Article:
Venneri, A., Jahn-Carta, C., Marco, M.D. et al. (2 more authors) (2018) Diagnostic and prognostic role of semantic processing in preclinical Alzheimer's disease. Biomarkers in Medicine, 12 (6). ISSN 1752-0363

https://doi.org/10.2217/bmm-2017-0324

Diagnostic and prognostic role of semantic processing in preclinical Alzheimer's disease

Annalena Venneri[1*], Caroline Jahn-Carta[1*], Matteo De Marco[1], Davide Quaranta[2], Camillo Marra[3],

[1]Department of Neuroscience, University of Sheffield, Sheffield, UK

[2]Neurology Unit, Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy

[3] Institute of Neurology, Università Cattolica del Sacro Cuore, Rome; Memory Clinic, Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy

- *These two authors share first authorship

Address for Correspondence

Professor Annalena Venneri
Department of Neuroscience,
Medical School,
University of Sheffield
Beech Hill Road, Sheffield, S10 2RX, UK
a.venneri@sheffield.ac.uk
Tel: +44 (0) 114 2713430
Fax: +44 (0) 114 2713158

Acknowledgements: CJ-C was partially supported by The Malta Government Scholarship Scheme. This works was partially supported by the European Union Seventh Framework Programme (FP7/2007 – 2013) under grant agreement no. 601055, VPH-DARE@IT to AV. This is a summary of independent research carried out at the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience). The views expressed are those of the

author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The authors thank Laura Wright for her revision of the manuscript.

Abstract

Relatively spared during most of the timeline of normal ageing, semantic memory shows a subtle yet measurable decline even during the preclinical stage of Alzheimer's disease (AD). This decline is thought to reflect early neurofibrillary changes and impairment is detectable using tests of language relying on lexical-semantic abilities. A promising approach is the characterisation of semantic parameters such as typicality and age of acquisition of words, and propositional density from verbal output. Seminal research like the Nun Study or the analysis of the linguistic decline of famous writers and politicians later diagnosed with AD supports the early diagnostic value of semantic processing and semantic memory. Moreover, measures of these skills may play an important role for the prognosis of patients with mild cognitive impairment.

Keywords

Semantic Memory, Mild cognitive impairment, Neuropsychological Markers, Alzheimer's Disease, Linguistic attainment, Category Fluency Task

Executive Summary

The quest for an early biomarker of Alzheimer's disease (AD) is paramount

- Pathophysiological markers of AD do not always reflect the clinical profile.
- The current diagnostic formulae are centred on the early symptomatic prodromal stages of AD.
- A cognitive marker centred on semantic memory decline could be the most valid route to detect preclinical AD.

Semantic memory changes differ in normal ageing and AD

- Semantic processing and semantic memory tend to be relatively preserved in normal ageing.
- A severe semantic decline is observed in AD since its earliest stages.

Tests of language as a central typology of tests for an early diagnosis of AD

- The organisational complexity of semantic processing is quite intricate, both at a computational and neural level.
- Language tests are the most common instruments to test semantic processing.
- Distinctive instruments such as the Boston Naming test or the Category Fluency test are helpful instruments to detect early semantic changes.

Tests of semantic abilities as a diagnostic and prognostic marker

- The analysis of verbal production of famous writers and politicians later diagnosed with AD strongly suggests that semantic changes are measurable during the preclinical stage.
- Semantic competence appears informative at predicting disease progression of patients with mild cognitive impairment.

Conclusions

- Conceiving semantic memory and semantic processing as the primary focus of diagnostic and prognostic paradigms for AD is based on neuroanatomical and neuropathological evidence.
- An approach centred on semantic memory and semantic processing could be fruitful and revolutionary.

Future Perspective

Indices of semantic processing could be valid and reliable measures in clinical settings for the preclinical detection of early changes associated with Alzheimer's disease (AD). A number of measures may be easily identified in compliance with ideal parametric properties, for single one-off measurements as well as for repeated measurements over time. Measures of semantic processing could also be at the centre of the diagnostic procedures to stratify patients for enrolment in clinical trials.

The implementation of tests of semantic processing can be converted into safe and cost-effective screening instruments to detect individuals at risk of developing AD.

Comparable screening instruments need to be designed for use in non specialist settings by medical staff who have minimal or no competence with the administration of cognitive tests.

Introduction

Alzheimer's disease (AD) is the most common form of degeneration of the central nervous system. Although the causative variables that trigger its neuropathological cascade are still unknown, a large number of histological studies have described the two distinctive peptidic hallmarks: extracellular deposition of Beta Amyloid plaques, and intracellular neurofibrillary hyper-phosphorylation of TAU. The presence of these neurotoxic peptides, at the foundation of the pathophysiological diagnostic criteria [1], can be visualised and quantified *via* three main routes: 1) by analysing levels in the cerebrospinal fluid, obtainable with a lumbar puncture; 2) by inspecting uptake and retention of specific neuromolecular tracers, in a Positron Emission Tomography scan; 3) at autopsy. Although the first and second route allow clinicians to detect traces of the distinctive AD-related proteins *in vivo*, this information is not always relevant at a clinical level. In fact, a number of studies have clearly demonstrated that a proportion of individuals who meet pathophysiological criteria for AD do not have any clinical symptom, and, *vice versa*, a proportion of patients who show a clinical picture of progressive cognitive decline with an AD profile do not fulfil the pathophysiological criteria [2]. On these grounds, a precise characterisation of the clinical features of the disease is crucial to support diagnosis and prognosis. The clinical diagnostic criteria for AD are dependent on the presence of decline in cortical functions, gradually compromised by neuronal dysfunction: declining cognitive abilities, with a central role played by declarative (or explicit) memory. These criteria are applied to make a clinical diagnosis and they focus mainly on episodic aspects of declarative memory.

The discovery of a cure for AD remains elusive [3], and many researchers argue that repeated failure of potential disease-modifying treatment trials is due to the late application in the disease course [4]. The focus of research has, therefore, been shifted to preclinical

identification of individuals at risk of developing the disease. Some researchers have suggested that attention should be focused on those aspects of declarative memory, namely semantic memory, that are more likely to be associated with those brain regions that are affected by the earliest pathological signs of the disease (e.g., [5]). This stage precedes the pathological phase that manifests with the classical episodic memory decline distinctive of AD, as it is normally characterised by current clinical and research criteria [1,6,7].

The cognitive and neural framework behind semantic memory

It has been widely established over the years that the *declarative memory* construct proposed by Cohen and Squire is composed of two sub-systems: episodic and semantic memory [8]. Episodic memory is a "*memory system that allows people to consciously re-experience past experiences*" [9, page 6], while semantic memory is "*the system which contains the psychological representations of the "meanings" of words and the processes which operate on such representations*" [10, page 723]. Since its original definition by Tulving in 1972 [11], the concept of semantic memory has been characterised as a memory function deputed to processing conceptual knowledge associated with lexical (either verbal or not) referents, and the relations existing among these components. In the history of neuropsychology, the episodic-semantic dichotomy has been functional to account for the diverse pieces of evidence that support a certain independence of these two memory processes; examples include evidence from cases of developmental amnesia following early brain injury [12], adult epilepsy [13], severe prefrontal damage [14], or, as illustrated in the main body of this review, the separation of AD-related cognitive symptoms from the "benign" memory decline experienced during the normal process of physiological ageing.

