Longitudinal Alteration of Intrinsic Brain Activity in the Striatum in Mild Cognitive Impairment

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Abstract. The striatum is a critical functional hub in understanding neurological disorders. However, the Alzheimer’s disease (AD)-associated striatal change is unclear, as is the relationship between striatal change and AD pathology. Three-year resting-state fMRI data from 15 healthy control (HC) and 20 mild cognitive impairment (MCI) participants were obtained. We analyzed the amplitude of low-frequency fluctuations (ALFF) (0.01–0.08 Hz) and two subdivided bands (slow-4:0.027–0.073 Hz; slow-5:0.01–0.027 Hz). We calculated Aβ/pTau ratio using baseline cerebrospinal fluid pTau and Aβ1-42 to represent AD pathology. Compared to HC, MCI participants showed greater decline in right putaminal ALFF, including the slow-4 band. Greater decline of ALFF in the right putamen was significantly related to the memory decline over time and lower baseline Aβ/pTau ratio regardless of age or group. The slow-4 band, relative to slow-5 band, showed a stronger correlation between Aβ/pTau ratio and decline of ALFF in the right putamen. The results suggest that the putaminal function declines early in the AD-associated neurodegeneration. The continuous decline in putaminal ALFF, especially slow-4 band, may be a sensitive marker of AD pathology such as Aβ/pTau ratio regardless of clinical diagnosis.

Keywords: Amyloid-beta, low-frequency fluctuation, mild cognitive impairment, pTau, resting state fMRI, striatum

INTRODUCTION

Identifying neural targets for early detection and prevention has become the focus of current Alzheimer’s disease (AD) research. Cumulative evidence reported that a wide range of brain regions becomes dysfunctional in AD, but the literature has been substantially focused on cortical areas (e.g., the prefrontal cortex, temporal gyrus) [1–3]. Although the hippocampus is known to be disrupted in AD-associated neurodegeneration [4, 5], little is known...
about other subcortical areas, such as the striatum, which serves as a hub, structurally and functionally connected to almost all cortical regions [6, 7]. Its widespread neural projections make the striatum sensitive to pathology seen in the neurodegenerative brain. For example, a recent study identified the striatum as among the first sets of brain regions to be affected by amyloid deposition among cognitively healthy older adults [8]. Emerging cross-sectional studies have reported that the structural and functional connectivity of the striatum with multiple brain areas are altered in mild cognitive impairment (MCI) and AD patients [2, 3, 9–11]. Moreover, some studies suggest that as a key node for dopamine transmission [12], the striatum is critical in transferring neural effects of interventions (e.g., cognitive stimulation) to different parts of the brain [13, 14]. Notably, AD is considered a connectivity syndrome [15]. Therefore, characterizing longitudinal change of the striatum itself in the early stage of AD-associated neurodegeneration may help better understand AD pathology. To the extent that striatal regions can be targeted, such knowledge may illuminate new therapeutic targets for slowing AD-related neurodegeneration.

Resting-state functional magnetic resonance imaging (rs-fMRI) is widely used in studying brain dysfunctions in MCI and AD [16] blood-oxygen-level dependent (BOLD) signals measured by fMRI reflect neural spontaneous activity [17]. The amplitude of low frequency fluctuations (ALFF) has been widely used to examine the brain function, by measuring the amplitude of spontaneous activity within a specific frequency range (e.g., 0.01–0.08 Hz) [18–20]. Of note, the ALFF assesses neural fluctuations within specific brain regions, different from the more commonly used rs-fMRI technique of evaluating temporal synchronization between brain regions. Greater decline in ALFF in the striatum and other brain regions (including the posterior cingulate cortex, and hippocampus/parahippocampus) has been reported in MCI patients compared to their healthy counterparts (HC) [21, 22].

Zuo et al. further decomposed the low frequency band in ALFF measurements into four distinct frequency bands termed slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz). The amplitude in the slow-4 band in striatum among young adults appears to be most pronounced [23]. In another study of older adults with MCI, slow-5 had greater abnormalities than slow-4 in multiple posterior cortical regions [21]. Both slow-4 (0.027–0.073 Hz) and slow-5 (0.01–0.027 Hz) may be particularly relevant to striatal function in AD-associated neurodegeneration.

