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Venneri, A., Mitolo, M. and De Marco, M. (2016) Paradigm shift: semantic memory decline as a biomarker of preclinical Alzheimer's disease. Biomarkers in Medicine, 10 (1). pp. 5-8. ISSN 1752-0363

https://doi.org/10.2217/bmm.15.53

Paradigm Shift: Semantic memory decline as a biomarker of preclinical Alzheimer's disease

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Keywords: AD, biomarkers, semantic memory, preclinical stage of AD

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Detection of Alzheimer's disease (AD) in routine neurological management of middle-aged/elderly adults is challenging. Standard assessments of episodic memory and brain atrophy are useful to detect the prodromal mild cognitive impairment stage of AD but fail to identify the earliest preclinical cases. Longitudinal research has indicated that at this earliest stage of AD there is a subtle decline of semantic memory. A focus on latent and more qualitative aspects of semantic performance (which transcend the simple raw quantitative score) might be a better biomarker of preclinical AD. Sticking to episodic memory may be effective to diagnose prodromal disease, but does not offer many opportunities for clinical research to progress towards cognitive biomarkers of earlier application.

Uncovering the presence of Alzheimer's disease (AD) in routine neurological management of middle-aged/elderly adults, and differentiating its combination of symptoms from those induced by the processes of normal ageing, neurovascular disease, or psychiatric conditions (e.g. depression), are challenges of primary importance. Usually, it is the onset of behavioural symptoms that encourages patients with AD and caregivers to seek medical attention for the first time. Research evidence, however, shows that the earliest changes triggered by the disease on the biology of the brain occur several decades prior to any behavioural change of clinical relevance [1]. Based on this large preclinical-stage/symptomatic-stage temporal discrepancy, it is of paramount importance to identify biomarkers that are more effective than those currently used in clinical practice. Alongside maximised levels of sensitivity and specificity, an ideal biomarker should be of as early diagnostic avail as possible along the disease-progression timeline. On this note, the use of cognitive tests is among the most proficient sources of clinical information in the early phases of AD, due to their validity, reliability, and simplicity/immediateness. A skilful interpretation of neuropsychological performance may offer an indirect, yet fruitful view of the pathological processes affecting the nervous system, which could be the result of incipient AD.

Although episodic memory impairment has been classically recognised as the main symptom of the prodromal AD stage characterised by mild cognitive impairment (MCI) [2], a temporally parallel decline of semantic memory has also been described [3, 4]. The basic clinical disadvantage associated with episodic memory is that a qualitatively (but certainly not quantitatively) similar memory decline is also "physiologically" visible in the absence of any pathologies in the general population of elderly adults. In contrast, semantic memory remains fairly stable across the lifespan, and aspects of lexical-semantic abilities even appear to improve with age [5]. Based on this, using the same logic argument that sustains all differential diagnoses, measuring semantic memory can be discriminative in separating healthy and pathological ageing.

Nevertheless, the most recent criteria for the detection of the earliest clinical manifestation of AD [6, 7] persist in highlighting the sole role of measures of episodic retrieval. A major reason behind the choice of episodic memory as the cognitive sub-domain "of reference" lies in the fact that prodromal, early-symptomatic AD (manifesting in the form of MCI) corresponds to the pathophysiological moment in which the neurofibrillary pathology intensifies within the hippocampal complex [8]. This mediotemporal structure sustains the neocortical circuitry responsible for context-associated, episodic memory [9]. Based on this, the theoretical convergence of peptidic accumulation of hypephosphorilated TAU protein within hippocampal cells, macrostructural volumetric loss of this same structure, and impaired performance in tests assessing episodic retrieval would represents a multi-domain ensemble which (as soon as TAU imaging is made routinely available) will be extremely powerful in the clinical setting for a diagnosis of symptomatic, probable AD. This diagnostic formula is meant to capture a very specific snapshot of the disease, which is bound to the Braak and Braak's limbic stages of AD, and which, simply, "does not need" to investigate semantic memory. This, however, does not mean that patients with MCI do not manifest any semantic decline. Converging evidence shows, in fact, that these patients suffer from semantic impairment across multiple domains: naming, category verbal fluency, spontaneous speech, knowledge about famous people, historical facts, famous public events, and even cultural knowledge [3].

