

INTRODUCTION

- Alzheimer's disease (AD) is a process of progressive neurodegeneration induced by cytotoxic elements such as amyloid- β deposition (A β).
- Significant amyloid burden may not eventually lead to disease development and the time window before the onset of the disease is known as the preclinical period.
- Greater pathology may be associated with compensatory increases in neural activation, such as increased spread of activation (i.e., greater neural resources) and greater bilateral activation [2].
- This is known as dedifferentiation, defined as a loss of brain functional specificity, and is a compensatory mechanism for the accumulation of cytotoxic proteins and atrophy [3].
- Dedifferentiation may not be associated with cognitive decline because of its suspected compensatory role [2]
- Greater dedifferentiation may include greater bilateral recruitment of neuronal resources [2] as well as greater spread of local activation (Figure 1) [4].
- We investigated dedifferentiation in the hippocampus and dorsolateral prefrontal cortex (DLPFC) during a memory encoding fMRI task.

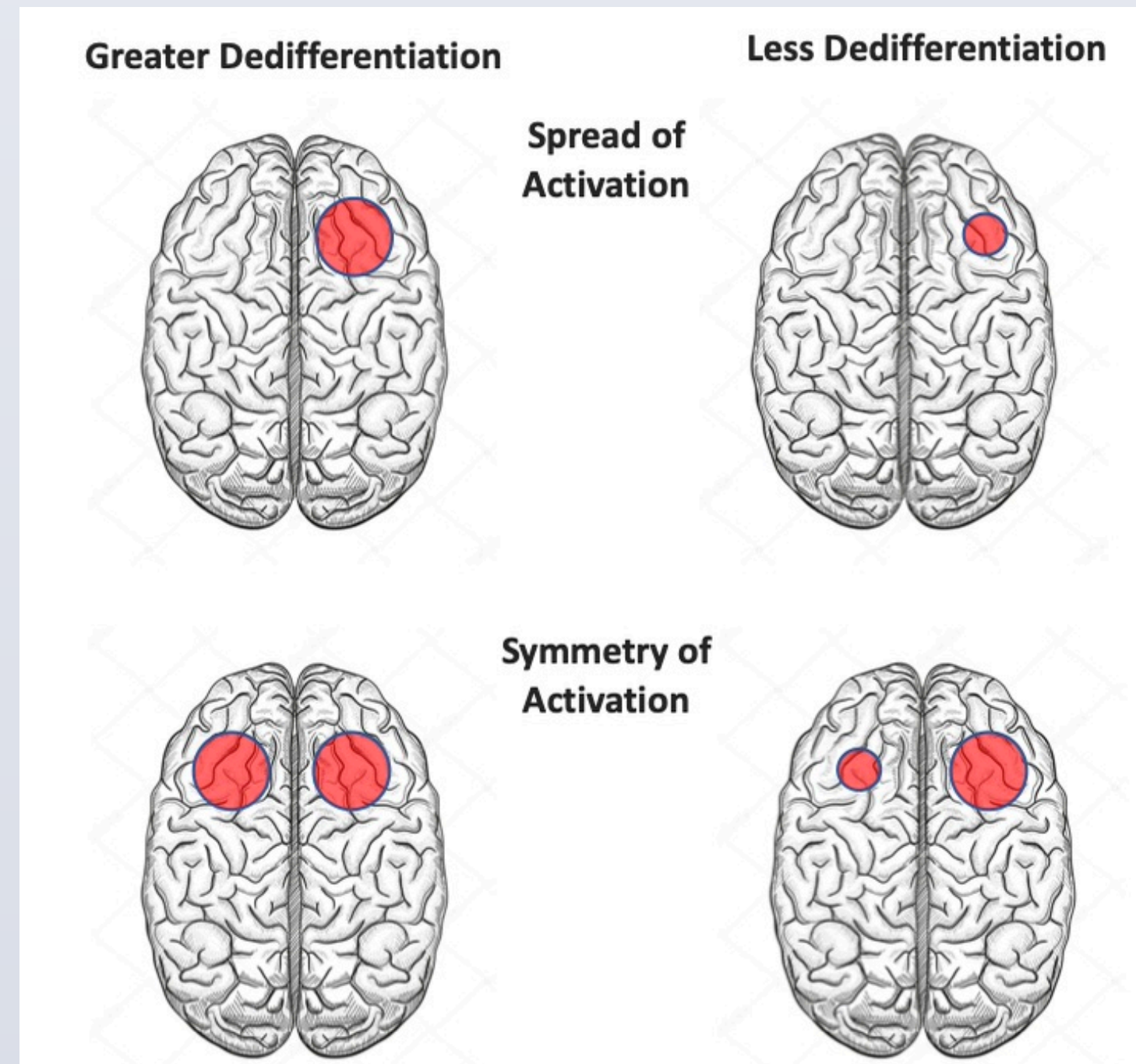


Figure 1. Greater dedifferentiation may be indicated by greater spread and symmetry of activation due to greater recruitment of neurons locally and laterally during a given task.

OBJECTIVE

To investigate the potential of extent of dedifferentiation as a biomarker for Alzheimer's Disease.

- We hypothesize that greater extent of dedifferentiation will be associated with greater AD related factors: APOE E4 status, greater global amyloid deposition, and lower global glucose metabolism.

METHODS

- We conducted a cross-sectional study of 87 cognitively normal older adults (mean age: 75 (6); 33% male; 25% APOE E4).
- APOE E4 allele status was recorded for each participant.
- Cerebral A β and glucose metabolism were measured with Pittsburgh Compound B (PiB) and fluorodeoxyglucose (FDG) tracers, respectively.

METHODS

- Participants were classified as PiB positive or PiB negative based on previous standard approaches [5].
- Each participant's cognitive performance was quantified using composite cognitive scores from neuropsychological assessments within the executive/attention, language, memory learning, memory retrieval, and visuospatial domains.
- Memory domain was split into learning and retrieval to isolate the role of the DLPFC in delayed memory retrieval.
- During an fMRI scan, participants were shown face-name pairs and instructed to make a subjective judgement on whether each name "fit" the face shown above it (Figure 2).
- Face-name encoding task mimics everyday life and elicits reliable activation in our regions of interest [6].