In the current study, we examined changes of striatal activation measured by rs-fMRI from baseline, 1-, to 2-year follow-up between amnestic MCI and HC groups using data from the Alzheimer’s Disease Neuroimaging Study (ADNI). The specific aims were to (1) examine the longitudinal changes in the ALFF in the caudate and putamen, in relation to diagnostic group and cognitive performance; (2) determine the association between change in the ALFF in these striatal regions and AD pathology; and (3) evaluate whether the amount of striatal ALFF change and the magnitude of the association between striatal ALFF change and AD pathology were frequency-band dependent.

METHODS

ADNI dataset

Data used in the preparation of this article were obtained in December 2015 from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with
Participants

The data used in this study were obtained from ADNI2 or ADNIGO where rs-fMRI data were collected using 3T scanners. We identified 20 amnestic MCI subjects aged 65–90 years with consecutive annual rs-fMRI and cognitive data from baseline to 2-year follow-up. We thereafter identified 15 age, sex, and education-matched HC subjects with the same length of rs-fMRI and cognitive data (see Table 1). Of note, our decision on sample selection was based on a balance between a reasonable length of follow-up for a longitudinal study and a properly involved sample size. The diagnosis of amnestic MCI was made by a psychiatrist or neurologist at each study site and reviewed by a Central Review Committee, based on a subjective memory complaint and performance on neuropsychological testing, including the Logical Memory II subscale of the Wechsler Memory Scale-Revised (score ≤8, cut-off adjusted for education level), the Mini-Mental State Exam (score 24–30), and the Clinical Dementia Rating (global score = 0.5).

Measures of AD pathology and health information at baseline

Amyloid-beta (1–42) (Aβ1-42) and pTau were derived from the cerebrospinal fluid aliquots, measured using the multiplex xMAP Luminex platform (Luminex Corp., Austin, Tex., USA) with immunoassay kit-based reagents (INNO-BIA AlzBio3; Innogenetics, Ghent, Belgium). An Aβ/pTau ratio was used as the ‘AD signature’ for which lower Aβ/pTau ratios indicated an increased burden of AD pathology [24]. Memory and executive function were measured using two composite scores developed based on a serial factor analyses, reported in previous studies [25, 26]. The composite memory index was based on the memory-related domains of the Mini Mental Status Examination, Alzheimer’s Disease Assessment Scale-Cognition subscale, Rey Auditory Verbal Learning Test, and Logical Memory test. The composite executive function index was based on the Wechsler Memory Scale-Revised Digit Span Test, Digit Span Backwards, Category Fluency, Trails A and B, and the Clock Drawing Test. Depressive symptoms were measured using Geriatric Depression Scale (GDS). Of note, two groups differed in their memory composite score, did not differ at the Aβ/pTau ratio, executive function, or GDS (see Table 1).

rs-fMRI data acquisition and preprocessing

In the current study, rs-fMRI data were collected yearly at baseline, one, and two-year follow-ups (three time points in total). All subjects were scanned on a 3.0 Tesla Phillips MRI. The rs-fMRI imaging data were obtained by using an echo-planar imaging (EPI) sequence (TR = 3000 ms, TE = 30 ms, slice thickness = 3.3 mm, matrix = 64 × 64, spatial resolution = 3 × 3 × 3 mm3, number of volumes = 140, number of slices = 48). The resting state functional imaging data were preprocessed using DPARSF [27].

ALFF analysis

After removing the linear trend, data was filtered using band pass (0.01–0.08 Hz) to do ALFF analysis. The ALFF values were calculated and extracted using Resting-State fMRI Data Analysis Toolkit (REST) [28]. Briefly, the time series of BOLD signal was converted to the frequency domain using the fast Fourier transform. The square root of the power spectrum was then calculated and averaged across 0.01–0.08 Hz for each voxel. The averaged square root was defined as the ALFF at the given voxel [18]. We also further decomposed the frequency range into the slow-4 (0.027–0.073 Hz) and slow-5 (0.01–0.027 Hz) bands [21], and relevant frequency-dependent ALFF values were calculated for each participant. To reduce the global effects across participants, the ALFF of each voxel was computed by dividing the global mean value [18, 29]. For the regions of interest (ROIs), the striatum was divided into the caudate and putamen. Bilateral caudate and putamen were defined and ROI masks were generated according to the Automated Anatomical Labeling atlas [30] (Fig. 1). Individual participant’s ALFF values in the putamen and caudate were then extracted to examine their association with Aβ/pTau ratio.