On the quest for an accurate biomarker, it is fair to acknowledge that there might be alternative and more adequate diagnostic routes than that centered on the combination of episodic memory impairment-hippocampal atrophy. Multiple theoretical models indicate that the clinical moment in which objective cognitive impairment is seen and a diagnosis is reached, is preceded by a rather long phase of preclinical changes. During this period, the cerebrospinal levels of TAU and β Amyloid protein are dysregulated [1] and neurofibrillary tangles start depositing on the basal, transentorhinal portion of the mediotemporal complex, including the perirhinal and entorhinal

cortices [8]. Interestingly, these two subcomponents are part of mediotemporal networks which connect to areas of the associative cortex mainly responsible for "context-free" retrieval processes (out of which semantic memory represents a major example), and are anatomically distinct from the mediotemporal-neocortical circuitry of the other aforementioned subcomponent based on hippocampal and parahippocampal gyri [9]. According to this view, the distribution of Braak Stage I lesions would induce functional disconnection within the transentorhinal, mediotemporal network responsible for semantic but not for episodic declarative memory. In fact, Stage I spares the hippocampus, which remains free of Alzheimer pathology. This indicates that differences in measures of semantic memory must be visible between healthy adults and future patients undergoing Braak Stage I. Using the neuropsychological instruments at clinical disposal, however, individuals in this asymptomatic or minimally-symptomatic phase result undistinguishable from healthy adults.

Cognitive tests have been mainly designed to classify performance as falling within normality, in a borderline "grey" area, or below cut-off. These instruments are not sufficiently fine-grained to quantify in detail the extent to which a cognitive function is down-regulated by the preclinical mechanisms of neurodegeneration. Furthermore, other factors such as, for example, cognitive reserve might mask/compensate for the effect of neurodegeneration [10]. Under normal conditions, common testing instruments such as the raw score on the Category Fluency test or on the "Similarities" WAIS subtest are not sufficiently helpful to characterise performance of people at the preclinical stage of the disease. Moreover, to further complicate the picture, no test taps only one subtype of declarative memory or is, in terms of neural correlates, exclusively related to a sole brain network. As for the aforementioned mediotemporal-neocortical circuitry, evidence indicates that semantic retrieval in adults with MCI is associated with an involvement of perirhinal/entorhinal areas, as expected, but also with anterior hippocampal regions [3]. In all likelihood, recall from the semantic storage is open to concurrent processing of episodic (e.g. autobiographical) nature.

Conversely, any meaningful episodic retrieval entails some degree of reliance on lexical-semantic material. In fact, tests like the Rey Auditory Verbal Learning Test or the Prose Memory Test are profoundly dependent on lexical-semantic processes.

A series of investigations, however, have demonstrated that other latent and more qualitative aspects of semantic performance (which transcend the simple raw quantitative score) are informative and of potential clinical utility for the characterisation of the earliest stages of the disease [11]. Individuals who are still asymptomatic but are destined to develop a hereditary form of AD due to a mutation of the Presenilin-1 gene, for instance, were found to score significantly lower than healthy controls in a series of tasks assessing semantic fluency, naming of famous people, and word definition [12]. Longitudinal evidence comes instead from a set of fascinating studies which investigated in a retrospective and detailed fashion the preclinical morphological-syntactical and lexical-semantic skills of adults, as a function of their future conversion to clinically-established AD. A well-acknowledged study is that authored by Snowdon and collaborators [13], carried out on a group of nuns who had written autobiographical diaries in their early adulthood (i.e. more than 50 years prior to neuropathological assessment carried out to confirm/rule out a diagnosis of AD). The findings indicated that the nuns with confirmed diagnosis of AD had lower levels of idea density in their early twenties. Moreover, lower levels of idea density and syntactical complexity were associated with lower cognitive scores at follow up. Along the same line, a single-case study examined in a detailed and unique way the literary performance of the famous British writer Iris Murdoch throughout her career, up until the last book plausibly written during the preclinical phase of AD. Results indicated that her later opuses were characterised by a more limited vocabulary and by the use of more high-frequency words [14]. Additional analyses on her life long literary productions showed that impoverished vocabulary and syntax were already present in her writings from her late 40s and 50s, decades before the clinical onset of AD [15]. A similarly semantic, but somehow even more abstract mechanism, was recently reported in the longitudinal characterisation

