Association between functional dedifferentiation and amyloid in preclinical Alzheimer's Disease

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SIGNIFICANCE STATEMENT

Preclinical Alzheimer's disease (AD) is a stage of AD defined by the presence of brain amyloid without overt cognitive impairment, occurring up to two decades prior to diagnosis. Amyloid may deposit asymmetrically, which has been shown to affect neural functional asymmetry in AD but not during the preclinical period. We show that altered functional asymmetry in the hippocampus may appear as early as the preclinical stages of AD and is associated with amyloid deposition.

ABSTRACT

Preclinical Alzheimer's disease (AD) is characterized by significant brain amyloid-β (Aβ) pathology without overt cognitive impairment. Aβ has been shown to deposit asymmetrically and has been shown to be associated with asymmetric brain glucose metabolism. In clinical AD, Aβ burden may exceed the compensatory reserve threshold, leading to greater neural functional asymmetry in AD individuals compared to elderly controls, where asymmetry is associated with

cognitive function. To better understand AD progression, we investigated the association between markers of asymmetry, AD pathology, and cognitive function in cognitively normal older adults. Using fMRI during a memory encoding task, we calculated functional asymmetry and spread of activation in the hippocampus and dorsolateral prefrontal cortex, which are part of the core and extended memory network. Using positron emission tomography (PET), we measured brain Aβ and global glucose metabolism. We also collected data on APOE allele status and cognitive function. We conducted multivariate linear regression with measures of dedifferentiation (i.e., asymmetry index and spread of activation) as the outcome and markers of AD as independent variables. We additionally investigated their associations with domains of cognitive function. We found that greater global Aβ deposition was associated with greater hippocampal functional asymmetry and lower left hippocampal activation spread during a memory encoding task. These markers were not correlated with cognitive function. Similar to studies on individuals with AD, we found that functional asymmetry was associated with greater Aβ pathology in individuals without overt cognitive impairment. This may hint at the early neurodegenerative effects of Aβ in preclinical AD.

CATEGORY: Experimental Research

KEYWORDS: preclinical Alzheimer's Disease, dedifferentiation, amyloid, memory encoding

INTRODUCTION

Alzheimer's disease (AD) is a process of progressive neurodegeneration which leads to severe cognitive dysfunction, including impairments in memory loss and executive control. AD has a devastating impact on both those afflicted and those who care for them [1]. AD is associated with a buildup of Amyloid-β (Aß) and neurofibrillary tangles in the brain. These cytotoxic proteins especially affect areas associated with memory, such as the hippocampus and dorsolateral prefrontal cortex (DLPFC) [2]. Greater Aß deposition, as measured by positron emission tomography (PET), is associated with functional changes in the brain including hippocampal

atrophy [3], low cerebral glucose metabolism [4] and functional changes in neural activation as measured by functional magnetic resonance imaging (fMRI) [5].

Aß deposition is gradual with a preclinical stage where significant Aß deposition can be detected but no cognitive dysfunction is observed [1]. Aß deposition is often asymmetric, burdening one hemisphere more than the other [6]. One hypothesis for this lack of cognitive dysfunction with significant Aß pathology during the preclinical stage, is that compensatory neural recruitment can help delay cognitive dysfunction. Greater bilateral recruitment as well as greater spatial extent of activation are thought to be two measures of compensatory activation which are termed dedifferentiation, or the general loss of neural specificity (i.e., regions become more domain general in terms of function). Dedifferentiation may allow the pathology-burdened hemisphere to recruit greater neural resources from the other hemisphere in order to maintain cognitive function [7]. Dedifferentiation in cognitively normal individuals is thus measured through both greater symmetry (bilateral) fMRI activation (i.e., left dominant DLPFC activation spilled over into right DLPFC), as well as greater spread of local activation (i.e., more widespread DLPFC activation within the hemisphere) (Figure 1) [7]. For example, according to the generalized aging phenomenon, Hemispheric Asymmetry Reduction in Old Adults (HAROLD), dedifferentiation in older adults may help maintain cognitive function despite the stresses of aging by recruiting greater neural resources, both bilaterally and locally [7]. These compensatory dedifferentiation mechanisms may still be in intact in preclinical AD and may help maintain cognitive function during early Aß deposition.