Other data analyses

Data analyses were conducted using SPSS 22.0. MCI-HC group comparisons on sample characteristics were made using independent t-tests for continuous variables or χ² tests for categorical variables. Generalized Estimating Equation (GEE) (Models (1) to (3)) or Generalized Linear Model
Table 1  
Baseline demographics and clinical characteristics of MCI and HC groups

<table>
<thead>
<tr>
<th></th>
<th>MCI (n = 20)</th>
<th>HC (n = 15)</th>
<th>t or χ² test (p value), df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>75.35 (8.57)</td>
<td>79.33 (5.00)</td>
<td>-1.60 (0.12), 34</td>
</tr>
<tr>
<td>Education, M (SD)</td>
<td>15.40 (2.58)</td>
<td>16.13 (1.60)</td>
<td>-1.03 (0.31), 34</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (26.7)</td>
<td>4 (60.0)</td>
<td>3.84 (0.087), 1</td>
</tr>
<tr>
<td>GDS, M (SD)</td>
<td>1.50 (1.50)</td>
<td>0.73 (1.03)</td>
<td>1.69 (0.10), 34</td>
</tr>
<tr>
<td>Memory, M (SD)</td>
<td>0.27 (0.43)</td>
<td>0.83 (0.37)</td>
<td>4.04 (&lt;0.001), 34</td>
</tr>
<tr>
<td>Executive function, M (SD)</td>
<td>0.37 (0.79)</td>
<td>0.84 (0.54)</td>
<td>2.00 (0.054), 33</td>
</tr>
<tr>
<td>Aβ/pTau ratio, M (SD)</td>
<td>5.19 (3.81)</td>
<td>7.76 (5.76)</td>
<td>1.53 (0.14), 30</td>
</tr>
</tbody>
</table>

HC, healthy control; MCI, mild cognitive impairment; GDS, Global Deterioration Scale; ADAS-13, AD Assessment Scale 13 item.

Fig. 1. The bilateral striatum areas were selected as ROIs based on AAL atlas. The bilateral putamen was labeled with blue, and caudate were labeled with green. ROI, region of interests; AAL, Automated Anatomical Labeling.

(GLM) (Models (4) to (6)) models with an identity link and linear scale response were used. For GEE analysis including within-subject factor (i.e., time or frequency band), Auto-regression (AR)-1 working correlation matrix was used to reflect the characteristics of correlations between times or the correlation between frequency bands.

(1) The change over all three points (from baseline to two-year follow-up) of striatum within-group (model equation: y = β₀ + β₁Time + ε) wherein y refers to the ALFF value (full band, slow-4, or slow-5) for the region of the striatum under analysis at each time point, and “Time” was a considered a continuous variable.

(2) The yearly change of ALFF in the striatal regions between-group (equation: y = β₀ + β₁Time + β₂Group + β₃Time×Group + ε) wherein “Group” was a dichotomous variable with HC coded as 0 (the reference) and MCI as 1. In this model, β₃ reflects the difference between the MCI and HC groups in the ALFF change per year.

(3) The relationships between changes of ALFF in the relevant striatal regions and cognitive changes over time (equation: y = β₀ + β₁...n Covariates + βₙ₊₁Striatum + ε) wherein covariates included age, education, GDS, group diagnosis, baseline Aβ/pTau ratios and time, while y and “Striatum” refer to time-correspondent cognitive and ALFF in the relevant striatal regions per year. In this model, βₙ₊₁ reflects the correlation coefficient between cognitive and ALFF changes per year.

