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Predicted sequence of cortical tau and amyloid-β deposition in Alzheimer disease spectrum

Hanna Cho [a], Hye Sun Lee [b], Jae Yong Choi [c,d], Jae Hoon Lee [c], Young Hoon Ryu [c], Myung Sik Lee [a], Chul Hyoung Lyoo [a,*]

[a] Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[b] Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, South Korea
[c] Department of Nuclear Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[d] Division of RI-Convergence Research, Korea Institute Radiological and Medical Sciences, Seoul, South Korea

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ABSTRACT

We investigated sequential order between tau and amyloid-β (Aβ) deposition in Alzheimer disease spectrum using a conditional probability method. Two hundred twenty participants underwent ^{18}F-flortaucipir and ^{18}F-florbetaben positron emission tomography scans and neuropsychological tests. The presence of tau and Aβ in each region and impairment in each cognitive domain were determined by Z-score cutoffs. By comparing pairs of conditional probabilities, the sequential order of tau and Aβ deposition were determined. Probability for the presence of tau in the entorhinal cortex was higher than that of Aβ in all cortical regions, and in the medial temporal cortices, probability for the presence of tau was higher than that of Aβ. Conversely, in the remaining neocortex above the inferior temporal cortex, probability for the presence of Aβ was always higher than that of tau. Tau pathology in the entorhinal cortex may appear earlier than neocortical Aβ and may spread in the absence of Aβ within the neighboring medial temporal regions. However, Aβ may be required for massive tau deposition in the distant cortical areas.

1. Introduction

Hyperphosphorylated tau and amyloid-β (Aβ) are the constituents of neurofibrillary tangles (NFT) and amyloid plaques, respectively, 2 major pathologies in Alzheimer disease (AD). The 2 proteins accumulate and spread in specific hierarchical patterns. Cortical Aβ spreads from the frontotemporal cortices to involve widespread neocortical areas (Thal's Aβ phase 1) and eventually reaches the medial temporal structures (phase 2) (Braak and Braak, 1991; Thal et al., 2002). In contrast, cortical tau spreads in a stepwise hierarchical pattern from the transentorhinal and entorhinal cortices (Braak's NFT stage I and II) toward the neighboring medial temporal structures (stage III and IV) and distant association cortices (stage V) and eventually reaches the primary cortices (stage VI) (Braak and Braak, 1991).

In our previous work, diffuse deposition patterns of neocortical Aβ and a hierarchical upward spreading pattern of tau were determined with in vivo ^{18}F-florbetaben and ^{18}F-flortaucipir positron emission tomography (PET) studies, based on the regional frequency of involvement by tau and Aβ (Cho et al., 2016a,b). Interestingly, the frequency of tau deposition in the entorhinal cortex was approximately 10% greater than that of Aβ deposition in the middle and inferior temporal cortices. Although we may suspect that tau deposition in the entorhinal cortex precedes neocortical Aβ deposition, this method based on the involvement frequency does not provide information about the sequential order of tau and Aβ deposition.

Conditional probability (CP) is a method for determining the likelihood of the occurrence of an event, given that a different event has occurred. It is thought to be theoretically more accurate for predicting temporal sequences of events with large cross-sectional data. A recent pathological study successfully applied this CP method to determine the spreading pattern of TAR DNA-binding protein 43 in AD (Josephs et al., 2016).

We sought to replicate cortical spreading patterns of tau and Aβ by using the CP method and investigated the sequential order of tau and Aβ deposition in the cortex by using a modified CP method.

2. Methods

2.1. Participants

From January 2015 to December 2016, we prospectively recruited 62 amnestic type mild cognitive impairment (MCI) and

* Corresponding author at: Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Research Center for Future Medicine, 20 Eonjuro 63-gil, Gangnam-gu, Seoul, South Korea. Tel.: +82 2 2019 3326; fax: +82 2 3462 5904.
E-mail address: lyoochel@yuhs.ac (C.H. Lyoo).

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66 AD patients at the Memory Disorder Clinic of Gangnam Severance Hospital. AD patients were diagnosed as probable AD using the guidelines proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (McKhann et al., 1984), and MCI patients were diagnosed using the Petersen's criteria (Petersen et al., 1999). All patients were presented with amnesia, and none of the patients showed clinical features atypical for AD such as posterior cortical atrophy, logopenic aphasia, or frontal-variant AD. In addition, 92 healthy controls who met the Christensen's diagnostic criteria (Christensen et al., 1991) and exhibited normal cognition on a neuropsychological test battery, no previous history of head trauma, neurological or psychiatric illness, and no abnormalities in brain magnetic resonance (MR) imaging.

All participants underwent a clinical interview, neuropsychological test battery, genotyping for apolipoprotein E (ApoE), brain MR imaging, and 2 consecutive PET scans with ^{18}F-flortaucipir and ^{18}F-florbetaben.

This study was approved by the institutional review board of Gangnam Severance Hospital, and a written informed consent was obtained from all subjects.