The “encyclopaedic” trait of semantic memory mentioned above captures only its general outline. Representations sustaining semantic material are structured in a complex architecture of abstract ideas, words and images characterised by associations and hierarchies (see for instance [15]). Although a detailed focus on the psycholinguistic theories of semantics is beyond the scope of this review, being aware of such complexity is a necessary pre-requisite to comprehend the mechanisms by which semantics is stored and managed at a biological/neurological level, because it is at this level that AD pathology affects the nervous system. Several models have been proposed to attempt an explanation of how semantic information is organised. Important frameworks are those that hypothesise the existence of domain-specificities, advocating that there are distinct neural mechanisms responsible for the storage of items belonging to distinct domains, such as living and non-living items [16]. A further subdivision of this model suggests that information is organised depending on their sensory and functional features [17], with living items being differentiated by their visual appearance, while inanimate objects are recognised by their functional properties. The simple distinction between animate and inanimate objects, however, has been overcome by other authors, who have focused on the different weight that different sensorial experiences and gender roles may have in the development of computational representations of the features distinctive of any single object [18]. From this perspective, in a connectionist view [19], semantic features could be either distinctive (unique) or non-distinctive (shared). Distinctive features are those factors associated with less than two concepts while non-distinctive features are common to many concepts. Non-distinctive features, therefore, are highly inter-correlated with numerous strong links while distinctive features have few weak inter-connections. It is thought that these inter-connections are lost with disease related changes and non-distinctive features would be more resilient to AD damage [20].

This computational complexity is mirrored by a dense neural implementation. Engaging in semantic processing can be broken down into two complementary types of computation, each of which is sustained by its distinctive network of brain regions. A distinction is made between automatic (bottom up) processes that involve the semantic representations stored in the cortex, and controlled (top down) processes that are executive in nature. Semantic representations are well known to be distributed throughout multiple regions [21], and recent evidence indicates that the level of conceptual resolution of the semantic atlas is extremely detailed [22]. Semantic control too, however, is sustained by a widespread set of anterior and posterior regions [23]. Arguably, this extensive anatomical involvement may be due to the diverse nature of the control processing, that may occur, for instance, at a lower computation level during the feature extraction phase [24] or higher up in the sequence of computations, when, for instance, semantic interference is addressed [25]. Different regions, then, may show some degree of specificity based on certain modalities (e.g., sensory, motor, or emotional), while the involvement of other areas spans across multiple modalities [26]. This picture characterises semantic processing, the object of semantic memory, as a complex multi-componential function both at a computational as well as neuro-structural and neuro-functional level. If on one hand semantic functioning has been described in such fine-grained terms, it has to be acknowledged that the instruments at the clinician's disposal to measure semantic functioning tend to allow the sole measurement of global levels of competence. Standard neuropsychological measures of semantic processing give us no opportunity to understand where in the computational cascade a deficit may exist. In this respect, to be informative, the performance obtained on a certain cognitive test always has to be contextualised in an appropriate way. This contextualisation includes, for example, taking the "semantic background" of the person into account (i.e., an individual might have personal expertise in certain semantic domains), but also interpreting a certain cognitive score in the

light of the performance shown in other cognitive domains associated with those invoked by tests of semantic processing (e.g., episodic memory, working memory, language comprehension), or interpreting a certain score in the light of other measurements acquired longitudinally (e.g., a follow up). For example, patients with AD may show a similar pattern of test scores to those of patients with the semantic form of frontotemporal lobe degeneration (semantic dementia), yet the components of semantic processing affected may be very different [27]. Widening the decision-making context, patients with semantic dementia tend to have normal levels of episodic memory [28], and the clinical history is also of aid, because their earliest complaint is usually a naming difficulty, not memory difficulties. Of additional decision-making help is the evidence from structural neuroimaging showing more localised cortical atrophy in semantic dementia.

It remains, however, that current provision of semantic memory tests is of limited quality and not specifically devised for assessing impairments due to neurodegeneration. More fine-grained instruments, informed by cognitive neuropsychology models, would allow a better segregation of semantic impairments underpinned by different forms of neurodegeneration. For example, tests that can differentiate between different components of semantic processing (e.g., semantic representation vs. semantic control) would most likely detect the difference in the types of impairment caused by different underlying diseases.

Semantic memory in healthy ageing and in AD

It is well established that semantic memory is not subjected to an age-related decline of comparable magnitude as episodic memory [29]. Although both types of declarative memory rely on mechanisms of encoding and retrieval, there seems to be a substantial difference between the set of regions that contribute to sustaining episodic memory processing, and the

set of regions that support instead the mechanisms of memory associated with semantic processing, as those described in the previous section. This anatomical distinction would be the basis of the functional discrepancies seen in the ageing population and in a number of clinical cases. The mediotemporal lobe, crucial for declarative memory, includes a series of interconnected structures. Among these structures, the hippocampus would be responsible for context-rich memory processing (i.e., episodic memory), while the sub-hippocampal portion, including the perirhinal and entorhinal cortices, would be responsible for context-free memory processing (i.e., spatial and semantic memory) [30].

This overview on episodic and semantic memory, the clinical dissociability of the two, and the neural differences in support of each function is necessary to understand the true potential that clinical measures of memory have in the early detection of AD. In fact, the neuropathological staging of neurofibrillary TAU deposition is intense in the mediotemporal complex during the early stages of the diseases, but the first areas of the cortex affected by tangles are the entorhinal and perirhinal cortices, with relative sparing of the hippocampus [31]. As a consequence, changes in some aspects of semantic memory function would represent the earliest memory change shown by AD patients. Disruption of semantic proficiency would occur before the onset of the typical episodic memory symptoms that would instead appear as the pathology spreads to the hippocampus [32]. This mechanism has implications on the possibility to take the current diagnostic criteria to a new level. In fact, the diagnostic criteria for the diagnosis of mild cognitive impairment (MCI) due to AD appropriately assign a central role to episodic memory [6]. The proposed criteria for preclinical AD (that is, before the typical episodic memory symptoms manifest), however, do not assign any role to semantic memory [33]. Arguably, an accurate characterisation of semantic memory would allow clinicians to detect the presence of AD pathology when it is

confined to the sub-hippocampal region, while criteria based solely on episodic memory would not enable any comparable diagnostic improvement [5].

Language as gateway to semantic memory in healthy ageing and AD

The concept of semantic memory is indissolubly linked to the manipulation of semantic material. One of the dogmas of neuropsychology is the shared nature of the semantic system, implying, therefore, that semantic representations can be accessed with a multitude of routes. The preferential pathway for semantic access is, without any doubt, verbal language. However, the same semantic content can be equally conveyed via other routes, such as non-verbal language (e.g., sign language) [34], music [35], or art [36]. Since language is the primary channel through which semantic content is conveyed, the study and assessment of semantic memory is carried out via tasks that are, to all intents and purposes, tests of language. In this respect, the study of semantics has become a central research topic in AD, both because of its link with the semantic memory system, but also due to its link with the neural systems that sustain it, and the ample degree of overlap these systems show with the regions subjected to an AD-dependent pattern of neural down-regulation.

Linguistic skills are the most resilient function to cognitive ageing. A decline in semantic abilities (measured by the analysis of propositional content) becomes noticeable only in the late adulthood, during the 7th decade of life [37]. However, there is a clear discrepancy between the observed changes in semantic processing and those changes that would be expected based on the well established anatomical and functional modifications that naturally affect the neural architecture. Ageing is associated with a non uniform progressive loss of cortical volume, particularly exacerbated in a set of regions, including the posterior cingulate cortex, the mediotemporal region, the medial prefrontal cortex, and a large portion of the

temporal lobe [38]. Astonishingly, this ensemble accurately reflects the complex of areas emerged from a meta-analysis of 120 fMRI studies of semantic activation [39]. These two converging pieces of evidence would suggest that, if anything, ageing should result in a prominent lexical-semantic decline. Instead, only a moderate decrease is detected, and there are studies showing either no effects [40], or even improvement with age [41]. In part, this counterintuitive observation could be due to neural compensation that is present in well-functioning older people. Examples of compensatory mechanisms are increases in contralateral activation [42], or an increased contribution of anterior regions during tasks for which posterior regions would be naturally designated [43]. Certainly, these compensatory mechanisms may play a role in attenuating the effects of age on linguistic abilities, but compensation alone would not explain why these mechanisms would be selective for language, while other functions (e.g., episodic memory) would not benefit in a similar manner. Attempting to come up with a theoretical reason on why linguistic skills are particularly robust against ageing falls beyond the scope of this review. Unequivocal, however, is the fact that language processing is an ability that remains highly functional in elderly adults. Very often what looks like a decline in this cognitive domain is actually just a response to changes in cognitive functions that are required for the processing of speech such as working memory and attention, rather than in the lexical-semantic system itself [44]. A linguistic domain that plays an essential role at conveying semantic content is syntax, an aspect of language that shows an age-related "simplification". Supported by specific anatomical evidence [45], syntactic decline is visible during spoken language, for instance, where older people tend to use simpler grammatical forms that are less memory-demanding [46]. In a similar manner as with syntax, mechanisms of retrieval contribute to downsize semantic performance. Older adults often complain about not being able to recall certain words [47] and about experiencing an increase in the tip-of-the-tongue phenomenon [48].