(4) The relationship between baseline Aβ/pTau ratio and ALFF change in the relevant striatal regions (model: y_striatal_change = β₀ + β₁Age + β₂Group + β₃Aβ/p Tau ratio + β₄Group × Aβ/pTau ratio + ε). In this model, β₃ represents the impact of baseline Aβ/pTau ratios on ALFF change, and β₄ represents the difference in MCI versus HC in this association. For y, we computed the change of ALFF in the striatal region by subtracting baseline data from the 2-year follow-up with lower score indicating greater decline.

(5) The effect of frequency bands on the relationship between baseline Aβ/pTau ratio and the striatal change, controlling for age and group diagnosis (equation: y_striatal_change = β₀ + β₁Age + β₂Group + β₃Frequency band + β₄Aβ/p Tau ratio + β₅Frequency band ×
Aβ/pTau ratio + ε). Here, y refers to the ALFF change in the relevant striatal region between baseline and two-year follow-up, and “Frequency band” was considered a dichotomous variable with “slow-5” coded as 0 (the reference) and “slow-4” coded as 1. In this model, β3 reflects the difference in the slow-4 versus slow-5 bands, and β5 indicates the differences between MCI and HC groups in the slow-4 versus slow-5 discrepancy.

(6) The effect of frequency bands on the relationship between the striatal and cognitive changes, controlling for age, group diagnosis, and baseline Aβ/pTau ratio (equation: y_cognitive change = β0 + β1Age + β2Group + β3Aβ/pTau ratio + β4Frequency band + β5Stratal change + β6Stratal change × Frequency band + ε). Cognitive change here was calculated as the difference between baseline and two-year follow-up. Other parameters were similar to those for model (5).

Of note, models (4) to (6) uses change of striatal ALFF (full or frequency-depended band) or cognitive as the outcome (lower scores indicate greater decline) rather than model (1) to (3) using repeated yearly measures of striatal ALFF or cognition. All tests with False Discovery Rate (FDR)-adjusted p value at two-tailed and less than 0.05 were considered significant. Of note, FDR adjustment was applied to address multiple comparisons between main ROIs (bilateral caudate and putamen), frequency bands (slow-4 and slow-5), and cognitive domains (memory and executive function).

RESULTS

Longitudinal changes of striatal ALFF

We first examined within-group 2-year change of the striatum (analytical Model (1)). The full band ALFF decreased yearly by 0.03 unit (SE=0.01, Wald’s χ² = 12.51, FDR-adjusted p=0.002) in R-putamen in the MCI group; conversely, there was no change in the putamen or caudate in the HC group. Since we did not find any significant decline in bilateral caudate, the further analysis was only focused on putamen.

Next, we examined between-group putaminal change (analytical Model (2)). The ALFF of the R-putamen declined 0.03 unit faster yearly in MCI group, compared to the HC group (see Table 2 “full band”). Figure 2 displays the longitudinal changes of bilateral putamen between MCI and HC groups.

Association between longitudinal changes of putaminal ALFF and cognitive trajectory

Applying analytical Model (3), controlling for age, education, GDS, group, baseline Aβ/pTau ratios, and time, decline of ALFF in R-putamen was significantly associated with the decline of memory (B = 1.31, SE=0.32, Wald’s χ² = 16.94, FDR-adjusted p<0.001). Longitudinal changes of putaminal ALFF were not associated with the change of executive function over time (FDR-adjusted p>0.10).

Association between change of putaminal ALFF and baseline Aβ/pTau ratio

Applying analytical Model (4), controlling for age, baseline Aβ/pTau ratio had a significant main effect on change of ALFF in R-putamen (B = 0.01, SE=0.004, Wald’s χ² = 5.11, FDR-adjusted p=0.048) (see Fig. 3A), but not in L-putamen (B = –0.005, SE=0.008, Wald’s χ² = 0.52, FDR-adjusted p=0.47). Thus, a one unit difference (reduction) in Aβ/pTau ratio resulted in a 0.01 decrease in ALFFs at two-year follow-up in the R-putamen. There was no main effect of group, or interaction effect of group and baseline Aβ/pTau ratio, suggesting that the association between AD pathology and decline of ALFF was similar across MCI and HC groups.

