

Cognitive assessment in Alzheimer's disease*

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No effective treatments are currently available to tackle Alzheimer's disease (AD), yet there seems to be a growing consensus in support to prevention initiatives [1-4]. This poses important challenges to the scientific community as prevention entails at least two targets, early detection and effective treatments neither of which meets current needs. Regarding the latter target, recent failures in clinical trials have led to question whether the undertaken treatments have been too little or too late [2,4]. This question seems to emerge from current understanding of the neuropathological changes underlying AD, which suggests that anti-amyloid treatments might need to be administered earlier than we thought [1]. However, to achieve this we first need to identify who could be suitable for such prevention trials and this requires early detection. Significant progress has been made in the area of biomarkers for AD, yet available tests still face important challenges [5-8]. Less has been done in the area of cognitive markers for AD, albeit cognition plays a fundamental role in the disease diagnosis, prognosis and follow up. The present short communication aims to reflect on current approaches to cognitive assessment in AD and the extent to which the conundrum "too little, too late" also applies to the early detection of cognitive impairments in this form of dementia.

Traditional assessment of cognitive functions in AD has largely focused on episodic memory. This tendency has been driven by neuropathological evidence which suggests that regions within the medial temporal lobe known to be crucial from long-term memory formation are affected by AD since very early. However, episodic memory, as assessed by available tests, reveals impairments which characterize the rather advanced stages of the disease. It might be that for AD-related episodic memory changes to reach the pathological threshold of these tests, substantial damage to the hippocampus needs to accumulate because this structure and associated functions also decline as part of the normal aging process.

Distilling age-related and AD-related decline of hippocampal functions is a subject which requires further research. Moreover, the negative results currently reported by clinical trials might also rest, at least in part, on the outcome measures used to assess memory functions. The disease mechanisms tackled by available drugs (e.g., anti-amyloid compounds) might impact on brain regions and functions different from those taxed by available episodic memory tests [9-11]. Episodic memory tests might be unveiling the impact of advanced pathological changes (e.g., Tauopathy and tangle formation; [12]). Memory tests capable of detecting the impact of earlier mechanisms would be desired (see Sperling *et al.* [13]).

In a recent hypothesis paper, Didic *et al.* [14] proposed a novel approach which calls for a new conception of memory assessment in AD. In their paper, the authors addressed the question of which memory system is impaired first in AD. They suggest a model which sees the hippocampal damage as a rather late consequence of AD. In the model, a subhippocampal phase precedes the hippocampal damage in the neurodegenerative course of AD. Interestingly, the hippocampal phase seems to correspond to the Braak's stages III-IV while the subhippocampal phase reflects earlier pathological stages (I-III), thus suggesting that memory tests capable of detecting this phase would be more promising in the early detection of AD. They suggest that tests measuring context-free memory (e.g., item memory, familiarity based recognition) as opposed to tests measuring context-rich memory (e.g., inter-item association, freed and cued recall), appear to be promising candidates (see Wolk *et al.* [15] for recent evidence). This proposal is appealing as regions supporting item memory and familiarity based recognition fall outside the hippocampus and map well onto areas known to be affected by amyloid-induced changes early in the course of AD (e.g., entorhinal cortex, perirhinal cortex, parahippocampus, and regions within the visual ventral stream; [9,12,14]). There is now accrued evidence suggesting that the neuropathological changes accompanying AD spread through these extra-

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hippocampal regions in the very early stages of the disease [16-22]. Of note, whereas healthy aging impacts on the hippocampus, it seems to spare these extra hippocampal regions which are affected by AD [23-25]. Hence, memory tests assessing the functions supported by these regions would help detect early AD-related changes not accounted for by age.

A recent methodology, namely short-term memory binding (STMB), adheres to this new conception of memory assessment in AD. STMB refers to the cognitive function responsible for retaining, on a temporary basis, intra-item features thus contributing to the formation of objects' identity. This function has been investigated using a change detection task during which the examinee judges whether arrays of shapes, colors or shape-color combinations presented in two sequential screens are the same or different. STMB has proved insensitive to healthy aging [26,27] but very sensitive to AD [28,29]. AD seems to impact on STMB much earlier than on other memory functions [28,30]. Relative to other dementias and depression, STMB declines only in AD [31,32]. A recent fMRI study confirmed that STMB does not rely on the hippocampus but it does recruit regions within the visual ventral stream [33]. Interestingly, recent studies carried out in the asymptomatic population of carriers of the mutation E280A of the PSEN1 gene [34] who will go on to develop familial AD with 100% probability and who had previously shown STMB deficits at a mean age of 35 [28,30], suggest that amyloid changes are the most prominent pathological feature of this pre-clinical stage [35,36]. Based on the evidence reviewed above, the STMB task appears to be taxing the subhippocampal phase of AD [4].

A shift in the conception of early cognitive assessment of AD and of the tools necessary to undertake this task is already due. Current revised guidelines continue to emphasize on tests that assess the hippocampal phase of AD (e.g., associative learning, cued recall, etc.) despite they detect changes late in the course of the disease and are sensitive to a number of unwanted factors (e.g., age, cognitive reserve, and other individual differences). Future assessment of AD should focus on theory-driven tests which tap into specific cognitive domains and are insensitive to confounding factors. More effort will be required in the forthcoming years to further investigate the usefulness of tests of subhippocampal memory functions in the prediction of AD among the elderly population. Such tests would become screening tools to detect individuals at risk who could then be referred to prevention programs.

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