This explanation is valid for proper nouns, possibly due to the detached nature of the lexical unit (the name/surname) from any semantic content [49], and for their uniqueness and lower frequency than other words [50]. On the other hand, when the task requires mechanisms of lexical retrieval (e.g., the Boston Naming test), an age-associated performance decrease is seen, although performance remains largely at levels of test accuracy well above 80%, in adults older than 70 years, as opposed to adults in their fifties, who obtain performance levels above 90% [51]. Although, again, this decline might be due to decreasingly functional mechanisms of retrieval, there are also studies indicating that, to a minimal extent, age-associated semantic degradation may be visible in adults older than 70 years, as measured with the Pyramids and Palm Trees test [52]. This finding, however, has not been consistently replicated (see for instance [53]). In conclusion, the mechanisms of ageing are associated with a relative preservation of semantic and, more generally, linguistic processing skills. A certain degree of disruption of these skills may be visible in old age, but semantic and linguistic impoverishment is of lower magnitude than the disruption seen in most other cognitive abilities and could be secondary to degradation of other cognitive processes. Tests of language indexing semantic processing are helpful instruments to delineate the cognitive profile of elderly adults, as they can act as a counterpart of episodic memory in the description of declarative memory decline.

The effect AD has on measures of language and semantic processing is diametrically opposed to ageing effects. Due to the marked atrophy of frontal and temporal lobes in AD, it is expected that linguistic abilities start deteriorating earlier on in the disease. Longitudinal analyses of connected discourse and experimental tasks that resemble real life conversations, such as spontaneous speech, narration and description of scenes [54,55] provide a large amount of information about the language deficit in AD, and how it differentiates from the difficulties observed in healthy ageing. Linguistic changes in verbal expression are present

during preclinical AD. During the early stage of the disease, articulation and melodic line are not greatly affected, and the length and number of sentences are similar to the linguistic production observable in healthy individuals matched for age and education [56]. Later on, however, AD patients tend to produce fewer words in a given time, speak slower than controls, have higher numbers of stutters, produce fewer self-corrections and engage in incomplete conversations [54]. Patients with mild to moderate AD also produce more word-finding delays, semantic paraphasias, empty phrases and indefinite sentences [56]. Language comprehension is relatively preserved in AD, although patients have difficulties understanding syntactically complex sentences. A degree of difficulty in complex syntactic comprehension is also found in healthy ageing, but the difficulty is more pronounced in AD, even during the MCI stage. Patients with early AD show difficulty in understanding both literal and non-literal speech, and the more complex the discourse is, the worse the performance [57]. Once again, the most dominant problems are related to the semantics of language, followed by lexical difficulties [58]. Language impairments observed earlier on in the disease are mainly semantic errors that are, then, accompanied by errors in phonological, visual and motoric aspects of speech. Motoric errors, however, do not appear until later on in the disease course, when cortical degeneration spreads to the frontal lobes, the neural substrates responsible for phonological processing and motor output [56].

A range of tests is available to assess semantic proficiency in clinical practice. The most widely used test of semantic memory in the assessment of neurodegenerative conditions is the Category Fluency test, either as a stand-alone test or embedded in screening instruments or short evaluations batteries. This instrument offers methodological and theoretical advantages over any other test of semantic processing. It is usually administered together with the Letter Fluency test, (not similarly affected by AD) that provides a methodological control for the interpretation of residual semantic abilities. Moreover, the Category Fluency

test is widely used world-wide, across different languages and cultures, a feature that is essential in societies where multiple cultures co-exist, and crucial when comparing studies carried out in different countries. Other tests of semantic abilities such processing of famous faces [59] or processing of knowledge of famous people [60] may certainly be clinically relevant when contextualised appropriately and extremely informative in the single patient, but cannot be transposed to other contexts as easily. Different cultures, different generations, and different diagnoses (e.g., patients with AD may not recognise a recent photo of an old famous person, but might be able to recognise them from a photo taken where they were young. Instead, a patient with vascular dementia would not show this effect), are factors that can influence performance. Methodological and theoretical factors, therefore, underlie the popularity of the Category Fluency test as a measure of semantic proficiency.

Although this instrument relies on executive functioning, the central computational role is played by language [61]. This test has been extremely helpful in the characterisation of pathological processes associated with AD. Asymptomatic carriers of the Apolipoprotein E ε_4 allele (the best established genetic risk factor for sporadic AD), for instance, generate fewer items than healthy participants [62]. A study that looked at different strategies used in the Category Fluency test to establish which technique best discriminates healthy ageing and AD found that the best discriminator is the score of total number of words generated during a given time [63]. This study showed that healthy individuals who later on developed dementia produced fewer words at baseline assessment five years before disease onset, than those persons who remained healthy. Category switching (the shift between different sub-categories that relies on prefrontal lobe processes) and clustering (the number of novel switched sub-categories) are also good measures to discriminate between the two types of ageing [64]. During the early disease stages, there appears to be no difference in the number of repetitions and perseverations, and this finding suggests that working memory is not

impaired at this stage [63]. AD patients produce fewer words, smaller cluster sizes and less switching compared to healthy people. People with memory complaints also produce fewer words and smaller cluster sizes compared to people with no memory deficits, but no difference in switching is observed between the two groups [65]. Therefore, cluster size is a better predictor of early AD than number of words. A longitudinal study that followed up people with memory complaints found that after two years they had greater alterations in semantic fluency and in cluster size than those people who did not develop dementia [65]. Furthermore, a change in word characteristics and number of words generated is observed in a clinical setting [54,66]. Studies using the Category Fluency test have also predicted changes in behavioural and psychological symptoms in patients [67].

Another test widely used to assess semantic processing is the Boston Naming test. Performance on this test is associated with the typical pattern of regions responsible for semantic processing [68]. Patients with AD show both lexical and semantic deficits on this test. They have difficulty accessing words and naming objects [69] and also tend to produce the superordinate of the item rather than the subordinate, for example saying 'animal' instead of 'tiger' [66]. These types of error suggest difficulty in verifying semantic attributes of concepts and retrieving the semantic category of that object. An association is also noted between naming living and non-living things and sex of participants. This could be due to sex-based familiarity effects [70]. Aside from the mere observation of global test scores as index of semantic processing, the performance on these tests is driven by a number of factors that have been shown to be intrinsically dependent on the integrity of semantic representations. This is the case, for instance, of age of acquisition [71,72], or typicality of words [73]. In summary, a detailed analysis of semantic properties of language allows what looks like a clear-cut separation between patients with AD and healthy controls. As illustrated in the next sections, this clinical characteristic could be potentially exploited

successfully for the diagnosis of AD when the disease is still in the pre-symptomatic (or pre-clinical) stage, i.e., when typical episodic memory deficits have not overtly manifested yet. Furthermore, reliance on detailed analysis of lexical-semantic decline may also have prognostic value at the prodromal MCI stage. In addition, there seems to be a strong anatomical convergence between the topographical distribution of early AD neuropathology and the conjunct effect of lexical-semantic features (i.e., age of acquisition and typicality) as ascertained by voxel-based correlational analysis of structural changes (see **Figure 1**). This convergence might be an important factor in the role played by lexical-semantic features in early AD diagnosis and prognosis.

