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An Emerging Model of Word Retrieval in Preclinical Alzheimer's Disease

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Abstract

Word retrieval deficit in persons on the Alzheimer's disease (AD) spectrum has been investigated mostly in AD dementia and, to a smaller degree, in patients with mild cognitive impairment. However, recent evidence suggests that changes in word retrieval abilities are also present in persons at the presumably earliest stage of AD, i.e. in preclinical AD. Considering this evidence as well as previous findings on word retrieval difficulties in cognitively healthy elderly persons, the present paper outlines a novel model of word retrieval in Alzheimer's disease that is emerging from research in these two fields.

Keywords: Preclinical Alzheimer's disease; Word retrieval; Functional overcompensation; lexical memory

Introduction

Word retrieval deficit in persons on the Alzheimer's disease (AD) spectrum [1] has been investigated mostly in AD dementia and, to a smaller degree, in patients with mild cognitive impairment (MCI). In contrast, word retrieval abilities in persons at the presumably earliest stage of AD, i.e. in preclinical AD have not been systematically investigated so far. Even though these persons do not present with cognitive symptoms characteristic of MCI and AD, they do exhibit subtle cognitive changes and changes in brain activation patterns [2]. Therefore, the preclinical stage of AD is a unique window into the earliest dynamics of cognitive deterioration emerging under the burden of Alzheimer's pathology.

One particularly intriguing question regarding initial cognitive deterioration in AD is how the ability to retrieve words from memory relates to structural and functional changes that have already taken place in the brain at this presumably earliest point in the AD trajectory. Among the brain changes that have been associated with preclinical AD are increased cortical levels of the amyloid-β (Aβ) protein and decreasedCSF amyloid levels together with high levels of tau proteins, considerable temporo-parietal hypometabolism spreading to the frontal lobe, less pronounced grey matter volume reductions and cortical thinning, changes in white matter integrity, and aberrant resting-state functional connectivity patterns [2-6]. This phase of illness may take more than 10 years [7] and "losing words" may begin at any point during this time. When and how this happens is currently not clear.

One part of the problem pertains to the fact that word retrieval is a complex process that requires fine-tuning of memory, attention, and language processes. Current theories of the human word-store postulate that the mental lexicon contains information on words' meanings (semantics), their role in a sentence (syntax), and what they sound like (phonology). The mental lexicon of a normal adult literate person contains 50-100 thousand words. The average rate of word production is 2-3 words per second, with only one or two errors occurring in 1000 words [8]. Most researchers agree that retrieving a word from the mental lexicon requires a preliminary conceptual step, followed by a lexical selection (which means access to semantic and syntactic features of the target word), and retrieval of its phonological code, with further steps involving the specifics leading to the word's articulation [9,10].

Traditional research on cognitive aging indicates that retrieving words from the mental lexicon is difficult not only for AD patients, but also for cognitively normal (CN) elderly people. According to one model, word retrieval difficulties in CN elderly persons are caused by impaired access to phonological information in lexical memory [11]. Retrieving a sequence of sounds from memory requires access to phonological representation of the target word. This process takes place before articulatory movements that make speech production possible. As an example, in tip-of-the-tongue states, the meaning of a word is available, but its form remains elusive. However, without this step, there is no word retrieval. On the other hand, word retrieval deficit in AD patients is related to marked deterioration of semantic memory [12], in addition to impaired phonological access [13]. Since until recently it was not possible to study *in vivo* brain changes associated with Alzheimer's pathology, previous research on word retrieval in normal cognitive aging could not differentiate between CN elderly persons with Alzheimer's pathology from CN elderly without it. Given that Alzheimer's pathology is more frequent in CN elderly persons than previously recognized [14,15], is it possible that previous findings that suggested impaired phonological access in "cognitively normal" aging actually pertain to persons with AD pathology, i.e. to preclinical AD [16]? This possibility strongly aligns with the fact that there is no convincing explanation of why CN elderly persons would have to have impaired phonological access [17].

Furthermore, subtle cognitive changes in preclinical AD may remain unnoticed on standard tests used for AD diagnosis [3]. For instance, subtle initial changes in word retrieval may include longer response times and changes in brain activation patterns. In persons with positive AD biomarkers these changes would indicate a beginning of disease-triggered network changes, with identifiable rate-limiting nodes in the relevant networks and/or use of compensatory strategies. Additional tests of lexical memory that would determine changes in

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processing phonological (e.g., as in rhyming, accent-cued or syllable-cued word retrieval, etc.) and semantic relations among words (e.g., as in synonyms, antonyms, homophones, polysemous words and so on) may be more sensitive in determining subtle changes in word retrieval in preclinical AD than the standard fluency tests. As an example, a category-cued fluency test is inspecting for only one type of semantic relations, regardless of how many categories or which type of category is involved (most commonly tested categories are animals, fruits/vegetables, and tools). It would be more informative to determine how resilient in preclinical AD the links between more- vs. less-closely associated words are. Similarly, letter-cued verbal fluency tests target a single type of retrieval, regardless of whether the cue is a specific letter (F, A, S), if it is an initial vowel or consonant, or whether the letter is in a specific position (e.g., word initial vs. final). Tests that would target more processes related to word form aspects of retrieval would include, for instance, rhyming-based, accent- or syllable-matching retrieval, among others.