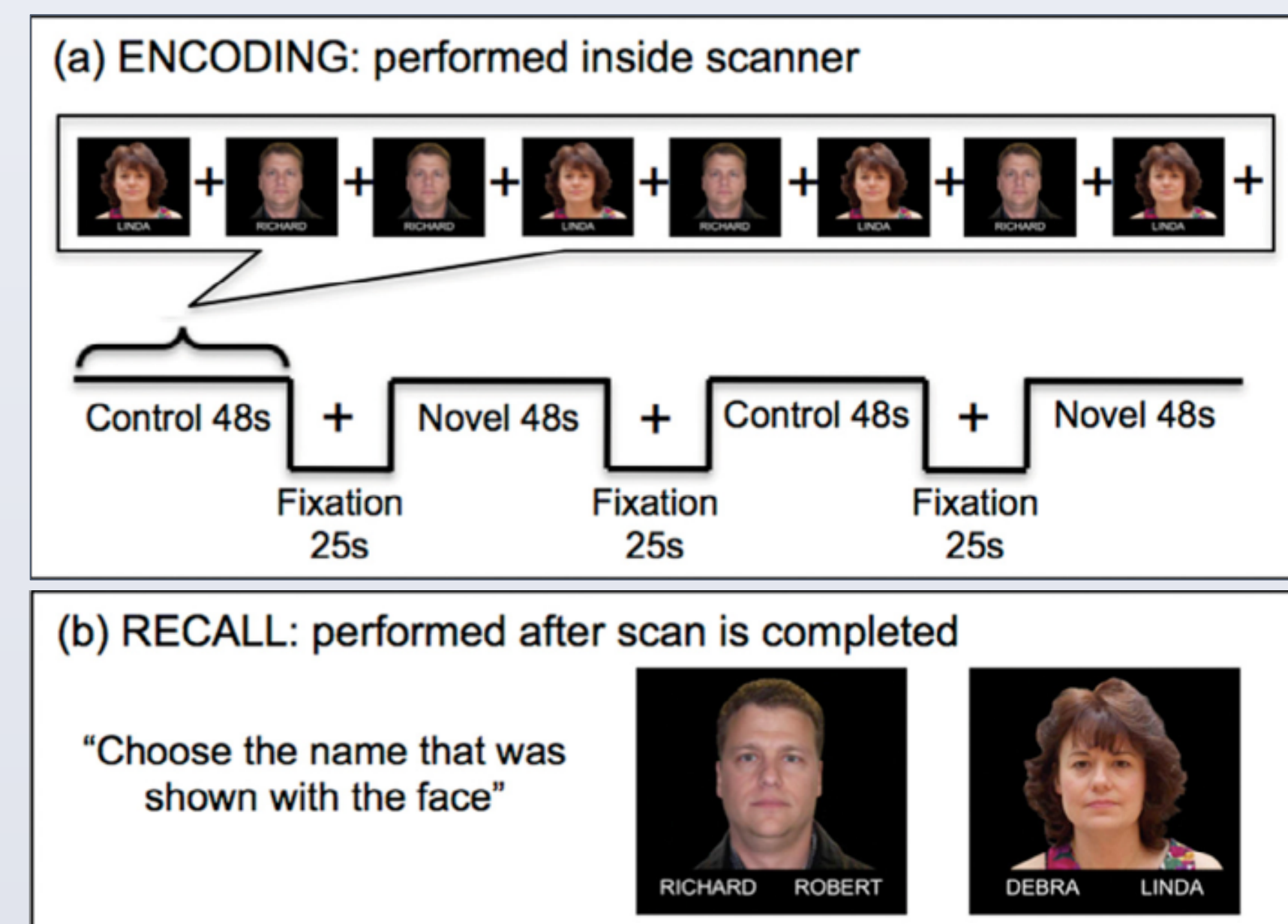


Figure 2. Face-name encoding task conducted by participants during fMRI scanning [7]. Participants were asked to subjectively determine whether each face fit the name below it. Participants encoded control face-name pairs before entering the scanner, novel face-name pairs were encoded in the scanner, and fixation periods (cross-hairs on a dark background) provided resting state activation. Contrast between control and novel activation (each measured with respect to resting state) was used for participant activation values. Recall accuracy after scanning yielded a task accuracy score for each participant.

Activation Asymmetry Index

- Activation values were extracted from an fMRI scan during the face-name encoding task (Figure 3).
- Asymmetry index (AI) is measured as the laterality of the mean activation in each region of interest (Figure 4) [8].
- A smaller absolute AI indicates greater dedifferentiation (i.e., greater bilateral activation).

