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Neuroimaging

Olfactory identification in subjective cognitive decline and mild cognitive impairment: Association with tau but not amyloid positron emission tomography

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Abstract

Introduction: We investigated the association between olfactory identification and Alzheimer's disease biomarkers, including amyloid, tau, and neurodegeneration.

Methods: Thirty-four older adults, including 19 cognitively normal (CN), 10 subjective cognitive decline (SCD), and 5 mild cognitive impairment, underwent amyloid positron emission tomography, magnetic resonance imaging, and the University of Pennsylvania Smell Identification Test (UPSIT). Twenty-six also underwent tau positron emission tomography. Associations between the UPSIT and regionally sampled amyloid, tau, and temporal atrophy were evaluated. Voxel-wise regression models were also utilized. Analyses were conducted with the full sample and only CN/SCD.

Results: Lower UPSIT scores were associated with increased temporal and parietal tau burden in regional and voxel-wise analyses in the full sample and in CN and SCD only. Temporal lobe atrophy was associated with lower UPSIT score. Amyloid was not associated with the UPSIT.

Discussion: Impairment on the UPSIT may be a good marker for tau and neurodegeneration in preclinical or prodromal Alzheimer's disease.

Keywords: Olfaction; Alzheimer's disease; [^{18}F]Flortaucipir (AV-1451); Tau; Neurodegeneration

1. Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disease and is characterized by gradually progressive impairment in cognitive function and dementia [1]. In addition to the dementia syndrome of AD and the more limited amnestic deficits typical of its prodromal stage, mild cognitive impairment (MCI) [2], changes in sensory function have also been reported. Olfactory identification (the ability to correctly identify a smell) is impaired in AD and MCI, as well as in patients with Parkinson's disease and other neurodegenerative conditions [3–10]. Furthermore, olfactory identification measured using the University of Pennsylvania Smell Identification Test (UPSIT) is sensitive to predicting future conversion from MCI to AD and even future cognitive decline in cognitively normal (CN) older adults and Parkinson's patients [4,11–14].

The precise biological correlates of the observed changes in olfactory identification have not been specifically

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identified. However, previous studies have sought to determine the impact of the two major pathophysiological hallmarks of AD, amyloid β plaques and tau neurofibrillary tangles, on olfaction in animal models of AD [15–22], autopsy studies [23–29], and more recently in living human beings using imaging biomarkers of amyloid pathology, measured using neuroimaging with positron emission tomography (PET) techniques [30–32]. Animal models of AD show considerable olfactory deficits that are related to the deposition of amyloid and tau in the olfactory bulb and throughout the olfactory network [15–22,33]. In human autopsy studies, amyloid and tau, as well as other pathologies such as progranulin and TDP-43 deposition, are found in the olfactory bulb and throughout the olfactory network (including temporal piriform cortex) in patients with AD and other neurodegenerative diseases, and levels of amyloid and tau deposition are associated with the level of olfactory deficits [23–29,34]. The associations of UPSIT performance with neurodegeneration and brain function, measured using magnetic resonance imaging (MRI) or [^{15}O]H_2O PET, have also been investigated [4,14,31,35–41]. *In vivo* imaging studies have shown weak associations between amyloid and olfactory impairments [30–32]. However, more significant relationships between olfactory impairment and atrophy are apparent in olfactory-related regions (amygdala, piriform cortex, entorhinal cortex, etc.) in MCI and AD patients, as well as amyloid-positive CN older adults [4,14,31,32,36,38,40]. Impaired olfactory identification on the UPSIT was also correlated with white matter degeneration in the splenium of the corpus callosum and superior longitudinal fasciculus, as measured with diffusion tensor imaging [38]. Schofield et al. (2012) also showed that poorer recovery on the UPSIT after cholinergic challenge with atropine was associated with a lower hippocampal volume in MCI and AD dementia patients [37]. Furthermore, *in vivo* activation of the primary olfactory cortex is reduced in patients with MCI and AD [35,40,41]. Despite the evidence for relationships between olfaction and amyloid, structural, and functional markers in AD, there are no *in vivo* assessments of the relationship between olfactory identification and tau deposition, likely due to the lack of an *in vivo* marker for tau until recently.

New PET tracers targeting tau neurofibrillary tangles have become available, including [^{18}F]Flortaucipir ([^{18}F] AV-1451) [42]. Our goal was to evaluate the association of UPSIT scores with tau deposition (indexed with [^{18}F]Flortaucipir PET), amyloid deposition ([^{18}F]Florbetapir or [^{18}F]Florbetaben), and neurodegeneration (structural MRI). Our cohort included CN older adults without significant cognitive concerns, older adults with subjective cognitive decline (SCD), and patients with MCI. Previous literature examining *in vivo* imaging has suggested a strong association of UPSIT performance and neurodegeneration on MRI, but a weaker association with amyloid deposition. Thus, we hypothesized that impairments on the UPSIT would be associated with tau deposition and neurodegeneration (gray matter [GM] loss) in regions involved in olfactory processing (i.e., medial temporal lobe) but show less of an association with cortical amyloid deposition.

2. Methods

2.1. Participants

Thirty-four older adults (age 55+ years) were recruited from the Indiana Alzheimer Disease Center to undergo advanced PET and MRI neuroimaging and sensory testing. UPSIT administration was performed as previously described, with UPSIT total score being the primary outcome measure of olfactory identification (maximum score = 40; higher scores reflect better performance) [43]. Individuals with a history of a broken nose, severe allergies, or who were currently experiencing an upper respiratory infection, as well as those who were unable to undergo MRI or PET imaging were excluded. Five participants were diagnosed with MCI using previously established guidelines. Briefly, MCI participants had a significant complaint about their cognition from themselves and/or an informant or a clinician, as well as a significant deficit (>1.5 standard deviation below normal) in either memory or another cognitive domain [2]. Ten individuals were characterized as SCD according to the following criteria: elevated levels of subjective memory concerns on the 20-item Cognitive Change Index (CCI-20) reflected as a score of 20 or more on the first 12 items, with or without increased levels of informant-based concerns [44] and without a measurable cognitive deficit. Nineteen older adults without significant memory concerns (12-item CCI total <20) and without measurable cognitive deficit were considered CN. All procedures were approved by the Indiana University School of Medicine Institutional Review Board, and informed consent was obtained according to the Declaration of Helsinki and the Belmont Report.

2.2. Amyloid PET

Amyloid PET scans were acquired with either [^{18}F]Florbetapir (Amyvid, Eli Lilly and Co.) or [^{18}F]Florbetaben (Neuraceq, Piramal Ltd.). Briefly, for the [^{18}F]Florbetapir scans, approximately 10 mCi of [^{18}F]Florbetapir was injected intravenously, and after a 50-minute uptake period, participants were imaged on a Siemens mCT for 20 minutes using continuous list-mode data acquisition. For the [^{18}F] Florbetaben scans, approximately 8 mCi of [^{18}F]Florbetaben was injected intravenously, and after a 90-minute uptake period, data were acquired for 20 minutes using continuous list-mode acquisition on a Siemens mCT. A computed tomography (CT) scan was acquired for scatter and attenuation correction. List-mode data were subsequently rebinned into four 5-minute frames. Reconstructions were conducted on the software platform (Siemens; Knoxville, TN). Ordered