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Early Detection of Semantic Memory Changes May Help Predict the Course of Alzheimer's Disease

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Over the course of Alzheimer's disease (AD), patients suffer from relentless progressive dementia. Characterization of at-risk stages of AD is crucial for targeted prevention of dementia [1]. Neuropathological evidence suggests that earliest AD affects declarative memory [2-4], which can be further categorized as either episodic memory or semantic memory [5,6]. Episodic memory deals with specific events of the past, whereas semantic memory deals with general knowledge of the world [6,7]. The earliest neuropathological changes in patients with AD may correlate more strongly with semantic memory than episodic memory [2,8,9]. Therefore, detecting early changes in the semantic memory of AD patients may be clinically important. Semantic memory impairment has been well-documented among patients with dementia of the Alzheimer type (DAT) [10-19] and among patients with prodromal stage of DAT (amnestic mild cognitive impairment, aMCI) [20-29]. Semantic memory deficits may occur early in the disease course of AD and therefore comprise useful markers of disease progression. However, the predictive value of semantic memory impairment remains controversial [20,22,27,29]. The previously observed inconsistencies may be attributable to distinct processes of semantic memory retrieval [10,30]. Many complex mental operations associated with semantic memory retrieval can be performed with minimal attentional capacity by dint of extensive practice. These types of mental operations are considered 'automatic'. Conversely, other tasks that involve semantic memory retrieval require considerable attentional capacity to perform and are commonly referred to as 'effortful'. AD patients display disproportionally poor performance on semantic tasks that require the effortful retrieval of semantic memories, whereas automatic retrieval tends to be better preserved [10]. Chang et al. [31]. Compared effortful and automatic retrieval of semantic memory among individuals with aMCI [32], DAT or subjective memory impairment (SMI) [1]. In this study, patients with DAT and aMCI-multiple domain (aMCI-md) [32] displayed poor performance on all semantic memory tasks. Conversely, patients with aMCI-single domain (aMCI-sd) [32] were found to have performed more poorly on a semantic memory task that required a relatively high degree of effortful retrieval. In addition, the risk of conversion from MCI to DAT (approximately 27 months after the first evaluation) among aMCI-sd patients who displayed poor performance on semantic memory tasks requiring effortful retrieval exceeded the risk faced by aMCI-sd patients who performed normally on the same tasks by more than two-fold in this study (50% vs. 23%). In contrast, aMCI-md patients who presented poor semantic memory in tasks that required automatic retrieval were at higher risk of conversion to DAT (58% vs. 38%). Nonetheless, the sensitivity of performance on the semantic memory task requiring high degree of effortful retrieval in predicting conversion from aMCI to DAT was relatively low compared to specificity in this study. Recent studies have suggested that combining performance on semantic memory tasks with biomarkers of AD may facilitate the prediction [22,28,33]. In addition, novel neurophysiological markers have been proposed by researchers to detect early neuropathological changes in AD and other cognitive disorders (e.g. increased excitability of motor cortex in transcranial magnetic stimulation studies [34-38]). The relatively low sensitivity of semantic memory performance in predicting DAT conversion among aMCI patients in Chang et al. [31] may be due to that the study did not incorporate the biomarkers of AD in the prediction. Moreover, combining other tasks requiring effortful semantic memory retrieval may also improve the sensitivity in predicting DAT conversion among aMCI patients [39-41].

Overall, neuropathological evidence has revealed that the deterioration of semantic memory generally occurs earlier than the deterioration of episodic memory in the disease course of AD. The controlled processes involved in semantic memory retrieval may provide cognitive markers for the characterization and prediction of neuropathological changes among patients in the prodromal stage AD. We suggest that future researchers perform a large-scale longitudinal study incorporating biomarkers to address various aspects of semantic memory retrieval that characterize the early disease stages of AD (e.g. SMI). Such a study should help to more fully elucidate the value of semantic memory in predicting the conversion of MCI to DAT.

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