- Insert **Figure 1** about here -

Decline in semantic processing as a cognitive marker of preclinical AD

The literature on experimental evidence in support of tests of semantic processing as diagnostic instruments for preclinical AD is quantitatively scant, but characterised by prominent benchmark studies. The study of preclinical sporadic AD requires large cohort and longitudinal designs that must span over several decades, and for this reason they are of tough pursuit. The most seminal work is the "Nun Study" that is based on the analysis of linguistic features extracted from autobiographical diaries written by female members of the clergy during early adulthood. The results of this study indicate that idea density during early adulthood is associated with the presence of AD pathology as emerged from histological assays at *post mortem*, several decades later [74]. A second study aligns with these results by reporting an association between clinical evidence of AD and low propositional density of

medical school essays authored by patients more than fifty years prior to diagnosis [75]. Gaining access to verbal production from the patient's past is a methodological requirement for this type of studies. In this respect, striking evidence emerges from the longitudinal analysis of written material published by famous novelist Iris Murdoch, diagnosed with AD a few years after writing her last, controversial book. Semantic features extracted from this opus show a significant decline as compared to her early career, and mirror those features believed to be the incipient signs of AD interfering with her lexical-semantic abilities [76]. Additionally, further analyses found that impoverishment of her vocabulary and syntax skills was detectable even in her earlier production, when she was in her late 40s and 50s, thus decades before the onset of any symptom [77]. Comparable analyses, conducted on the written production of Dutch novelist Gerard Reve (who was diagnosed with AD shortly after his last release) revealed a similar picture [78]. Analogous results emerged from the analysis of presidential speeches given by Ronald Reagan during his United States presidency, years before his diagnosis of AD [79]. Further evidence in support of impoverishment of semantic ability as a preclinical marker of AD is found in studies of asymptomatic individual carriers of genetic mutations determining the familial form of the disease. Asymptomatic individuals in their 40s who carry a mutation in the Presenilin 1 locus who are in the preclinical stage of familial AD show reduced semantic skills when compared with adults with no genetic burden, as measured by the Category Fluency test and by a task in which participants had to provide definitions for words [80]. The evidence from life-long longitudinal designs is limited due to a range of methodological issues. The emerging results are, however, convergent and unequivocal, and suggest that a deep focus on semantic processing may help anticipate a diagnosis of AD by a large number of years, as opposed to the clinical possibilities offered by the current widely recognised criteria.

Defining a biomarker, however, is a complex process that requires extensive validation. Although measures of semantic abilities have still to be fully validated before qualifying as a proper biomarker, a number of studies have confirmed the presence of a significant association between performance on typical tests of semantic processing and markers of neurodegenerative and pathophysiological changes distinctive of AD. Beyond a certain degree of inter-study variability, performance on the Category Fluency test was consistently found to be associated with fluorodeoxyglucose metabolism in frontal and parietal regions, prevalently in the left hemisphere, in patients with AD dementia [81-83]. Following comparable methodologies, performance on the Boston Naming test showed positive associations with temporo-polar and infero-temporal metabolism [83,84]. These two tests were also associated with the variability of left prefrontal, temporal, and mediotemporal volumes [85]. If, however, the claim is that indices of semantic processing are informative at the pre-symptomatic stage of the disease, it is particularly important to confirm their validity for the purpose in that specific population of interest. This approach is necessary because the neural correlates of semantic memory are different between healthy and diseased individuals [86,87]. A number of studies bring confirmatory evidence in support of this claim. In healthy adults, performance on both the Category Fluency and Boston Naming tests is associated with the temporal and mediotemporal volume, including the hippocampus and the parahippocampal gyrus [88]. In this population, semantic processing is also associated with both central and peripheral indices of *in vivo* amyloid pathology [89,90], and with the cortical thickness of the sub-hippocampal complex, including perirhinal and entorhinal cortices, a change believed to be the consequence of the early deposition of neurofibrillary tangles [91]. The evidence of this study, however, provides only an indirect connection, and no clear-cut association has yet been described between semantic abilities and neurofibrillary pathology in the preclinical stage of AD. Overall, there is promising evidence in support of a future

formal definition of semantic processing and semantic memory breakdown as an early AD biomarker. At this stage, this proposition remains a valid working hypothesis, but more solid findings are needed.

The prognostic value of measures of linguistic-semantic processing

In addition to the urgency for a diagnostic aid at the preclinical stage, in clinical practice there is a pressing need for a prognostic aid at the prodromal phase, commonly referred to as MCI stage. Since its very early definition [92], the MCI construct has been developed to define individuals affected by cognitive impairments, not severe enough to be diagnosed as demented ("not normal nor demented"), but who may eventually progress to overt dementia. Such a concept has emerged as highly attractive from both a clinical and a theoretical point of view, with a large number of studies aiming at the identification of markers that could aid the detection of those MCI individuals who will actually progress to dementia. The very first step in this direction was based on the distinction of MCI in different sub-types (amnestic vs. non-amnestic and single-domain vs. multiple-domain) [93]. The characterisation of these different sub-types suggested that the amnestic forms (aMCI) were those that more specifically converted to AD [93]. The prognostic reliability of this approach, however, soon became questionable, at its best [94]. Great attention, therefore, has been paid to the identification of specific neuropsychological markers that could reliably flag up an increased risk of progression to dementia [95]. There is a general agreement that neuropsychological tests assessing episodic memory (delayed recall in particular) are the most reliable neuropsychological predictors of progression to AD at this stage [1,95,96]. As reviewed above, it is conceivable that subtle lexical-semantic deficits may be already detectable at the preclinical stage of AD and there is evidence that these deficits are also present during the

MCI phase [97]. It follows that tests assessing language and semantic memory might also play a part in prognosis and might be reliable predictors of conversion from MCI to AD, yet, the results of previous studies are not always consistent with this hypothesis. This inconsistency is mainly due to methodological shortcomings and the different methods used to assess semantic competence. In most cases, language and semantic memory were assessed using various versions of the Category Fluency test, mainly focusing on the total number of words retrieved. Some studies have reported that individuals who later progressed to dementia generated fewer words than non-converters at baseline evaluation (e.g., [98,99]). In addition, several studies have failed to replicate these findings (e.g., [100,101]). Even in studies reporting univariate group differences in Category Fluency total score, the predictive value of the total number of words produced on Category Fluency tests was not confirmed by multiple variable regression models [73,98]. A review study that surveyed the ability of different semantic tasks to differentiate MCI and preclinical AD from normal ageing elderly concluded that Category Fluency tests are more reliable than Naming tests and Letter Fluency tests in distinguishing MCI due to AD from MCI individuals who do not progress to AD or from normal ageing elderly [102]. A number of studies has confirmed such observation. Furthermore, it is interesting to note that good performance on Category Fluency tests can predict who will revert to normal performance on neuropsychological tests at follow up among the MCI population [103]. At variance with Category Fluency, contrasting results come from studies that assessed confrontation naming, with some reporting that naming tests have some predictive value [100,104], while others have not confirmed such findings (e.g., [101]).

It is possible that such variability in findings might be the outcome of more general issues that affect longitudinal studies on MCI, such as sample heterogeneity, inclusion criteria, etc. It needs to be acknowledged, however, that there are specific characteristics of the Category

Fluency test that, better than other linguistic tasks, can predict outcome over time. Such characteristics probably refer to specific competence and the distinctive organisation of semantic memories, the disruption of which can only be detected by specific tests. For example, very few studies have investigated the possible differential predictive value of various semantic categories in Category Fluency tests. Clark and colleagues [105] reported that individuals converting to dementia at follow up, at baseline, produced fewer words than stable individuals on the categories of "articles of clothing", "fruits and vegetables", "things one finds in a supermarket", and "vegetables", but not on "animals" (animals is the category assessed in the widely used CERAD verbal fluency test). More generally, the investigation of items that rely on unique idiosyncratic pieces of information such as proper names and unique entities might be earlier affected by neurodegeneration than other general categories of semantic knowledge such as objects that share more common attributes with other exemplars of their category. Research has reported evidence in support of this hypothesis by showing that in MCI recognition of famous people is affected earlier than recognition of objects [59,106]. Indeed, knowledge of famous people, because it relies more on unique idiosyncratic information, similarly to proper nouns is more vulnerable to disease effects and therefore more greatly affected than knowledge of objects in aMCI and AD [60], with object knowledge relying more on sensory and functional properties. Although sensitive, tests involving famous people suffer from methodological shortcomings as highlighted in one of the earlier sections in this review.