of the painting skills of a Chinese painter, who showed a progressive impoverishment in his work, concurrent with the progression of AD [16]. These studies are accompanied by other research that has looked at latent aspects of lexical performance in the spectrum from normal ageing to MCI and AD [17, 18]. This latter research has shown that older adults outperformed people with clinical AD, its prodromal MCI stage and also young controls in category fluency, producing more words which are later acquired, less typical and less familiar [18]. Furthermore, other evidence suggests that these same parameters can differentiate MCI carriers of the APOE ε4 mutation who are at increased genetic risk of progression to AD from those who are more genetically protected [19]. Alterations of semantic memory can also be revealed in the preclinical phase of AD using object naming [20] or naming of famous faces. An area of semantic memory that also appears to be especially affected is the naming of famous faces (NFF), with some evidence indicating that NFF is one of the best tasks to identify people who might develop future AD [20].

These studies clearly do not represent a body of evidence sufficiently robust to discard the "classic" diagnostic paradigm centered on episodic memory and embrace a qualitative analysis of semantic memory as the core clinical aspect. Multidimensional evidence, however, indicates that tracking the decline in semantic memory may help 1) separate the effects of non-pathological ageing from neurodegeneration more clearly, and 2) measure those aspects of lexical-semantic processing which are susceptible to AD even when the disease is in its preclinical asymptomatic stages. This would reflect the clinical moment in which transentorhinal but not hippocampal regions are primarily affected by AD pathology in the initial preclinical stages.

In conclusion, we suggest that research should focus more on the role of mechanisms of semantic memory in prodromal and, above all, preclinical AD. Sticking to episodic memory may be effective to diagnose prodromal disease, but does not offer many opportunities for clinical research to progress towards cognitive biomarkers of earlier application.

References

1. Jack CR, Jr., Knopman DS, Jagust WJ et al. Tracking pathophysiological processes in alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 12(2), 207-216 (2013).

2. Petersen RC, Doody R, Kurz A et al. Current concepts in mild cognitive impairment. Arch Neurol 58(12), 1985-1992 (2001).

3. Barbeau EJ, Didic M, Joubert S et al. Extent and neural basis of semantic memory impairment in mild cognitive impairment. J Alzheimers Dis 28(4), 823-837 (2012).

4. Chertkow H, Whatmough C, Saumier D, Duong A. Cognitive neuroscience studies of semantic memory in alzheimer's disease. Prog Brain Res 169, 393-407 (2008).

5. 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).

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. Dubois B, Feldman HH, Jacova C et al. Research criteria for the diagnosis of alzheimer's disease: Revising the nincds-adrda criteria. Lancet Neurol 6(8), 734-746 (2007).

8. Braak H, Braak E. Staging of alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 16(3), 271-278; discussion 278-284 (1995).

9. 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).

10. Stern Y. Cognitive reserve in ageing and alzheimer's disease. Lancet Neurol 11(11), 1006-1012 (2012).

11. 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).

12. 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).

13. 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).

14. 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).

15. 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).

16. Lee YT, Tsai YC, Chen LK. Progressive changes in artistic performance of a chinese master with alzheimer's disease. Cortex, (2015).

17. 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).

18. Wakefield SJ, Mcgeown WJ, Shanks MF, Venneri A. Differentiating normal from pathological brain ageing using standard neuropsychological tests. Curr Alzheimer Res 11(8), 765-772 (2014).

19. Biundo R, Gardini S, Caffarra P et al. Influence of apoe status on lexical-semantic skills in mild cognitive impairment. J Int Neuropsychol Soc, 1-8 (2011).

20. Vogel A, Gade A, Stokholm J, Waldemar G. Semantic memory impairment in the earliest phases of alzheimer's disease. Dementia and Geriatric Cognitive Disorders 19(2-3), 75-81 (2005).