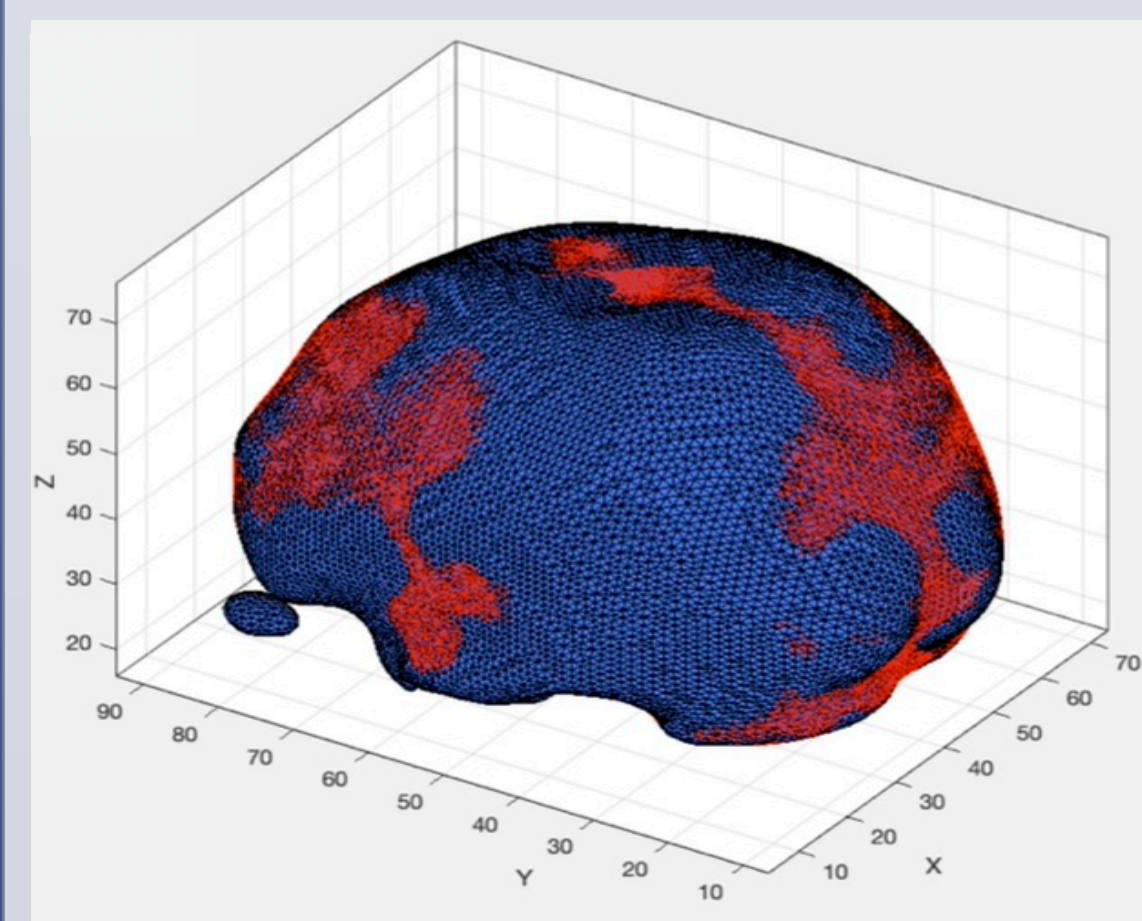


Figure 3. Extracted activation during fMRI scan of face-name encoding task. Blue regions are resting or deactivated, red is activated.

$$AI = \frac{L - R}{abs(L) + abs(R)}$$

Figure 4. AI calculation for each ROI was found with the left and right hemisphere average activation (L and R, respectively) [8]. A negative or positive AI indicates right or left hemispheric dominant activation, respectively. For final regressions, abs(AI) was used in order to measure extent of asymmetry without reference to direction.

Spread of Activation

- To quantify the spread of neural activity, the peak activation voxels were first located at the four ROIs for all participants.
- From the peak of the activation we approximated a gaussian curve emulating the drop of the activity as the region increases (Figure 5).
- Greater FWHM indicates greater spread or dedifferentiation.
- Multivariate linear regressions in R yielded the association between measures of dedifferentiation with AD related factors.

