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Featured Article

Imaging correlations of tau, amyloid, metabolism, and atrophy in typical and atypical Alzheimer's disease

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Abstract

Introduction: Neuroimaging modalities can measure different aspects of the disease process in Alzheimer's disease, although the relationship between these modalities is unclear.

Methods: We assessed subject-level regional correlations between tau on [^{18}F]AV-1451 positron emission tomography (PET), β amyloid on Pittsburgh compound B PET, hypometabolism on [^{18}F] fluorodeoxyglucose PET, and cortical thickness on magnetic resonance imaging in 96 participants with typical and atypical Alzheimer's disease presentations. We also assessed how correlations between modalities varied according to age, presenting syndrome, tau-PET severity, and asymmetry.

Results: [^{18}F]AV-1451 uptake showed the strongest regional correlation with hypometabolism. Correlations between [^{18}F]AV-1451 uptake and both hypometabolism and cortical thickness were stronger in participants with greater cortical tau severity. In addition, age, tau asymmetry, and clinical diagnosis influenced the strength of the correlation between [^{18}F]AV-1451 uptake and cortical thickness.

Discussion: These findings support a close relationship between tau and hypometabolism in Alzheimer's disease but show that correlations between neuroimaging modalities vary across participants.

Keywords: Positron emission tomography; Tau; β amyloid; Cortical thickness; Alzheimer's disease; Magnetic resonance imaging; Posterior cortical atrophy; Logopenic aphasia

1. Introduction

Neuroimaging modalities are now available that can measure many different aspects of the disease process in Alzheimer's disease (AD). Brain structure can be assessed using structural magnetic resonance imaging (MRI), brain metabolism can be assessed using [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET), and the presence in the brain of the two cardinal proteins typically associated with AD, that is, tau and β amyloid, can also now be assessed using radioactive ligands and PET imaging.

Patterns of atrophy on MRI and hypometabolism on FDG-PET have been well described in AD, with involvement of the temporoparietal lobes shown to be a relatively

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specific biomarker to differentiate AD from other molecular pathologies [1,2]. However, within the spectrum of AD, patterns of atrophy on MRI and metabolism on FDG-PET have been shown to vary according to clinical presentation and also age. Participants who present with early and prominent memory impairment that is considered typical for AD [3] tend to show atrophy and hypometabolism in the medial temporal lobe and temporoparietal cortices [4–6]. However, participants with young age at onset tend to show greater involvement of the isocortex than participants who present at older age [7–12]. Striking isocortical atrophy and hypometabolism are also observed in participants with atypical clinical presentation of AD, such as logopenic progressive aphasia [13] and posterior cortical atrophy [14]. However, in contrast to typical AD, these participants tend to show relative sparing of the medial temporal lobe [15,16] and the patterns of cortical involvement differ, with logopenic aphasia typically showing left-sided patterns of temporoparietal atrophy and hypometabolism [15,17,18] and posterior cortical atrophy showing striking involvement of temporal, parietal, and occipital lobes [16,19,20]. There is some suggestion that the pattern of cortical atrophy may also differ by age at onset in atypical AD [21]. Molecular PET imaging has shown that the regional distribution of β amyloid deposition is relatively consistent regardless of clinical presentation [18], with deposition in AD differing from patterns of atrophy and observed predominantly in the prefrontal and parietal cortices [22]. In contrast, patterns of tau uptake on PET imaging appear to match well with regional patterns of atrophy and hypometabolism across typical and atypical AD participants [23–28] and normal elderly [29], with tau uptake in the isocortex also greater in early-onset compared to late-onset AD [30].

Evidence from group-level studies, therefore, suggests good concordance between patterns of tau uptake on PET and patterns of atrophy and hypometabolism in AD. However, little is known about how well these imaging modalities correlate within individual participants and whether concordance between metrics varies by clinical presentation, age, or pattern or severity of tau uptake across the brain. In addition, it is unclear whether regional patterns of tau-PET uptake correlate better with regional patterns of atrophy or hypometabolism. In this study, we used a large cohort of 96 typical and atypical AD participants who underwent tau-PET imaging with [^{18}F]AV-1451, β amyloid PET with Pittsburgh compound B (PiB), MRI, and FDG-PET, to assess individual-level correlations between tau-PET and the other imaging metrics, and to determine the degree to which the strength of these correlations varies across participants. Determining the relationship between these different aspects of the disease will increase understanding of the disease process in AD. It will also help us understand whether MRI and FDG-PET measures of neurodegeneration are specific for the molecular pathologies underlying AD. Unlike tau-PET, MRI and FDG-PET are both widely available and hence could prove to be very valuable biomarkers of molecular pathology for centers that do not have access to tau-PET. Measures of neurodegeneration are also already being used as outcome measures in clinical treatment trials, and hence it is critically important to understand how these measures relate to underlying molecular pathologies. This knowledge will help guide the inclusion and interpretation of biomarker findings in different populations of AD participants from clinical treatment trials, particularly those that assess therapies targeting tau or β amyloid.

2. Methods

2.1. Participants

We identified all participants with a clinical diagnosis of typical or atypical AD who had elevated β amyloid deposition on PiB-PET and had undergone [^{18}F]AV-1451 tau-PET and 3T MRI at Mayo Clinic, Rochester, MN, between 2/25/2015 and 4/12/2017. Ninety-six patients were identified of which 55 were diagnosed with typical Alzheimer's dementia [3] and 41 were diagnosed with atypical AD because the dominant cognitive deficit was in domains other than episodic memory [31]. Of the 41 atypical AD participants, 19 were diagnosed with posterior cortical atrophy [14], 16 were diagnosed with logopenic aphasia [13], and six were diagnosed with behavioral/dysexecutive AD [32]. Of the 96 participants, 80% had also undergone FDG-PET (47 typical AD and 30 atypical AD). These participants had been recruited as part of an NIH-funded grant studying atypical AD (PI Whitwell) or as part of the Mayo Clinic Alzheimer's Disease Research Center (PI Petersen). All participants, regardless of recruitment mechanism, underwent a detailed neurological examination by a behavioral neurologist, and diagnoses were rendered based on established clinical criteria. Clinical and neuropsychological tests that were available for analysis across both cohorts included the Montreal Cognitive Assessment, Clinical Dementia Rating (CDR) scale to measure functional impairment, Trail Making Tests A and B to measure attention, processing speed and mental flexibility, letter (F) and animal fluency to assess lexical and semantic access, Auditory Verbal Learning Test to assess memory, and the Rey-Osterrieth Complex Figure Test–Copy Trial to assess visuospatial function. Apolioprotein E (APOE) genotyping was also performed. Q2

The study was approved by the Mayo institutional review board. All participants consented to research in writing; in the situation of persons with dementia, a family informant also provided written consent.

2.2. Image acquisition

All PET scans were acquired using a GE PET/CT scanner. Q3 For tau-PET, participants were injected with approximately 370 MBq (range 333–407 MBq) of [^{18}F]AV-1451, followed by a 20-minute PET acquisition performed 80 minutes after injection. For PiB-PET, participants were