Apart from categorical dissociations, other markers of prediction in MCI could be derived by studying intrinsic psycholinguistic markers extracted from word production during Category Fluency tests. A fine-grained analysis of the lexical characteristics of words produced by persons with MCI has shown that those MCI who will progress to dementia generate words with higher typicality than MCI who will remain stable [73] **(Figure 2)**.

- Insert **Figure 2** about here -

Thus, it is conceivable that the lack of consistency of findings among published studies might be explained by the fact that the mere assessment of the total number of generated words ("how many words does the patient generate?") should be accompanied by a qualitative analysis of lexical entries ("which words does the patient generate?"). In this respect, the availability of reliable norms for lexical frequency, age of acquisition and typicality may be of some advantage [107]. Further putative markers of progression to AD could also be supplied by answering the question "how does the patient generate words?". As reported in earlier sections in this review, category switching, clustering [64], number of repetitions and intrusions [63] are good measures to discriminate between normal and pathological ageing. The investigation of how the sequences of words are produced (to examine path, similarity, repetition, and network of production) has shown a progressive simplification from normal elderly controls to amnestic MCI to AD [108].

The timing of word generation (specifically, the difference between the number of words generated in the first time segment (i.e., the first 15 s) of each trial and the number of words generated during the last time segment (i.e., the last 15 s) of the same trial in the Category Fluency test) could be exploited as another interesting marker to unmask the exhaustibility of semantic storage. In fact, normal adults tend to produce significantly more words during the first 15 s of the task (n = 8, on average), than in any of the other quartiles, with less than 3 words generated on average during the last quartile [109]. The decrement from quartile to quartile in the number of correct entries reflects, in all likelihood, an increased involvement of semantic control, necessary to explore the category assigned more thoroughly. This

indicates that the degree of decrement might be a variable of particular interest. Most of these potential markers need further investigation to determine operational cut-offs and finalise a methodology more suitable for clinical assessment.

The entangled picture of the relationship between lexical-semantic impairment and progression of MCI is made even more complex by some observations made on subtypes of AD. In fact, a subtype of AD featuring the association of episodic and semantic memory impairment, with reduced involvement of other cognitive domains, has been described [110]. Follow-up studies have shown that this neuropsychological pattern was associated with a slower rate of cognitive decline than the decline observed in patients with the cognitive profile of "typical" AD [111]. Studies based on cluster analysis have reported that a similar pattern of disruption could be identified even at the MCI stage of the disease [112]. Follow-up studies showed that MCI people with a profile characterised by episodic and semantic memory impairments had a low rate of progression towards dementia [112]. These pieces of evidence suggest that this cognitive profile may be the clinical manifestation of a specific subtype of AD, with a somewhat "benign" course. These findings should be taken into account when pooling data in large studies and, maybe, even when stratifying patients for enrolment in clinical trials.

In conclusion, the role of classical tests assessing lexical-semantic processing in prognosis is still not clear. On the basis of the available evidence, the prognostic value of such measures may be improved by implementing a new approach, including the assessment of qualitative aspects of semantic impairment alongside specific attention towards putative subtypes of MCI that may herald different patterns of progression to dementia.

Conclusive remarks

The opportunity offered by semantic memory, semantic processing, and language to aid diagnostic procedures for sporadic AD, and to track its clinical development is, today, of crucial importance. This review has highlighted important progress, but it has also identified important weaknesses and the need for further investigations. Although throughout the years the study of AD has allowed us to gain a considerable amount of knowledge about the biological mechanisms of the disease, the community is still crying out for ground-breaking research breakthroughs. Specifically, what we need are novel and revolutionary approaches to early detection [113]. On this note, not only can the study of semantic memory represent an instance of a new approach because of its sound theoretical basis, it is also characterised by a convenient costs-benefit ratio, as it is cost-effective, non-invasive, suitable for large scale screening and linked to the possibility of carrying out a large amount of retrospective research. We argue that a similar approach could be translated into the diagnostic and prognostic characterisation of other neurodegenerative conditions. We obviously do not mean that semantic memory is the sole cognitive domain that deserves this type of attention. For instance, a number of studies have investigated the potential clinical role of non-cognitive behavioural symptoms as preclinical markers of neurological conditions [114]. Hopefully, such early detection will allow for early interventions, especially once disease-modifying therapies will be available.

References

Papers of special note have been highlighted as: * of interest; ** of considerable interest

1. Dubois B, Feldman HH, Jacova C et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol*. 13(6), 614-629 (2014).

2. Ince PG. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet*. 357(9251), 169-175 (2001).
   * This histological study brings evidence of dissociability between clinical and pathological evidence of Alzheimer's disease. There are patients who fulfil clinical but not pathophysiological criteria of the disease and, *vice versa*, there are patients who fulfil pathophysiological but not clinical criteria of the disease.

3. Cummings J. Lessons learned from Alzheimer disease: Clinical trials with negative outcomes. *Clin Transl. Sci*. In Press. doi: 10.1111/cts.12491 (2017).

4. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: Implications for prevention trials. *Neuron*. 84(3), 608-622 (2014).

5. Venneri A, Mitolo M, De Marco M. Paradigm shift: Semantic memory decline as a biomarker of preclinical Alzheimer's disease. *Biomark. Med*. 10(1), 5-8 (2016).

6. Albert MS, DeKosky ST, Dickson D *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7(3), 270-279 (2011).

7. McKhann GM, Knopman DS, Chertkow H *et al.* The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-

Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7(3), 263-269 (2011).

8. Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science*. 210(4466), 207-210 (1980).

9. Tulving E. Episodic memory: From mind to brain. *Annu. Rev. Psychol*. 53, 1-25 (2002).

10. Griggs RA. Semantic memory: A bibliography, 1968-1975. *Percept. Mot. Skills*. 43(3 pt. 1), 723-728 (1976).

11. Tulving E, Donaldson W, Bower GH. Organization of memory. United States. Office of Naval Research: Academic Press (1972).

12. Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*. 277(5324), 376-380 (1997).

13. Tramoni E, Felician O, Barbeau EJ *et al*. Long-term consolidation of declarative memory: Insight from temporal lobe epilepsy. *Brain*. 134(Pt 3), 816-831 (2011).

14. Squire LR, Zola SM. Episodic memory, semantic memory, and amnesia. *Hippocampus*. 8(3), 205-211 (1998).

15. Wettler MN. The formation of a semantic network by induction. *Psychol Forsch*. 35(4), 291-316 (1972).

16. Caramazza A, Shelton JR. Domain-specific knowledge systems in the brain the animate-inanimate distinction. *J. Cogn. Neurosci*. 10(1), 1-34 (1998).

17. Warrington EK, Shallice T. Category specific semantic impairments. *Brain*. 107(Pt 3), 829-854 (1984).

18. Gainotti G, Spinelli P, Scaricamazza E, Marra C. The evaluation of sources of knowledge underlying different conceptual categories. *Front. Hum. Neurosci*. 7:40 (2013).

19. Rumelhart DE, McClelland JL. Parallel distributed processing: Explorations in the microstructure of cognition (Vol. 1). Cambridge: MIT Press (1986).

20. Flanagan KJ, Copland DA, Chenery HJ, Byrne GJ, Angwin AJ. Alzheimer's disease is associated with distinctive semantic feature loss. *Neuropsychologia*. 51(10), 2016-2025 (2013).

21. Small SL, Hart J, Nguyen T, Gordon B. Distributed representations of semantic knowledge in the brain. *Brain*. 118(Pt 2), 41-53 (1995).