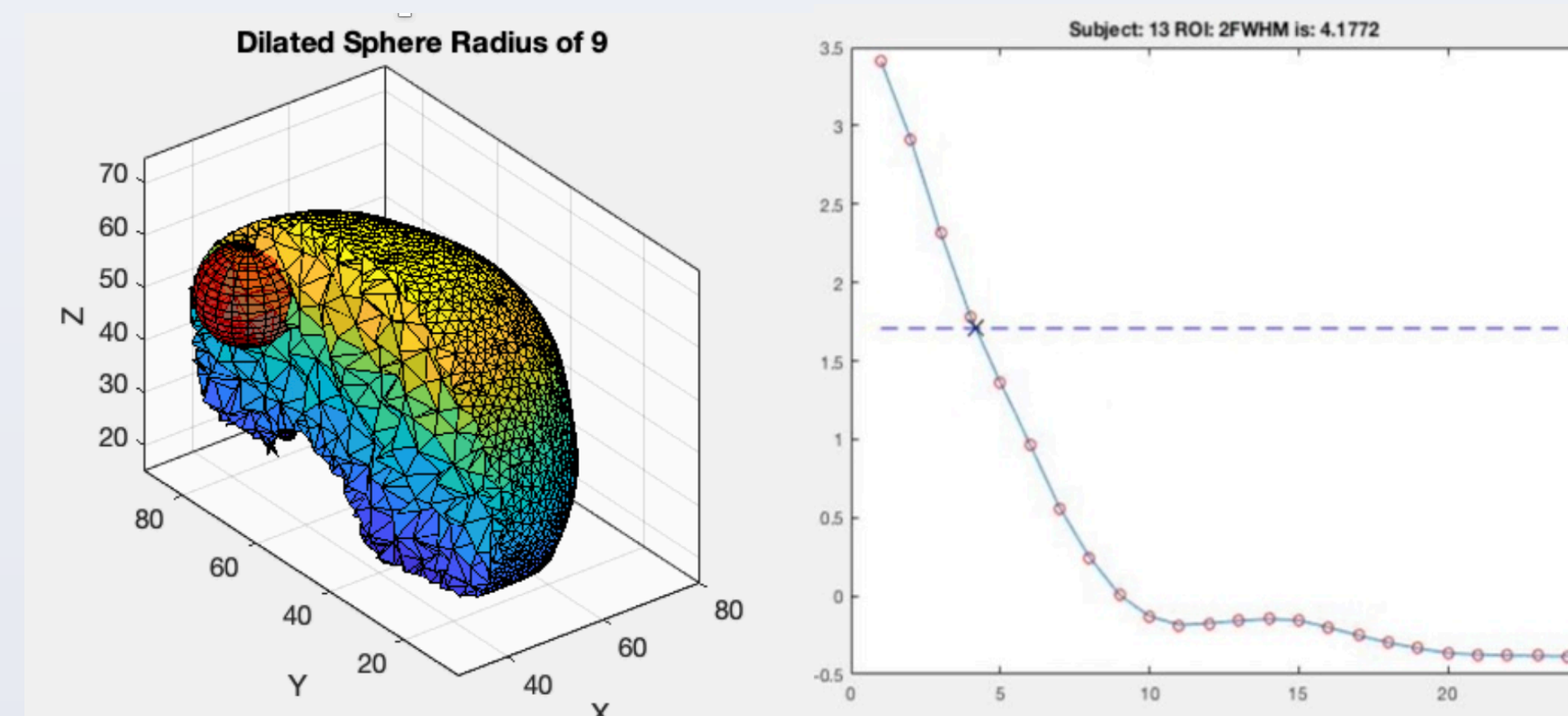


Figure 5. Spheres within each region of interest centered on peak activation were dilated and the spherical radius with an average activation equal to half the peak activation was recorded as the ROI FWHM.

RESULTS

- Hippocampus AI was significantly explained with AD related factors ($F_{(7,53)} = 1.95, R^2 = 0.205, p = 0.08$)
 - PiB positive individuals showed more asymmetric activation ($\beta = 0.33, p = 0.024$, Figure 6a).
- Left hippocampus FWHM was significantly explained with AD related factors ($F_{(7,53)} = 2.07, R^2 = 0.215, p = 0.063$)
 - PiB positive individuals showed lower spread of activation ($\beta = -4.18, p = 0.019$, Figure 6b).
- DLPFC dedifferentiation measures were not associated with any AD related factors.
- Cognitive function was not significantly associated with any measure of dedifferentiation.

