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Memory concerns in the early Alzheimer's disease prodrome: Regional association with tau deposition

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Abstract

Introduction: Relationship between self– and informant memory concerns and tau aggregation was assessed in adults at risk for Alzheimer's disease (AD).

Methods: Regional mean standardized uptake value ratios were extracted from [^{18}F]flortaucipir positron emission tomography (PET) scans of 82 at-risk adults in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Associations between self– and informant ECog memory scores and tau aggregation were analyzed on both regional and voxelwise bases. Analyses were completed both on the whole sample and restricted to amyloid-positive individuals only.

Results: Memory concerns were associated with tau aggregation. Self-perception was more associated with frontal tau. In contrast, informant scores were more associated with parietal tau. This source-by-region interaction was more prominent in amyloid-positive participants and observed in both regional and voxelwise analyses.

Discussion: Quantitative assessment of perceived memory functioning may be useful for screening older adults at risk for Alzheimer's disease. Individuals and their informants may provide complementary information relating to the anatomical distribution of tau.

Keywords: Significant memory concern; SMC; Subjective cognitive decline; SCD; Early mild cognitive impairment; EMCI; Neuroimaging; AV1451; Tau PET; Alzheimer's disease neuroimaging initiative; ADNI

1. Introduction

Alzheimer's disease (AD), the leading cause of neurodegenerative dementia associated with aging, affects over 5 million adults in the United States and is predicted to increase to 16 million affected by 2050 [1]. There are presently no approved pharmacological treatments that can stop the progression of AD. Treatment is likely to be most effective during the preclinical or early prodromal stages of AD, before substantial permanent neurodegenerative and cognitive damage has occurred. Therefore, there has been considerable recent interest in measures to identify older adults at highest risk for progression to AD who may benefit most from early intervention [2,3].

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Adults with subjective cognitive decline (SCD) in the presence of normal neuropsychological test scores are at an increased risk of progression to AD. These adults have been shown to progress to mild cognitive impairment (MCI) and eventually AD or a related dementia at higher rates than cognitively normal (CN) adults who do not have SCD [2,4–8]. Adults with SCD also show subtle, subclinical differences in objective cognitive performance compared to adults without SCD and experience more functional decline over time [9]. Therefore, it has been suggested that SCD is potentially a preclinical AD stage [9]. However, SCD has also been linked to depression, other affective disorders, and personality traits [7,10–13]. Therefore, it is necessary to determine the factors that influence the clinical and prognostic significance of SCD.

In addition to capturing self-based estimates of SCD, investigators often also assess the extent of concerns about cognitive decline from an informant (spouse, child, other caregiver, or clinician). Informant-based cognitive concerns are particularly important in the later stages of cognitive decline, when individuals' insight into their own cognitive problems diminishes and informant perceptions of cognition are more accurate [12,14,15]. In CN adults, however, self- and informant perceptions of cognitive decline are both predictive of future progression to MCI or AD, and the use of both measures together is a better predictor than either measure alone [5]. This finding suggests that, in very early stages of disease, both at-risk adults and their informants can provide important information about subclinical cognitive decline. Thus, using both sources of concern together may provide complementary information regarding subtle pathological changes in adults in very early preclinical stages of AD.

Many adults with SCD exhibit structural and pathological changes that are typically associated with MCI or dementia. For example, adults with SCD show patterns of neurodegeneration, such as decreased gray matter and hippocampal volumes, that are similar to those seen in adults with MCI [16–18]. Similarly, some adults with SCD and early mild cognitive impairment (EMCI) show AD-related pathology, such as amyloid plaques, tau tangles, and cerebrospinal fluid (CSF) profiles that are similar to those observed in AD (decreased levels of amyloid and increased levels of total and phosphorylated tau; [19–21]). Adults with SCD or EMCI who also show AD-like pathology are more likely to progress to later stages of MCI or AD [21,22].

Tau aggregation is an important biomarker of disease severity along the spectrum of preclinical and clinical stages of AD. It has been previously established from measurements of tau in CSF and *postmortem* studies of brain tissue that tau aggregation correlates with neurodegeneration both temporally and spatially during progression of AD [23,24], as well as the resultant cognitive decline. The recent development of tau-specific radiotracers has allowed the *in vivo* positron emission tomography (PET) measurement and visualization of the spatial distribution of tau aggregation for the first time [25]. Tau radiotracers have permitted *in vivo* correlation of tau aggregation and other markers of disease progression, including increased cognitive decline, amyloid deposition, and CSF measures of amyloid and tau [26]. Spatial information about the tau anatomical distribution has also been shown to provide important clinical information, as brain regions with high levels of tau aggregation often correspond to declines in cognitive functions related to those regions [27].

Because tau aggregation correlates spatially with brain areas implicated in cognitive decline, it is possible that self-based memory concerns correlate more strongly with tau aggregation in brain regions involved in introspection or internal thought processes, for example, the medial prefrontal cortex. More generally, the frontal cortex has been implicated in several aspects of conscious internal processing, such as planning, decision-making, and inhibition of actions by thinking through consequences. It is possible that preclinical pathological changes in frontal brain regions would be noticeable to the patient before these changes causing outward changes in behavior due to impacts on the processes of internal thought. On the other hand, informant memory concerns may correlate more strongly with tau aggregation in brain regions typically seen in patients with MCI and AD, as these may be involved in common initial symptoms of AD (i.e., memory decline) that are more likely to be noticed by an observer.

To determine how self- and informant perceptions of cognitive decline are each related to tau deposition in the early stages of AD, we assessed the relationship between self- and informant scores on the memory subscale of the Test of Everyday Cognition (ECog; [28]), as well as the association of each with regional and global tau aggregation as measured by the tau PET radiotracer [^{18}F]flortaucipir (T-807; AV-1451). Our goal was to evaluate the relationship between self– and informant memory concerns and tau deposition to investigate the biological basis for the predictive power of cognitive concerns and whether the self- and informant concerns could be utilized as part of a screening protocol to assess preclinical AD in individual adults. We included older adults enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who were defined as CN controls, had significant memory concerns (SMCs), or had EMCI. These adults comprise a continuum of risk for developing clinical AD. A subset of the CN older adults are amyloid negative and apolipoprotein E (*APOE*) ε4 noncarriers and thus are at risk for AD due to age alone and are on the "low-risk" end of the continuum. On the "high-risk" end are adults with EMCI who have subtle cognitive decline, presence of self– and informant cognitive concerns, and are amyloid positive and/or *APOE* ε4 carriers. We examined the association of self– and informant ECog memory scores with one another and with tau aggregation in all participants. Following these analyses, we completed a subanalysis using only participants who are amyloid positive because these participants are at a relatively higher risk of