22. Huth AG, de Heer WA, Griffiths TL, Theunissen FE, Gallant JL. Natural speech reveals the semantic maps that tile human cerebral cortex. *Nature*. 532(7600), 453-458 (2016).

23. Whitney C, Kirk M, O'Sullivan J, Lambon Ralph MA, Jefferies E. Executive semantic processing is underpinned by a large-scale neural network: Revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J. Cogn. Neurosci*. 24(1), 133-147 (2012).

24. Neri P. Semantic control of feature extraction from natural scenes. *J. Neurosci*. 34(6), 2374-2388 (2014).

25. Canini M, Della Rosa PA, Catricalà E *et al*. Semantic interference and its control: A functional neuroimaging and connectivity study. *Hum. Brain Mapp*. 37(11), 4179-4196 (2016).

26. Binder JR, Desai RH. The neurobiology of semantic memory. *Trends. Cogn. Sci.* 15(11), 527-536 (2011).

27. Libon DJ, Rascovsky K, Powers J *et al*. Comparative semantic profiles in semantic dementia and Alzheimer's disease. *Brain*. 136(Pt 8), 2497-2509 (2013).

28. Irish M, Bunk S, Tu S, *et al.* Preservation of episodic memory in semantic dementia: The importance of regions beyond the medial temporal lobes. *Neuropsychologia.* 81, 50-60 (2016).

29. Lövdén M, Rönnlund M, Wahlin A, Bäckman L, Nyberg L, Nilsson LG. The extent of stability and change in episodic and semantic memory in old age: Demographic predictors of level and change. *J. Gerontol. B. Psychol. Sci. Soc. Sci*. 59(3), P130-P134 (2004).

30. Mishkin M, Suzuki WA, Gadian DG, Vargha-Khadem F. Hierarchical organization of cognitive memory. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 352(1360), 1461-1467 (1997).

31. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging*. 16(3), 271-278 (1995).

32. Didic M, Barbeau EJ, Felician O *et al*. Which memory system is impaired first in Alzheimer's disease? *J. Alzheimers Dis*. 27(1), 11-22 (2011).

** This review summarises the evidence in support of an association between semantic memory and changes observed in the sub-hippocampal regions crucial in

Braak Stages I and II. This is at the basis of semantic memory changes predating episodic memory changes in Alzheimer's disease.

33. Dubois B, Hampel H, Feldman HH *et al*. Proceedings of the meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The preclinical state of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 12(3), 292-323 (2016).

34. Marshall CR, Rowley K, Mason K, Herman R, Morgan G. Lexical organization in deaf children who use British Sign Language: Evidence from a semantic fluency task. *J. Child Lang*. 40(1), 193-220 (2013).

35. Koelsch S, Kasper E, Sammler D, Schulze K, Gunter T, Friederici AD. Music, language and meaning: Brain signatures of semantic processing. *Nat. Neurosci*. 7(3), 302-327 (2004).

36. Takahashi S. Aesthetic properties of pictorial perception. *Psychol. Rev*. 102(4), 671-683 (1995).

37. Kemper S, Marquis J, Thompson M. Longitudinal change in language production: Effects of aging and dementia on grammatical complexity and propositional content. *Psychol. Aging*. 16(4), 600-614 (2001).

38. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB; Alzheimer's Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog. Neurobiol*. 117, 20-40 (2014).

39. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex*. 19(12), 2767-2796 (2009).

* This meta-analysis outlines the map of regions sustaining semantic processing, and illustrates its spatial overlap with the default mode network.

40. Lacombe J, Jolicoeur P, Grimault S, Pineault J, Joubert S. Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. *Brain Lang*. 149, 118-127 (2015).

41. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging*. 17(2), 299-320 (2002).

42. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage*. 17(3), 1394-1402 (2002).

43. Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. *Cereb. Cortex*. 18(5):1201-1209 (2008).

44. Baddeley A. Working memory and language: An overview. *J. Commun. Disord*. 36(3), 189-208 (2003).

45. Antonenko D, Brauer J, Meinzer M *et al*. Functional and structural syntax networks in aging. *Neuroimage*. 83,513-523 (2013).

46. Kynette D, Kemper S. Aging and the loss of grammatical forms: A cross-sectional study of language performance. *Lang. Commun*. 6(1-2), 65-72 (1986).

47. Schmitter-Edgecombe M, Vesneski M, Jones DW. Aging and word-finding: A comparison of spontaneous and constrained naming tests. *Arch. Clin. Neuropsychol*. 15(6), 479-493 (2000).

48. Burke DM, MacKay DG, Worthley JS, Wade E. On the tip of the tongue: What causes word finding failures in young and old adults? *J. Mem. Lang*. 30, 542-579 (1991).

49. Cohen G. Why is it difficult to put names to faces? *Br. J. Psychol*. 81(3), 287-297 (1990).

50. Evrard M. Ageing and lexical access to common and proper names in picture naming. *Brain Lang*. 81(1-3), 174-179 (2002).

51. Mackay AI, Connor LT, Albert ML, Obler LK. Noun and verb retrieval in healthy aging. *J. Int. Neuropsychol. Soc*. 8(6), 764-770 (2002).

52. Verhaegen C, Poncelet M. Changes in naming and semantic abilities with aging from 50 to 90 years. *J. Int. Neuropsychol. Soc*. 19(2), 119-126 (2013).

53. McGeown WJ, Shanks MF, Forbes-McKay KE, Venneri A. Patterns of brain activity during a semantic task differentiate normal aging from early Alzheimer's disease. *Psychiatry Res*. 173(3), 218-227 (2009).

54. Forbes-McKay KE, Venneri A. Detecting subtle spontaneous language decline in early Alzheimer's disease with a picture description task. *Neurol. Sci.* 26(4), 243-254 (2005).

55. Cuetos F, Arango-Lasprilla JC, Uribe C, Valencia C, Lopera F. Linguistic changes in verbal expression: A preclinical marker of Alzheimer's disease. *J. Int. Neuropsychol. Soc*. 13(3), 433-439 (2007).

56. Forbes-McKay K, Shanks MF, Venneri A. Profiling spontaneous speech decline in Alzheimer's disease: A longitudinal study. *Acta Neuropsychiatr*. 25(6), 320-327 (2013).

57. Cardoso S, Silva D, Maroco J, de Mendonça A, Guerreiro M. Non-literal language deficits in mild cognitive impairment. *Psychogeriatrics*. 14(4), 222-228 (2014).

58. Ahmed S, Haigh AM, de Jager CA, Garrard P. Connected speech as a marker of disease progression in autopsy-proven Alzheimer's disease. *Brain*. 136(Pt 12), 3727-3737 (2013).

59. Brambati SM, Benoit S, Monetta L, Belleville S, Joubert S. The role of the left anterior temporal lobe in the semantic processing of famous faces. *Neuroimage.* 53(2), 674-681 (2010).

60. Benoit S, Rouleau I, Langlois R, Dostie V, Kergoat MJ, Joubert S. The impact of time and repeated exposure on famous person knowledge in amnestic mild cognitive impairment and Alzheimer's disease. *Neuropsychology.* 31(7), 697-707 (2017).

61. Whiteside DM, Kealey T, Semla M *et al*. Verbal fluency: Language or executive function measure? *Appl. Neuropsychol. Adult*. 23(1), 29-34 (2016).

62. Rosen VM, Sunderland T, Levy J *et al*. Apolipoprotein E and category fluency: Evidence for reduced semantic access in healthy normal controls at risk for developing Alzheimer's disease. *Neuropsychologia*. 43(4), 647-658 (2005).

63. Raoux N, Amieva H, Le Goff M *et al*. Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: Results from the PAQUID longitudinal study. *Cortex*. 44(9), 1188-1196 (2008).

64. Haugrud N, Crossley M, Vrbancic M. Clustering and switching strategies during verbal fluency performance differentiate Alzheimer's disease and healthy aging. *J. Int. Neuropsychol. Soc*. 17(6), 1153-1157 (2011).