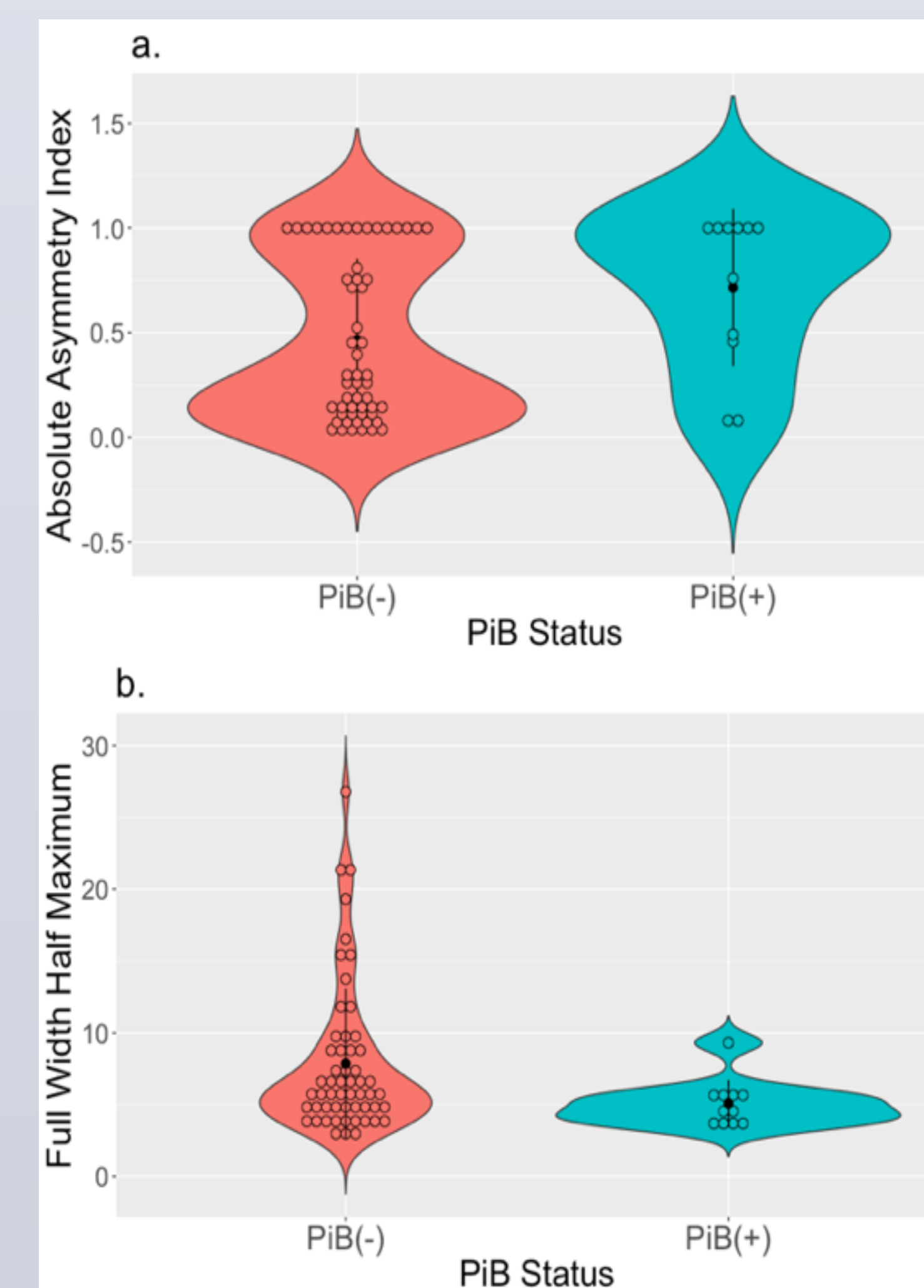


Figure 6. Differences in (a) absolute asymmetry of the hippocampus and (b) FWHM of the left hippocampus between PiB positive and PiB negative groups.

DISCUSSION

- PiB positive individuals were associated with greater asymmetry and lower spread of activation in the hippocampus.
- Past studies have found that face-name encoding tasks generally involve symmetric activation [6], thus greater pathology may be associated with a loss of symmetry in this task.
- Amyloid burden may overwhelm dedifferentiation mechanisms and hinder neuronal activation in the left hippocampus.
- Greater asymmetry in PiB positive participants may be a product of lower overall activation and reduced spread of activation in the left hippocampus (Figure 7).
- We found no association with cognitive function, which was not unexpected since these compensatory mechanisms may help to maintain cognitive function.

