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Regional tau deposition and subregion atrophy of medial temporal structures in early Alzheimer's disease: A combined positron emission tomography/magnetic resonance imaging study

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Abstract

Introduction: Molecular imaging and selective hippocampal subfield atrophy are a focus of recent Alzheimer's disease (AD) research. Here, we investigated correlations between molecular imaging and hippocampal subfields in early AD.

Methods: We investigated 18 patients with early AD and 18 healthy control subjects using ^{11}C-Pittsburgh compound-B (PIB) positron emission tomography (PET) and ^{18}F-THK5351 PET and automatic segmentation of hippocampal subfields with high-resolution T2-weighted magnetic resonance imaging. The PET images were normalized and underwent voxelwise regression analysis with each subregion volumes using SPM12.

Results: As for ^{18}F-THK5351 PET, the bilateral perirhinal cortex volumes were significantly associated with the ipsilateral or bilateral temporal lobar uptakes, whereas hippocampal subfields showed no correlations. ^{11}C-PIB PET showed relatively broad negative correlation with the right cornu ammonis 3 volumes.

Discussion: Regional tau deposition was correlated with extrahippocampal subregional atrophy and not with hippocampal subfields, possibly reflecting different underlying mechanisms of atrophy in early AD. Amyloid might be associated with right cornu ammonis 3 atrophy.

Keywords: Tau PET; Hippocampal subfield; Alzheimer's disease; Entorhinal cortex; Perirhinal cortex

1. Introduction

Alzheimer's disease (AD) is the most common type of neurodegenerative dementia. Abnormal accumulations of extracellular amyloid β and intracellular neurofibrillary tangles (NFTs) of tau proteins are hallmarks of AD. Recently, AD research has begun taking advantage of various emerging advanced neuroimaging methods, with tau positron emission

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tomography (PET) considered particularly promising for in vivo estimations of AD pathology [1]. A recent study revealed that tau PET uptake patterns strongly reflect regional associations with clinical and anatomic variability, whereas amyloid PET shows a more diffuse distribution and less regional associations with other parameters [2].

Hippocampal atrophy is a key structural imaging finding in AD [3]. The selectivity of hippocampal subfield atrophy has attracted attention for its diagnostic and predictive potential [4,5], and specific cortices such as the entorhinal cortex (ERC) and perirhinal cortex (PRC) are also considered important for memory networks [6,7].

Because tau deposition can potentially affect clinical and morphologic parameters in AD and medial temporal subregions may also have diagnostic and/or predictive value, investigation of the relationships between subregional atrophy and abnormal accumulations such as tau deposition is required. We conducted this study to explore imaging correlations using ^{11}C-Pittsburgh compound-B (PIB) PET, ^{18}F-THK5351 PET [8], and automatic segmentation of hippocampal subfields (ASHS) with high-resolution T2-weighted magnetic resonance imaging (MRI), which is a reliable method for subregional volumetry in various neurologic diseases [3,9,10].

2. Methods

2.1. Patients and control subjects

We recruited 18 Japanese patients (13 women, 5 men) with early AD at our institute. AD was diagnosed based on the clinical criteria for probable AD [11] and the presence of an abnormal cortical accumulation of amyloid revealed by the visual assessment of ^{11}C-PIB PET images. The patients were 70.3 ± 8.5 years old (mean ± standard deviation [SD]), their average Mini–Mental State Examination (MMSE) score was 22.6 ± 4.1 (mean ± SD), and their global Clinical Dementia Rating ranged from 0.5 to 1.0. Almost all patients had less than 1 year disease duration except two patients with a few years' history from the diagnoses.

For reciprocal comparisons of abnormal depositions on PET and subregional atrophy, we also recruited 18 healthy Japanese control subjects (10 women, 8 men) with normal cognition who showed visually normal ^{11}C-PIB and ^{18}F-THK5351 PET results. The control subjects were 66.8 ± 9.5 years old, with an average MMSE score of 29.2 ± 1.0 and a global Clinical Dementia Rating of 0. There were no significant differences in the mean age or sex proportion between the early AD patient and healthy control groups. All clinical assessments and imaging scans were performed within a 12-week period.

All subjects gave written consent to participate in the study, which was approved by the Institutional Review Board at Japan's National Center of Neurology and Psychiatry.

2.2. Imaging acquisition

All participants underwent MRI scanning on a 3.0-T MRI system (Verio, Siemens, Erlangen, Germany). The sequence parameters were as follows. Three-dimensional sagittal T1-weighted magnetization prepared rapid acquisition with gradient echo images: repetition time/echo time, 1900 ms/2.52 ms; flip angle, 9°; in-plane resolution, 1.0 × 1.0 mm; 1.0-mm effective slice thickness with no gap; 300 slices; matrix, 256 × 256; field of view, 25 × 25 cm; acquisition time, 4 minutes 18 seconds.

High-resolution T2-weighted images were designed for hippocampal subfield segmentation and obtained as follows: repetition time/echo time, 7380 ms/76 ms; flip angle, 150°; in-plane resolution, 0.4 × 0.4 mm; 2-mm slice thickness with no gap; 30 slices; matrix of 512 × 432; 22 × 22 cm field of view; acquisition time, 6 minutes 33 seconds.

All the PET/computed tomography (CT) scans were performed on a combined PET/CT scanner (Biograph 16; Siemens). For ^{11}C-PIB imaging, ^{11}C-PIB at a dose of 555 MBq was injected intravenously 50 minutes before the PET/CT scan, and the emission scan duration was 20 minutes. For ^{18}F-THK5351 imaging, ^{18}F-THK5351 at a dose of 185 MBq was injected 40 minutes before the scan, and the scan duration was 20 minutes. PET/CT images were reconstructed using a combination of Fourier rebinning and ordered subset expectation maximization.

2.3. ASHS volumetry of hippocampal and mesiotemporal subfields

We input both the T1- and high-resolution T2-weighted images obtained from all subjects into an open-source ASHS software program (https://sites.google.com/site/hipposubfields/) [9]. The "UPenn PMC Atlas" [9] was selected as the atlas set. The software calculated the volumes of each subfield fully automatically with a combination of multiatlas label fusion and learning-based error correction. The following 10 regions of interest were delineated: cornu ammonis (CA) 1, CA2, CA3, dentate gyrus (DG), subiculum, ERC, Brodmann area (BA) 35, BA36, collateral sulcus, and miscellaneous parts. Experienced neuroradiologists visually confirmed that the parcellation quality was good or fair.

2.4. PET normalization

After partial volume correction by PETPVE12 toolbox [12], both the ^{11}C-PIB and ^{18}F-THK5351 PET images were normalized using the statistical parametric mapping software 12 program (SPM12; http://www.fil.ion.ucl.ac.uk/spm). The subjects' T1-weighted images were coregistered to their PET images and normalized with diffeomorphic anatomic registration using the exponentiated lie method [13]. A transformation matrix was applied to each PET image, which had been coregistered to T1-weighted image through the partial volume correction process.

After spatial normalization, all the PET images were divided by the individual's positive mean uptake value of cerebellar gray matter. Finally, each PET image was smoothed by an 8-mm full width at half maximum Gaussian