65. Fagundo AB, López S, Romero M, Guarch J, Marcos T, Salamero M. Clustering and switching in semantic fluency: Predictors of the development of Alzheimer's disease. *Int. J. Geriatr. Psychiatry*. 23(10), 1007-1013 (2008).

66. Hodges JR, Patterson K. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*. 33(4), 441-459 (1995).

67. Stopford CL, Snowden JS, Thompson JC, Neary D. Variability in cognitive presentation of Alzheimer's disease. *Cortex*. 44(2), 185-195 (2008).

68. Baldo JV, Arévalo A, Patterson JP, Dronkers NF. Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex*. 49(3), 658-667 (2013).

69. Balthazar ML, Martinelli JE, Cendes F, Damasceno BP. Lexical semantic memory in amnestic mild cognitive impairment and mild Alzheimer's disease. *Arq. Neuropsiquiatr*. 65(3A), 619-622 (2007).

70. Marra C, Ferraccioli M, Gainotti G. Gender-related dissociations of categorical fluency in normal subjects and in subjects with Alzheimer's disease. *Neuropsychology*. 21(2), 207-211 (2007).

71. Cuetos F, Herrera E, Ellis AW. Impaired word recognition in Alzheimer's disease: The role of age of acquisition. *Neuropsychologia*. 48(11), 3329-3334 (2010).

72. Forbes-McKay KE, Ellis AW, Shanks MF, Venneri A. The age of acquisition of words produced in a semantic fluency task can reliably differentiate normal from pathological age related cognitive decline. *Neuropsychologia*. 43(11), 1625-1632 (2005).

** Age of acquisition of words generated during the Category Fluency test classified 95% of healthy controls and 88% of patients with Alzheimer's disease.

73. Vita MG, Marra C, Spinelli P *et al*. Typicality of words produced on a semantic fluency task in amnesic mild cognitive impairment: Linguistic analysis and risk of conversion to dementia. J. *Alzheimers Dis.* 42(4), 1171-1178 (2014).

** In this longitudinal study, it is reported that patients with amnestic mild cognitive impairment who tend to generate more typical words during the Category Fluency test are more at risk of progressing to dementia. This would be due to the presence of exacerbated semantic disruption.

74. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the nun study. *JAMA*. 275(7), 528-532 (1996).

** This is a longitudinal study in which a large cohort of nuns was followed up over time. The autobiographical diaries they had written in their youth were examined to extract an index of semantic abilities. This variable was found to be a significant predictor of the amount of AD pathology at *post mortem*, highlighting the role of preclinical semantic changes as potential cognitive markers.

75. Engelman M, Agree EM, Meoni LA, Klag MJ. Propositional density and cognitive function in later life: Findings from the Precursors Study. *J. Gerontol. B Psychol. Sci. Soc Sci*. 65(6), 706-711 (2010).

76. Garrard P, Maloney LM, Hodges JR, Patterson K. The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author. *Brain*. 128(Pt 2), 250-260 (2005).

** In this study the literary production of the renowned British novelist Iris Murdoch was examined with procedures of automated text analysis. An accurate analysis of three of her novels revealed that her last opus was characterised by significant lexical-semantic impoverishment, presumably in correspondence with the progression of AD from the transentorhinal region to the temporal neocortex.

77. Le X, Lancashire I, Hirst G, Jokel R. Longitudinal detection of dementia through lexical and syntactic changes in writing: A case study of three British novelists. Lit. Linguist. Comput. 26(4), 435-461 (2011).

78. van Velzen M, Garrard P. From hindsight to insight – retrospective analysis of language written by a renowned Alzheimer's patient. *Interdiscip. Sci. Rev*. 33(4), 278-286 (2008).

79. Berisha V, Wang S, LaCross A, Liss J. Tracking discourse complexity preceding Alzheimer's disease diagnosis: A case study comparing the press conferences of Presidents Ronald Reagan and George Herbert Walker Bush. *J. Alzheimers Dis*. 45(3), 959-963 (2015).

80. Arango-Lasprilla JC, Cuetos F, Valencia C, Uribe C, Lopera F. Cognitive changes in the preclinical phase of familial Alzheimer's disease. *J. Clin. Exp. Neuropsychol*. 29(8), 892-900 (2007).

81. Welsh KA, Hoffman JM, Earl NL, Hanson MW. Neural correlates of dementia: Regional brain metabolism (FDG-PET) and the CERAD neuropsychological battery. Arch. *Clin. Neuropsychol*. 9(5), 395-409 (1994).

82. Teipel SJ, Willoch F, Ishii K, *et al*. Resting state glucose utilization and the CERAD cognitive battery in patients with Alzheimer's disease. *Neurobiol. Aging*. 27(5), 681-690 (2006).

83. Schönknecht OD, Hunt A, Toro P, *et al.* Bihemispheric cerebral FDG PET correlates of cognitive dysfunction as assessed by the CERAD in Alzheimer's disease. *Clin. EEG Neurosci.* 42(2), 71-76 (2011).

84. Melrose RJ, Campa OM, Harwood DG, Osato S, Mandelkern MA, Sultzer DL. The neural correlates of naming and fluency deficits in Alzheimer's disease: An FDG-PET study. *Int. J. Geriatr. Psychiatry.* 24(8), 885-893.

85. Dos Santos V, Thomann PA, Wüstenberg T, Seidl U, Essig M, Schröder J. Morphological cerebral correlates of CERAD test performance in mild cognitive impairment and Alzheimer's disease. *J. Alzheimers Dis.* 23(3), 411-420 (2011).

86. Rodríguez-Ferreiro J, Cuetos F, Monsalve A, Martínez C, Pérez AJ, Venneri A. Establishing the relationship between cortical atrophy and semantic deficits in Alzheimer’s disease and mild cognitive impairment patients through voxel-based morphometry. *J. Neurolinguistics*. 25(3), 139-149 (2012).

87. Gardini S, Cuetos F, Fasano F, *et al.* Brain structural substrates of semantic memory decline in mild cognitive impairment. *Curr. Alzheimer Res.* 10(4), 373-389 (2013).

88. Zhang H, Sachdev PS, Wen W, *et al.* Grey matter correlates of three language tests in non-demented older adults. *PLoS One*. 8(11), e80215 (2013).

89. Aschenbrenner AJ, Balota DA, Tse CS, *et al.* Alzheimer disease biomarkers, attentional control, and semantic memory retrieval: Synergistic and mediational

effects of biomarkers on a sensitive cognitive measure in non-demented older adults. *Neuropsychology.* 29(3), 368-381 (2015).

90. Papp KV, Mormino EC, Amariglio RE, *et al.* Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology.* 30(5), 624-630 (2016).

91. Hirni DI, Kivisaari SL, Krumm S, *et al.* Neuropsychological markers of medial perirhinal and entorhinal cortex functioning are impaired twelve years preceding diagnosis of Alzheimer's dementia. *J. Alzheimers Dis.* 52(2), 573-580 (2016).

92. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. Arch. Neurol. 56(3), 303-308 (1999).

93. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med*. 256(3), 183-194 (2004).

94. Göthlin M, Eckerström M, Rolstad S, Wallin A, Nordlund A. Prognostic accuracy of mild cognitive impairment subtypes at different cut-off levels. *Dement. Geriatr. Cogn. Disord*. 43(5-6), 330-341 (2017).

95. Gainotti G, Quaranta D, Vita MG, Marra C. Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. *J. Alzheimers Dis*. 38(3), 481-495 (2014).

96. Sperling RA, Aisen PS, Beckett LA *et al*. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7, 280-292 (2011).

97. Venneri A, Gorgoglione G, Toraci C, Nocetti L, Panzetti P, Nichelli P. Combining neuropsychological and structural neuroimaging indicators of conversion to Alzheimer's disease in amnestic mild cognitive impairment. *Curr. Alzheimer Res*. 8(7), 789-797 (2011).

98. Amieva H, Letenneur L, Dartigues JF *et al*. Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement. Geriatr. Cogn. Disord*. 18(1), 87-93 (2004).