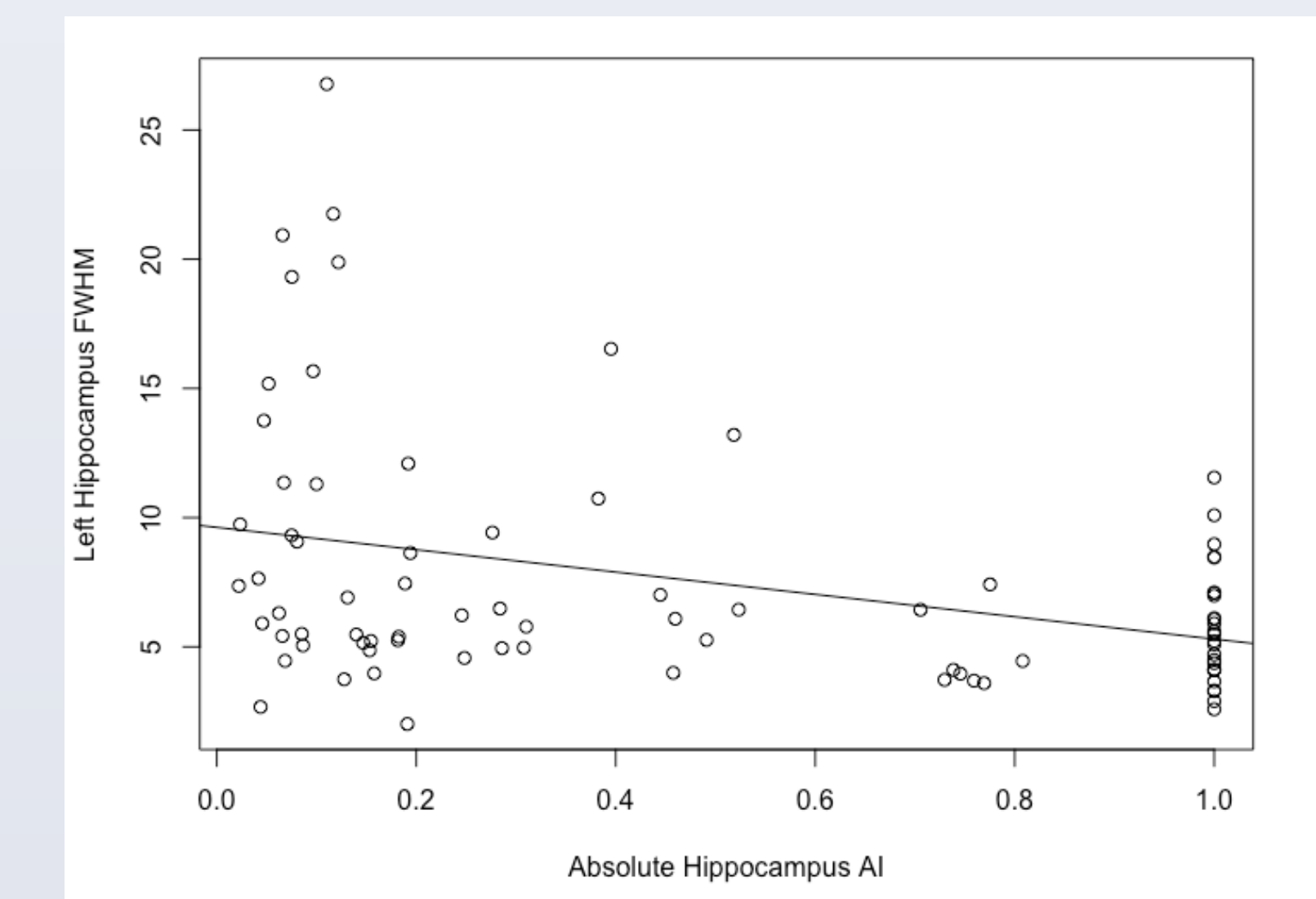


Figure 7. Significant association between greater asymmetry index and less spread of activation in the left hippocampus.

- Longitudinal studies are required to observe changes in activation asymmetry and spread with respect to AD related factors.
- Biomarker thresholds for the progression of AD vary drastically between individuals so rate of change of activation asymmetry and spread as seen longitudinally may be a more useful biomarker for AD.
- Empirical regions of interest could be identified by extracting all voxel clusters with both significant average group-level activation and asymmetry during the face-name encoding task.

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