Frequency band-dependent effects

We examined the within-group change of the putamen for each subdivided band (slow-4 and -5) (analytical Model (1)). For MCI group, slow-4 band of the bilateral putamen (B: –0.02 to –0.03, Wald’s χ²: 5.37 to 12.12, FDR-adjusted p: 0.001 to 0.028), as well as slow-5 band of the R-putamen (B = –0.03, SE=0.008, Wald’s χ² = 11.06, FDR-adjusted p<0.001) declined significantly at two-year follow-up. There was no change for the HC group.

We examined between-group change of the putamen for each subdivided band (slow-4 and -5) (analytical Model (2)). ALFF in slow-4 band, but not slow-5, of the R-putamen declined significantly more at two-year follow-up in the MCI group, compared to the HC group (see Table 2).
Fig. 2. Longitudinal trajectories of ALFF (full band (A), slow-4 band and slow-5 band (B)) in the bilateral putamen of MCI and HC groups. ALFF, amplitude of low frequency fluctuations; HC, healthy control; MCI, mild cognitive impairment; L, left; R, right.

Table 2
GEE Analysis of longitudinal ALFF values (full band, slow-4, and slow-5) in the putamen between MCI and HC Group

<table>
<thead>
<tr>
<th>Group×Time</th>
<th>B (SE)</th>
<th>p</th>
<th>B (SE)</th>
<th>p</th>
<th>B (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full band</td>
<td>0.09 (0.04)</td>
<td>0.050</td>
<td>0.02 (0.02)</td>
<td>0.60</td>
<td>-0.04 (0.02)</td>
<td>0.059</td>
</tr>
<tr>
<td>Slow-4</td>
<td>0.09 (0.04)</td>
<td>0.08</td>
<td>0.02 (0.02)</td>
<td>0.58</td>
<td>-0.04 (0.02)</td>
<td>0.066</td>
</tr>
<tr>
<td>Slow-5</td>
<td>0.07 (0.05)</td>
<td>0.17</td>
<td>-0.001 (0.02)</td>
<td>0.95</td>
<td>-0.02 (0.02)</td>
<td>0.51</td>
</tr>
<tr>
<td>R-putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full band</td>
<td>0.06 (0.03)</td>
<td>0.064</td>
<td>0.001 (0.01)</td>
<td>0.89</td>
<td>-0.03 (0.01)</td>
<td>0.042</td>
</tr>
<tr>
<td>Slow-4</td>
<td>0.07 (0.03)</td>
<td>0.08</td>
<td>0.003 (0.01)</td>
<td>0.95</td>
<td>-0.04 (0.01)</td>
<td>0.048</td>
</tr>
<tr>
<td>Slow-5</td>
<td>0.02 (0.04)</td>
<td>0.53</td>
<td>-0.02 (0.01)</td>
<td>0.52</td>
<td>-0.007 (0.02)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Note. Applying analytical model (2). p here refers to FDR-adjusted p value. ^ taking HC as the reference. HC, healthy control; MCI, mild cognitive impairment; ALFF, amplitude of low-frequency fluctuations.

Next, we examined the influence of frequency band on the relationship between baseline Aβ/pTau ratio and change of the putamen in ALFFs (analytical Model (5)) using the entire sample. Compared to the slow-5 band, there was a more pronounced relationship between Aβ/pTau ratio and ALFF change of the R-putamen in the slow-4 band (β5 in Model (5): B = 0.004, SE = 0.002, p = 0.044). This result obtained controlling for age and diagnostic group (see Fig. 3B).

Finally, we did not find the influence of frequency band on the relationship between striatal and cognitive changes (analytical Model (6)).
DISCUSSION

The current study examined the longitudinal changes in the ALFF in the striatum using rs-fMRI, as well as the relationship of these changes with baseline Aβ/pTau ratio and MCI status. We found that (1) compared to the HC group, ALFF values in the R-putamen declined significantly more over 2 years in MCI group; (2) the decline in the R-putamen was significantly related to the memory decline over time and more severe AD pathology (i.e., lower Aβ/pTau ratio) at baseline across groups; and (3) the slow-4 band of the ALFF in the R-putamen was more sensitive to AD-associated pathology than the slow-5 in its significant trajectory of decline and its stronger association with baseline Aβ/pTau ratio.