99. Gallucci M, Di Battista ME, Battistella G, Falcone C, Bisiacchi PS, Di Giorgi E. Neuropsychological tools to predict conversion from amnestic mild cognitive impairment to dementia. The TREDEM Registry. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn*. In Press. doi: 10.1080/13825585.2017.1349869 (2017).

100. Callahan BL, Ramirez J, Berezuk C, Duchesne S, Black SE; Alzheimer's Disease Neuroimaging Initiative. Predicting Alzheimer's disease development: A comparison of cognitive criteria and associated neuroimaging biomarkers. *Alzheimers Res. Ther*. 7(1), 68 (2015).

101. Russo MJ, Campos J, Vázquez S, Sevlever G, Allegri RF; Alzheimer's Disease Neuroimaging Initiative. Adding recognition discriminability index to the delayed recall is useful to predict conversion from mild cognitive impairment to Alzheimer's disease in the Alzheimer's Disease Neuroimaging Initiative. *Front. Aging Neurosci*. 9, 46 (2017).

102. Taler V, Phillips NA. Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review. *J. Clin. Exp. Neuropsychol*. 30(5), 501-56 (2008).

103. Pandya SY, Lacritz LH, Weiner MF, Deschner M, Woon FL. Predictors of reversion from mild cognitive impairment to normal cognition. *Dement. Geriatr. Cogn. Disord.* 43(3-4), 204-214 (2017).

104. Ellendt S, Voβ B, Kohn N *et al*. Predicting stability of mild cognitive impairment (MCI): Findings of a community based sample. *Curr. Alzheimer Res*. 14(6), 608-619 (2017).

105. Clark DG, Kapur P, Geldmacher DS *et al.* Latent information in fluency lists predicts functional decline in persons at risk for Alzheimer disease. *Cortex*. 55, 202-218 (2014).

106. Joubert S, Brambati SM, Ansado J *et al*. The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia*. 48(4), 978-988 (2010).

107. Quaranta D, Caprara A, Piccininni C, Vita MG, Gainotti G, Marra C. Standardization, clinical validation, and typicality norms of a new test assessing semantic verbal fluency. *Arch. Clin. Neuropsychol*. 31(5), 434-445 (2016).

108. Bertola L, Mota NB, Copelli M *et al*. Graph analysis of verbal fluency test discriminate between patients with Alzheimer's disease, mild cognitive impairment and normal elderly controls. *Front. Aging Neurosci*. 6, 185 (2014).

109. Venegas MJ, Mansur LL. Verbal fluency: Effect of time on item generation. *Dement. Neuropsychol*. 5(2), 104-107 (2011).

110. Cappa A, Calcagni ML, Villa G *et al*. Brain perfusion abnormalities in Alzheimer's disease: comparison between patients with focal temporal lobe

dysfunction and patients with diffuse cognitive impairment. *J. Neurol. Neurosurg. Psychiatry*. 70(1), 22-27 (2001).

111. Marra C, Villa G, Quaranta D, Valenza A, Vita MG, Gainotti G. Probable Alzheimer's disease patients presenting as "focal temporal lobe dysfunction" show a slow rate of cognitive decline. *J. Int. Neuropsychol. Soc*. 18(1), 144-150 (2012).

112. Quaranta D, Vita MG, Spinelli P *et al*. Does semantic memory impairment in amnestic MCI with hippocampal atrophy conform to a distinctive pattern of progression? *Curr Alzheimer Res*. 11(4), 399-407 (2014).

113. Coleman PD, Mastroeni D. A call for new approaches to Alzheimer's disease research. *Neurobiol. Aging*. 57, iii-iv (2017).

114. Ismail Z, Agüera-Ortiz L, Brodaty H *et al*. The Mild Behavioral Impairment Checklist (MBI-C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *J. Alzheimers Dis*. 56(3), 929-938 (2017).

Figure legends

Figure 1.

Areas showing a significant association for the conjunct effect of age of acquisition and typicality of words generated by patients with mild AD dementia during the Category Fluency test. Patients with more grey matter volume in the anterior portion of the parahippocampal gyrus and in the left inferior and superior temporal gyri were found to generate words that, on average, are usually acquired later in life, and are less typical of their respective category. [Reproduced with permission from Venneri A, McGeown WJ; Hietanen HM, Guerrini C, Ellis AW, Shanks MF. The anatomical bases of semantic retrieval deficits in early Alzheimer's Disease. *Neuropsychologia*, 46, 497-510, (2008)]

Figure 2

This graph illustrates the clinical progression of the cohort of patients described by Vita and colleagues [73]. In this study, patients with a diagnosis of mild cognitive impairment had completed a Category Fluency task (categories: “birds” and “furniture”). Normative data obtained on healthy volunteers were used as reference to assign an index of category-dependent typicality to each word generated during the task. The cohort was then divided into low-typicality and high-typicality patients based on a median split. At the two-year follow up, only 5 out of 20 patients that converted to AD dementia had produced low typicality words above the median value (Yates’ corrected *chi-squared* test = 6.07; $p < 0.014$)

Figure 1

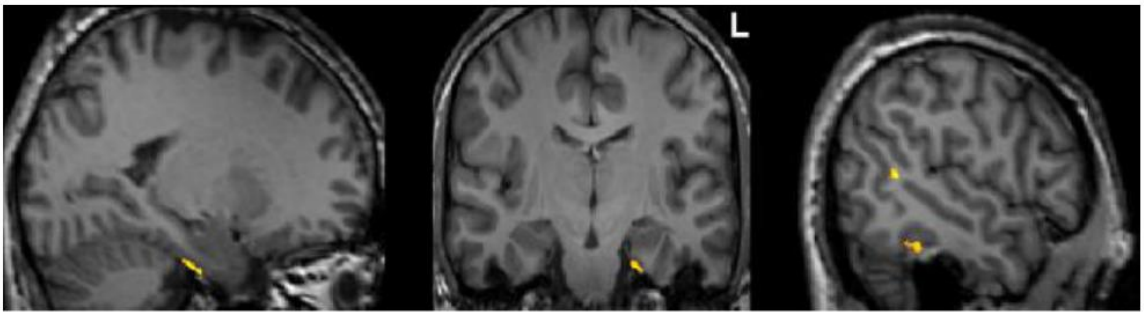
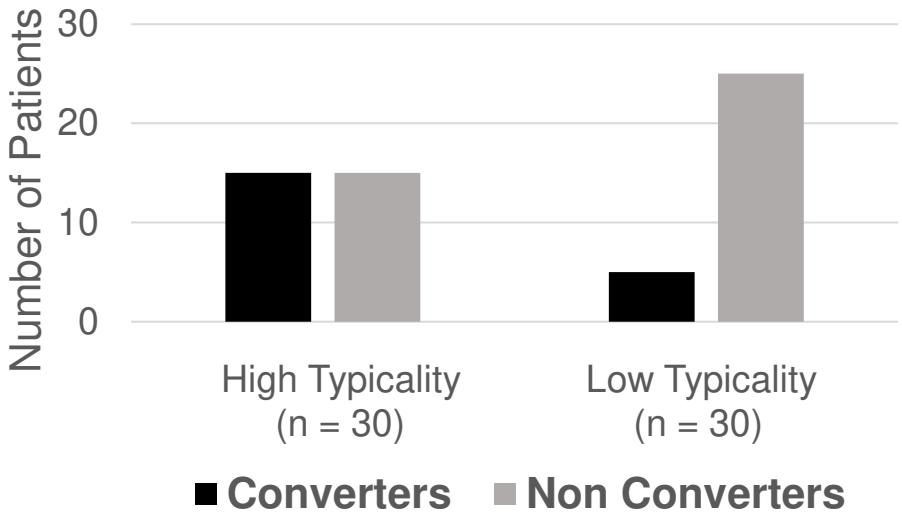


Figure 2


Number of Patients
30
20
10
0
High Typicality
(n = 30)
Low Typicality
(n = 30)
Converters
Non Converters