of episodic memory. Vice versa, when lexical-semantic parameters are measured during preclinical AD, they show unequivocal decline, as demonstrated in the Nun Study (Snowdon, Kemper, Mortimer, Greiner, Wekstein, & Markesbery, 1996), by the longitudinal analyses of the linguistic production of well-known writers (Garrard, Maloney, Hodges, & Patterson, 2005; Le et al, 2011; van Velzen & Garrard, 2008), by the analysis of presidential speeches given by former U.S. president Ronald Reagan, diagnosed with AD years after his presidency (Berisha, Wang, LaCross, & Liss, 2015) and by other cases of longitudinal evaluations of linguistic abilities across the lifespan, such as the evidence emerging from the longitudinal analysis of the PAQUID cohort, in which an index of lexical-semantic competence was found to predate diagnosis of AD by 12 years (Amieva et al., 2008), or the analysis of discourse in picture description in pathologically confirmed cases of AD that identified cases 7-9 years prior to death (Pekkala et al., 2013). Furthermore, the value of lexical-semantic parameters in predicting conversion to AD has been demonstrated by a clinical study which suggested that a measure of typicality of words could have prognostic valence in mild cognitive impairment (Vita et al, 2014).

Despite accumulating heuristic evidence of the sensitivity of linguistic measures based on lexical-semantic processing to the earliest pathological changes in the disease course, current clinical and research criteria highlight testing of episodic retrieval as the main focus of assessment (Dubois et al., 2016). The goal in clinical assessment, however, needs to be moved to the detection of signs in the preclinical stage/risk stage for any preventative strategy, either through modification of lifestyle factors (Di Marco et al, 2014) or through pharmacological treatment (Buckley et al, 2016), to be effective in delaying the dementia stage of the disease. Semantic measures such as the Category Fluency test more than any measure of episodic retrieval can take clinical assessment closer to this goal. The evidence of this study shows that Category Fluency test performance may represent a proxy of early AD-related pathological changes independent from episodic memory. It is known

that the greater sensitivity of measures of lexical-semantic performance depends on its reliance not only on the integrity of the hippocampus but most importantly of perirhinal cortex (Hirni et al., 2013). Models of disease progression estimate that the clinical stage of AD is preceded by a decades long preclinical phase. In this preclinical phase, changes occur at the pathological level with abnormal regulation of TAU and β Amyloid proteins. In this phase AD neurofibrillary pathology appears more laterally in the transentorhinal region of the perirhinal cortex (including entorhinal and perirhinal cortex) in what defines Braak stage I, and only at a later stage does AD pathology spread to the hippocampus (Braak & Braak, 1995). Perirhinal cortex plays a central role within the functional networks supporting retrieval of semantic information - a major requirement for high level linguistic performance and an important cognitive prerequisite of semantic fluency abilities - and a major computational center for retrieval of context-free memory of which semantic processing is the main component. Its centrality in lexical-semantic processing makes the perirhinal cortex a likely candidate region for the future definition of a preclinical AD biomarker. The association of Category Fluency test performance with volumetric values of perirhinal cortex observed in this study suggests that scores on this test might express this structure's level of anatomical and functional integrity. This confirms the findings of other studies which have detected an association between variance in lexical-semantic parameters and volumetric variance in perirhinal cortex in mild AD (Venneri, McGeown, Hietanen, Guerrini, Ellis, & Shanks, 2008; Venneri et al., 2011). This association was even greater in MCI patients, carriers of the AD risk gene Apolipoprotein ε_4 allele (Venneri, McGeown, Biundo, Mion, Nichelli, & Shanks, 2011). Category Fluency test scores, therefore, may be part of a computational algorithm for a clinical proxy of early AD pathology (Papp et al., 2016) and, as such, show reduced decline among healthy adults free of AD pathology when compared to adults with early encroachment of AD pathology. Indeed, further evidence indicates that the addition of a measure of Category Fluency performance to a composite cognitive score explains unique variance in amyloid related decline in amyloid positive healthy older adults. When these latters were stratified by neurodegenerative markers,

longitudinal assessment showed that those who had more severe neurodegenerative markes had more severe decline in Category Fluency, suggesting that performance on this test declines very early in the preclinical AD trajectory (Papp et al., 2017). It has to be acknowledged, however, that in our study the association between the size of the left perirhinal cortex and lexical-semantic skills was no longer significant after controlling for performance on an episodic memory test with a semantic load. This finding most likely indicates that by the prodromal stage of the disease both lexical-semantic abilities and abilities in episodic memory with a semantic load explain most of the structural variance in perirhinal cortex and the net contribution of each of these functions is no longer distinguishable. In contrast, when a test of episodic memory without any semantic load is used as a covariate the significant association with perirhinal cortex remains for Category Fluency.