The current study is among the first to report a prospective relationship between AD-related pathology (i.e., lower Aβ/pTau ratio) and the decline of striatal activation. Previous cross-sectional studies reported disrupted functional connectivity involving the striatum, or structural or functional abnormality of the striatum in individuals with MCI relative to their healthy counterparts [21, 31, 32]. Our results revealed that a significant 2-year decline of ALFF values in MCI was most evident in the putamen. This finding is in line with two previous studies. One reported that atrophy of the putamen, but not caudate, was significantly associated with cognitive decline in patients with probable AD [33]. The other reported abnormally high perfusion in the putamen, but not caudate in MCI relative to HC patients [34]. Although the decline of ALFFs was more significant in the R-putamen, the selective lateral effect must be regarded cautiously due to the small sample size. However, previous studies did report neural disruptions can be more pronounced on the right side in AD-associated neurodegeneration [35, 36]. Further study is needed to clarify laterality issues.

We showed that the decline of putaminal ALFF was also corresponded to the memory decline regardless of the diagnosis. Previous studies reported that the putamen was activated in probabilistic learning tasks [37] and working memory tasks [14]. In a cross-sectional study, reduced putamenal volumes were significantly correlated with impaired cognitive performance [33]. Along with these evidences, our results confirm the role of striatum in retaining cognitive function in both aging and neurodegeneration. Our study was also amongst the first to discover a relationship between baseline AD pathology (i.e., Aβ/pTau ratio in the present study) and the progress of the putaminal dysfunction. Abnormally low Aβ/pTau ratio is constantly observed in AD-associated neurodegeneration [38–41]. Our study suggests that, in spite of a continuous decline of putaminal ALFF in MCI, the predictive role of Aβ/pTau ratio for putaminal change was not different between the HC and MCI groups. A previous study found the relationship between amyloid deposition and aberrant neural activity to be the same in cognitively normal older adults and AD patients [42]. Other studies reported that dopaminergic striatal system is more involved in pTau or Aβ related neurodegenera-
tive processes than other neurotransmission systems [43–45]. Converging these evidences, a continuous decline in putaminal ALFF may reflect an initiation, or even the progression, of the AD-associated neurodegeneration regardless of the clinical status.

Previous studies have reported that abnormality of ALFF depends on the frequency bands in neurologic disorders. For example, there was greater ALFF decrease in the striatum in slow-4 than that in slow-5 in Parkinson’s disease [19]. Along this line, in the current study the longitudinal decline of putaminal ALFF was only found in slow-4, and the association with Aβ/pTau ratio was stronger in slow-4 relative to slow-5. Of note, the frequency-band dependent effect may be regionally relevant. In a previous cross-sectional study, ALFF in slow-5 showed a greater decrease in a wide range of posterior cortical regions than that in slow-4 in MCI [21]. ALFF values in slow-4 band were stronger mainly in subcortical regions, which may indicate the restriction of higher frequency oscillations in small neural networks [46, 47]. Consistently, our results suggest the ALFF in slow-4 band be more sensitive to the striatal dysfunction in the early stage of AD-associated neurodegeneration. These findings urge the future use of different frequency bands to study different brain regions when measure intrinsic brain activity.

Limitations need to be acknowledged. Given the relatively small sample size and short follow-up (relative to the full course of cognitive decline), we did not examine the striatal changes in any non-linear relationship, including the within-subject over time random effect, or in individuals who actually converted to AD. Future work pursuing this issue may provide further evidence for the sensitivity of ALFF in the striatum to AD pathology.

In conclusion, ALFF in the putamen, especially for the slow-4 band, declined early in the AD neurodegenerative process, and such continuous decline appears to be associated with memory decline over time and Aβ/pTau ratio at baseline. Putaminal ALFF may be a sensitive early index for detecting the risk of AD-associated neurodegeneration even before the clinical manifestation.

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