Considering the hypothetical model of staging of AD [18], it remains a theoretical possibility that CN elderly persons retain normal word retrieval as they age, as long as their AD biomarkers' values remain within the normal range. In contrast, CN persons with positive AD biomarkers would have the type of word retrieval deficit related to phonological access that was previously ascribed to "normal" cognitive aging. If corroborated, this would suggest that word retrieval deficit in AD begins with the deterioration of phonological access, which is followed by weakening of semantic associations among words; as the disease further develops, the semantic deficit becomes more salient leading to a full-blown loss of concepts at the dementia stage. If this model is correct, then a transition from the deterioration of lexical associations between words in MCI to deterioration of concepts and conceptualization processes in those MCI patients who have converted to AD may serve as a cognitive marker of disease progression. More importantly, the model provides a context for testing the hypotheses on subtle changes in lexical memory in preclinical AD. Thus, unlike the traditional approaches to word retrieval difficulties in typically aging population, which do not convincingly explain why phonological access should be impaired in cognitively healthy elderly persons in the first place, the model proposed here suggests that these difficulties are associated with neuropathological processes characteristic of preclinical AD.

The model is also consistent with the evidence suggesting that neurofibrillary tangles in AD, which are associated with tau protein pathology, first appear in the medial temporal lobe [19]. This region supports declarative memory, within which two separate subsystems have been discerned: episodic memory and semantic memory [20]. Semantic memory includes knowledge about the world and language, therefore including also knowledge about words. Some evidence points to the role of the medial temporal lobe in language, not only at the word level [21], but also at the level of syntax [22]. Thus, it seems reasonable to assume that early brain changes in the AD trajectory may influence cognitive processes associated with semantic memory, including lexical memory. Furthermore, whereas the classic approach to language assigned a special role in the "auditory images of words" to the temporal region associated with Wernicke's area, current models of the functional anatomy of language assume a large-scale network, involving the frontal, temporal and parietal lobes. Crucially, these models suggest that the temporal lobe is involved in memorizing, i.e. storage and retrieval of linguistic material, suggesting also a superior-to-inferior gradient, with the phonetic/phonological information being mapped more superiorly/dorsally, semantic information more inferiorly/ventrally and syntactic information in between [23]. Testable anatomical hypotheses relevant to word retrieval changes in preclinical AD need to recognize these developments.

A recent longitudinal study involving 275 clinically normal persons (70 with abnormal levels of cortical amyloid-β, 205 with normal levels of this protein in the brain), investigated whether amyloidosis was associated with letter and category fluency [24]. Amyloid-β positive participants were significantly older than the amyloid-β negative group, had lower scores on a measure of general cognition, and a higher chance of carrying ApoE4, which is a major risk factor for AD [25]. Curiously, this group performed considerably better on letter-cued word retrieval than the amyloid-β negative group at baseline. Longitudinally, they had more decline in category-cued word retrieval.

These findings only seemingly run against the proposed model: they indicate that word retrieval deficit begins with changes in phonological memory, where better performance in amyloid-β positive persons most likely reflects functional overcompensation, as a result of an early reliance on compensatory strategies. This interpretation is consistent with recent evidence suggesting compensatory task-induced hyperactivation in CN persons with increased amyloid-β load [26] as well as with the earlier findings on overrecruitment of brain areas associated with word retrieval in CN elderly persons [17]. Assuming that the research model of AD as a continuum that begins with cerebral amyloidosis is on the right track, and given that preclinical AD is heterogeneous [14], two questions are pending. First, does word retrieval deteriorate differently in subpopulations that have different trajectories in dementia development? Second, to what extent the interactions between amyloidosis and abnormalities in tau proteins affect word retrieval in preclinical AD? Answering these questions and teasing apart how various aspects of lexical memory actually decline across the stages of AD require more sophisticated tests.

In conclusion, determining how word retrieval deteriorates in preclinical AD is an important research question that needs to be addressed in longitudinal studies. Crucially, these studies need to combine a range of neuroimaging techniques (structural and functional) with novel lexical tests that need to be more sensitive to subtle changes in lexical memory than the standard verbal fluency tests.

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