Recently it was suggested that to achieve the goal of preclinical detection of individuals with early AD pathology, or of individuals at risk of developing AD, a cultural shift had to be made, and especially the framework which describes early AD as a pathological entity limited to the hippocampus and its primary episodic memory function had to be revised (Barbeau et al., 2004; Didic et al., 2011; Venneri et al, 2016). This is for certain the case at the prodromal, symptomatic stage of the disease, but for earlier detection a more powerful tool is the evaluation of lexical-semantic skills, which mirrors more closely the presence of subtle AD pathology at the pre-hippocampal earlier stage of the disease. In addition, this evidence challenges earlier views of AD as an episodic memory disorder with sparing of language, suggesting instead that testing of linguistic semantic skills, and an accurate qualitative analysis of verbal productions might reveal itself as a better diagnostic tool that can be of assistance within the procedures optimised by clinicians at the preclinical stage. This tool would have the potential for extensive screening of older adults, and, because of its non invasive nature, could become an early and cheap biomarker proxy. The evidence of this study supports earlier claims that volumetric measures of the transentorhinal/perirhinal cortex could be a surrogate early marker of AD (Taylor & Probst, 2008),

which can easily be obtained in a non invasive way by MRI scanning, and calls for a refinement of imaging protocols which should focus on quantitative imaging of structures that have the earliest vulnerability to the neuropathological threats of AD. The increasing clinical use of high field scanners should also contribute to improving imaging protocols of these structures.

One final comment that deserves to be mentioned is the role of mediotemporal areas in a network context. It is today widely established that cognitive function is sustained by widespread networks in which individual regions act as computational hubs. Although the default-mode network is the network most distinctively affected by AD pathology (Pasquini et al., 2017; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Sperling et al., 2009), this involvement likely occurs in a gradual way, following the spread of pathology across Braak stages. On this note, it is not yet understood how changes in volume or thickness of subhippocampal regions are linked to network disfunction. Published findings indicate significant links between context-free semantic retrieval and network connectivity in the anterior temporal lobe (Gour et al., 2011) but more evidence is needed to assess changes of whole-brain networks in a longitudinal context.

This study is not free from limitations. Although patients were followed up clinically over time, we did not follow up controls. It is possible that some of the controls, healthy at baseline, were actually at the preclinical stage of the disease. We accept this as a possibility which, however, would have little effect at a group level. Furthermore, our procedures did not include a measure of underlying AD pathophysiology. Clinical diagnostic criteria were applied for the identification of patients and controls, and diagnostic status reached by consensus among clinicians. It is possible that the use of methods such as amyloid imaging or the analysis of cerebrospinal fluid levels of typical peptidic hallmarks of AD may have resulted in the exclusion of a small percentage of the participants. Again, however, this would have had only a mild effect at the group level. Another limitation lies in the multi-componentiality of the Prose Memory test, which to some extent relies on episodic as well as semantic processing. It is in the nature of neuropsychological tests to be sustained by a

multitude of cognitive components of which one represents the core of interest. Based on this, it is not possible to go beyond our speculation that Prose Memory is particularly suitable for tracking down the neuroanatomical modification triggered by AD due to its reliance on an interplay of episodic memory and semantic processing. Experimental evidence is required to address this point.

In conclusion, the findings of this study indicate that a skill of language (i.e., lexical-semantic processing in the form of retrieval of lexicon following a semantic route) is an ability that is strongly associated with the volume of the mediotemporal lobe. Furthermore, this skill is statistically associated with this region, crucial in AD, in a way which is independent of episodic memory. The Category Fluency test has good levels of diagnostic classification for AD (Canning, Leach, Stuss, Ngo, & Black, 2004) and our findings support that claim by showing a link with the underlying cerebral structures, harshly affected by AD pathology insidiously and very early in the disease course.

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Figure Captions

Figure 1

Regions investigated in this study. The hippocampus is shown in red in the left hemisphere, whereas the perirhinal and entorhinal cortices are shown in blue and green, respectively, in the right hemisphere. The temporal pole is shown in white. The lateral portion of the orbitofrontal region (in yellow) was chosen as a control area. MNI slices are: y = -22, x = 34, z = -32, z = -12, z = -8