2.2. Neuropsychological tests

Seoul Neuropsychological Screening Battery was used for the assessment of cognitive function (Ahn et al., 2010; Kang and Na, 2003). Scorable items in the battery were selected for the assessment of each cognitive domain: backward digit span for attention, Korean version of the Boston Naming Test for language, copy item in the Rey-Osterrieth Complex Figure Test for visuospatial function, 20-minute delayed recall tests in the Seoul Verbal Learning Test and the Rey-Osterrieth Complex Figure Test for the verbal and visual memory, and Controlled Oral Word Association Test-Semantics for frontal executive function. Mini-Mental State Examination and Clinical Dementia Rating sum of boxes scores were used to assess the participants' global cognitive function.

2.3. Acquisition of PET and MR images

Before the PET scan, a head holder was applied to minimize head motion during the scan and brain computed tomography (CT) images were acquired for attenuation correction. PET images were acquired for 20 minutes in a Biograph mCT PET/CT scanner (Siemens Medical Solutions; Malvern, PA, USA) at 80 minutes after the injection of 282.4 $\pm$ 36.2 MBq of ^{18}F-AV-1451 and 90 minutes after the injection of 303.1 $\pm$ 38.8 MBq of ^{18}F-florbetaben. After the correction for attenuation and scatter, 3D-PET images were finally reconstructed in 256 $\times$ 256 $\times$ 223 matrix with 1.591 $\times$ 1.591 $\times$ 1 mm voxel size by using the ordered-subsets expectation maximization algorithm.

T1-weighted brain MR images were acquired in a 3.0 Tesla MR scanner (Discovery MR750, GE Medical Systems, Milwaukee, WI, USA) with 3D-spoiled gradient-recalled sequences (3D-SPGR sequences; repetition time = 8.28 ms, echo time = 1.6–11.0 ms, flip angle = 20°, 512 $\times$ 512 matrix, voxel spacing 0.43 $\times$ 0.43 $\times$ 1 mm).

2.4. Image-processing steps

To obtain regional standardized uptake value ratio (SUVR) values of ^{18}F-AV-1451 and ^{18}F-florbetaben PET, we used same image-processing steps as our previous work (Cho et al., 2016a,b). In brief, the FreeSurfer 5.3 software (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu) was used for the initial processing of T1-weighted images such as segmentation of subcortical structures, creating 3D-surface models of cortical gray matter and underlying white matter, and parcellation of cortical regions. Thereby, participant-specific composite volume-of-interest (VOI) mask images for 36 cortical and subcortical regions were created after merging the VOIs of anatomically related regions. By overlaying participant-specific composite VOI mask images on the individual PET images coregistered to their own MR images, SUVR images were created with cerebellar cortex as a reference region, and finally regional SUVR values for 25 cortical regions (superior, middle and inferior frontal, orbitofrontal, precentral, paracentral, superior and inferior parietal, supramarginal, precuneus, postcentral, medial and lateral occipital, lingual, anterior and posterior cingulate, insula, superior, middle and inferior temporal, fusiform, entorhinal and parahippocampal cortices, hippocampus, and amygdala) were measured. Finally, image-based tau stages for each participant were determined by using the fully automated method proposed by our previous work (Cho et al., 2016a,b). Although we primarily used the data uncorrected for partial volume effect (PVE), for additional analysis, we also obtained regional SUVR values corrected for PVE by using the region-based voxel-wise method (Thomas et al., 2011). Because of undesirable segmentation result for the choroid plexus, where the "off-target" binding of ^{18}F-AV-1451 exists, only the VOI masks for brain regions were used for PVE correction.

For the surface-based visualization and statistical analysis, surface-based SUVR maps were created by sampling the SUVR values at the midpoint between the cortical gray and white matter surfaces. SUVR maps were spatially normalized to template surface and smoothed by Gaussian kernel with 8 mm full-width at half maximum.

2.5. Creation of Z-score maps of tau, Aβ, and cognitive impairment

We binarized regional involvement of tau and Aβ separately based on the regional Z-scores like our previous work (Cho et al., 2016a,b). We first selected 58 reference controls who were relatively unaffected by tau or Aβ by using the following criteria: (1) negative for Aβ determined by the neocortical ^{18}F-florbetaben SUVR value $<$1.4 (Villemagne et al., 2011); and (2) ^{18}F-flortaucipir SUVR value for the entorhinal cortex $<$1.2 (Schwarz et al., 2016). By using the regional means and standard deviations derived from the regional SUVR values of these 58 controls, regional Z-scores were calculated for all 220 participants. We used a Z-score of 2.5 (representing a less than 1% false positive rate) as the cutoff to determine involvement of tau or Aβ.

Likewise, for the surface-based analysis, surface maps for the mean and standard deviation were created with the same 58 controls' SUVR maps, and then surface-based Z-score maps were created for all 220 participants. By using the same cutoff Z-score of 2.5, surface maps for the binarized involvement of tau and Aβ were separately created.

By using the cutoff Z-score of $-$1.5 of the age- and education-adjusted norms as proposed by Petersen's criteria (Petersen et al., 1999), we created a binarized table for each participant showing the presence of impairments in each cognitive function domain as well as global cognitive function.

All steps were completed automatically by using an in-house software implemented in MATLAB 7.1 (MathWorks, Natick, MA, USA).

2.6. CP analysis

The theoretical background and details of the CP method for determining the sequential order of 2 conditions have been described in a previous article (Josephs et al., 2016). We modified the original method to determine the sequential order between 2