Tables

Table 1. Characterization of the sample included in this study

Variable	**Controls**	**Patients**	**Group Difference**	
Demographic Indices			**p $U_{\text{Mann Whitney}}$ / χ^2**	
Age (years)	69.54 (5.88)	73.86 (6.31)	< 0.001	
Education (years)	10.94 (4.60)	10.70 (4.33)	0.840	
Gender (f/m)	31/19	25/25	0.157	
MMSE (score out of 30)	28.98 (1.32)	27.46 (1.92)	< 0.001	
Neuropsychological Tests			**p $U_{\text{Mann Whitney}}$**	**p $F_{\text{Corrected}}$**
Letter Fluency Test (number of valid entries)	34.74 (12.81)	31.34 (11.08)	0.145	0.234
Category Fluency Test (number of valid entries)	41.36 (9.92)	30.18 (8.66)	< 0.001	< 0.001
Prose Memory Test – Recall (score out of 25)	13.10 (4.71)	7.32 (4.48)	< 0.001	< 0.001
Rey-Osterrieth Complex Figure – Recall (score out of 36)	15.98 (5.66)	8.44 (4.58)	< 0.001	< 0.001
Volumetric Measures			**p $U_{\text{Mann Whitney}}$**	
Left Hippocampal Fraction	0.00658 (0.00062)	0.00595 (0.00084)	< 0.001	
Right Hippocampal Fraction	0.00674 (0.00069)	0.00605 (0.00099)	< 0.001	
Left Perirhinal Fraction	0.00471 (0.00057)	0.00431 (0.00076)	0.012	
Right Perirhinal Fraction	0.00319 (0.00052)	0.00304 (0.00056)	0.089	
Left Entorhinal Fraction	0.00331 (0.00049)	0.00309 (0.00059)	0.059	

Right Entorhinal Fraction	0.00298 (0.00059)	0.00282 (0.00060)	0.124
Left Temporal Pole Fraction	0.00908 (0.00089)	0.00944 (0.00097)	0.059
Right Temporal Pole Fraction	0.00924 (0.00139)	0.00951 (0.00127)	0.321
Lateral Orbitofrontal Fraction	0.02302 (0.00170)	0.02317 (0.00149)	0.530

Except for gender ratio, means and standard deviations are indicated. Between-group differences in neuropsychological scores were tested both with uncorrected models and with statistical comparisons corrected for age and years of education. Brain regional fractions were calculated by dividing the regional volume by the total volume of gray matter.

Table 2. Coefficients of partial correlation between mediotemporal volumes and measures of episodic memory and lexical-semantic processing

Brain Region	Healthy Controls				MCI Patients				Entire Cohort			
	ROCF	**PM**	**CF**	**LF**	**ROCF**	**PM**	**CF**	**LF**	**ROCF**	**PM**	**CF**	**LF**
Left Hippocampal Fraction	0.005	0.207	0.141	-0.137	0.121	**0.464** ***	**0.371** **	-0.061	**0.224** °	**0.447** ***	**0.369** ***	-0.051
Right Hippocampal Fraction	-0.098	0.182	0.027	-0.126	0.162	**0.473** ***	**0.442** **	-0.059	0.198	**0.440** ***	**0.356** ***	-0.051
Left Perirhinal Fraction	0.099	**0.412** **	0.136	0.101	0.153	**0.316** °	0.190	0.080	**0.209** °	**0.400** ***	**0.234** °	0.116
Right Perirhinal Fraction	0.035	0.270	-0.067	-0.087	0.214	**0.311** °	0.279	-0.092	0.146	**0.288** **	0.131	-0.071
Left Entorhinal Fraction	0.169	0.221	0.019	0.090	0.239	**0.334** °	0.243	0.098	**0.225** °	**0.301** **	0.172	0.105
Right Entorhinal Fraction	0.183	0.085	0.006	-0.009	0.190	0.207	0.309	-0.145	**0.227** °	0.190	0.194	-0.055
Left Temporal Pole Fraction	0.189	0.037	-0.016	-0.260	-0.096	-0.033	< 0.001	-0.030	-0.036	-0.074	-0.076	-0.165
Right Temporal Pole Fraction	-0.081	-0.066	-0.006	-0.045	0.113	0.009	-0.034	-0.127	-0.053	-0.075	-0.063	-0.099
Lateral Orbitofrontal Fraction	0.161	-0.116	0.051	-0.040	-0.014	0.015	0.040	-0.148	0.035	-0.083	0.008	-0.076

Age and years of education were used as correction factors. Significant ($p < 0.05$) coefficients of correlations are indicated in bold.

ROCF: recall of the Rey-Osterrieth Complex Figure; PM: Prose Memory; CF: Category Fluency; LF: Letter Fluency; °: $p < 0.05$; **: $p < 0.005$; ***: $p < 0.001$

Table 3. Predictive exclusivity shown by the Prose Memory test (episodic memory for semantically relevant material), the recall of the Rey-Osterrieth Complex Figure (episodic memory for non-semantically relevant material) and the Category Fluency test (lexical-semantic processing)

Brain Region	Prose Memory		Rey-Osterrieth Complex Figure		Category Fluency	
	net of CF	**net of ROCF**	**net of PM**	**net of CF**	**net of PM**	**net of ROCF**
Left Hippocampal Fraction	**0.077** (0.083)**	**0.135** (0.156)***	0.008	0.018	**0.031** (0.320)°	**0.100** (0.111)***
Right Hippocampal Fraction	**0.068** (0.073)**	**0.121** (0.138)***	0.005	0.013	0.024	**0.086** (0.094)**
Left Perirhinal Fraction	**0.116** (0.131)***	**0.140** (0.163)***	0.002	0.022	0.002	**0.045** (0.047)°
Right Perirhinal Fraction	**0.065** (0.070)*	**0.058** (0.062)°	0.003	0.019	< 0.001	0.009
Left Entorhinal Fraction	**0.058** (0.062)°	**0.046** (0.048)°	0.013	0.034	< 0.001	0.009
Right Entorhinal Fraction	0.007	0.006	0.025	0.025	0.010	0.009
Left Temporal Pole Fraction	0.004	0.010	0.001	0.001	0.005	0.012
Right Temporal Pole Fraction	0.004	0.007	< 0.001	0.001	0.001	0.004
Lateral Orbitofrontal Fraction	0.011	0.012	0.008	0.001	0.005	< 0.001

ROCF: Recall of the Rey-Osterrieth Complex Figure; PM: Prose Memory; CF: Category Fluency. r^2 change statistics are shown and f^2 effect sizes are shown in parentheses. Significant r^2 change statistics are shown in bold. °: $p < 0.05$; *: $p < 0.01$; **: $p < 0.005$; ***: $p < 0.001$

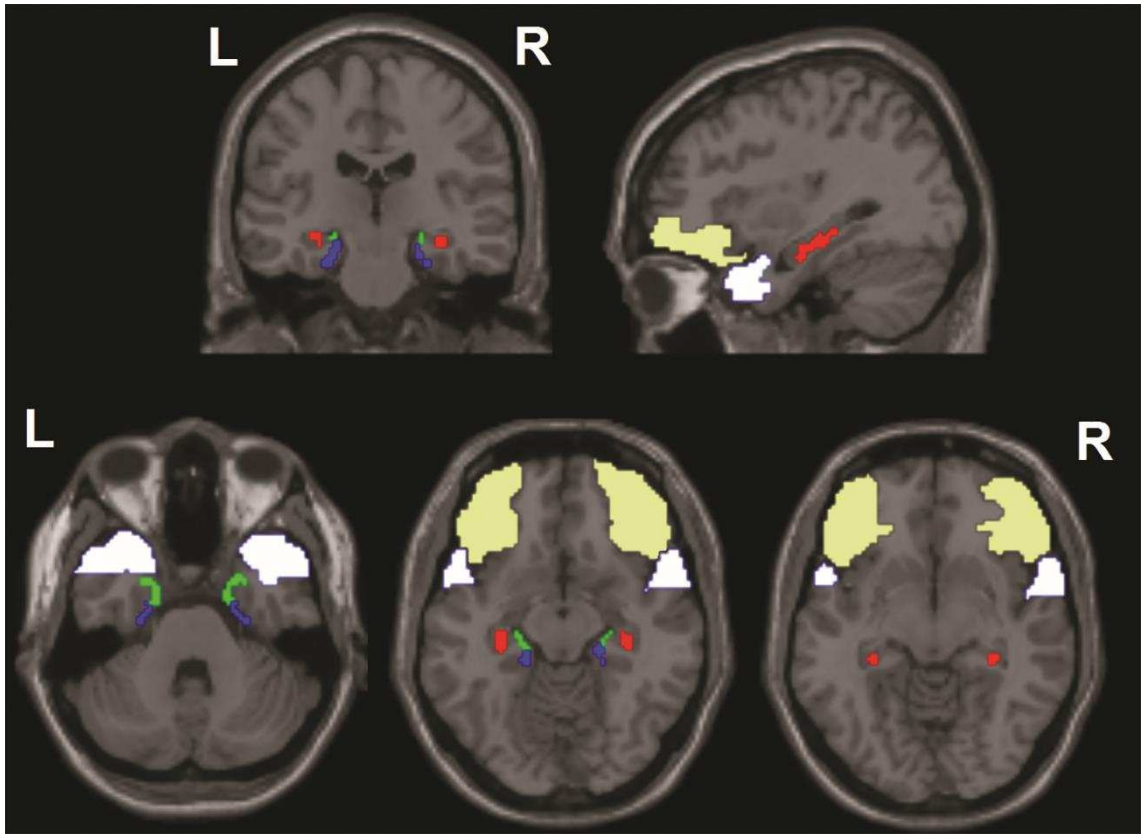

Figure 1