(**Figure 1 Here**)

Later stages of AD are characterized by even greater Aß pathology, tau pathology, and cognitive impairment [8]. In later stages of AD, Aß burden may exceed compensatory capacity, which may result in cognitive impairment [4]. In prodromal [i.e., mild cognitive impairment (MCI)] and mild-to-moderate AD, asymmetric Aß deposition is associated with asymmetric cerebral

hypometabolism [6]. Asymmetric (i.e., lateralized to left hemisphere) glucose hypometabolism is associated with Aβ positive (i.e., greater Aß burden than a cut-off) MCI patients [9]. Thus, later stages of AD are associated with functional asymmetry.

In this study, we sought to characterize the relationship between neural activation asymmetry and Aß in preclinical AD. We hypothesized that in cognitively normal individuals, greater AD pathology (e.g., Aß deposition and cerebral hypometabolism) would be associated with greater dedifferentiation, measured with greater symmetry and spread of activation. Due to the suspected compensatory role of dedifferentiation in preclinical AD and the requirement for participants to be cognitively normal at study entry, we did not expect to observe an association between cognitive function and activation symmetry or spread. We investigated dedifferentiation in the hippocampus and DLPFC during a memory encoding fMRI task. The hippocampus is critical for memory and learning and shows neuronal degeneration early in the onset of AD [10], while the DLPFC is part of an extended memory encoding network by coordinating the relational information [11].

METHODS

Participants and Assessments: We analyzed cross-sectional data from 87 cognitively normal older adults (>65 years). All participants underwent a neuropsychological test battery used by the University of Pittsburgh Alzheimer Disease Research Center (ADRC) to assess cognitive function. Test scores were combined into domain composite z-scores including memory (Logical Memory, Modified Rey-Osterreith Figure, ADRC Word List); visuospatial abilities (Block Design, Modified Rey-Osterreith Figure Copy); language (Animal and Letter Fluency, the 60-Item Boston Naming Test); and executive attention (Trail Making Test A and B, Clock Drawing, Maximum Digit Span Forward and Backward, Stroop Interference Score, and Digit Symbol Substitution) [12] (Table 1). The memory domain was split into learning and retrieval to isolate the role of the DLPFC in delayed memory retrieval. In addition to demographic data (age, sex, race/ethnicity, etc.), we also collected genetic APOE status.

Neuroimaging Data Acquisition and Preprocessing: PET scans were used to measure participant cerebral Aβ deposition with Pittsburgh Compound B (PiB) and glucose metabolism with fluorodeoxyglucose (FDG) tracers. Participants were classified as PiB positive or negative based on previous standard approaches using a set of previously identified regions [13]. MRI scanning was conducted on a 3T Siemens Trio scanner at the University of Pittsburgh Magnetic Resonance Research Center. We collected whole-brain (excluding cerebellum) fMRI during a face-name memory encoding task, which is heavily utilized in cognitive aging and AD research [14] as it reliably activates the hippocampus and prefrontal regions [15]. During the task, participants were shown a face-name pair and were asked to subjectively determine whether each face fit the name. This task consisted of two blocks: unfamiliar face-name pairs (novel condition) and familiar (i.e., previously seen) face-name pairs (control condition). After functional preprocessing and normalization to a standard space, we modeled neural activity associated with each condition using a generalized linear model. This task was administrated over three runs and contained 50 face-name pairs. We computed the contrast between novel and control. For our analysis, we extracted functional activation in the hippocampus and DLPFC regions of the brain based on the automated anatomical labeling atlas. After performing the task in the scanner, participants took a post-scan test in which they saw the same faces with two name options. They were asked to select the name they saw in the scanner as an estimate of recognition accuracy.

Computation of Dedifferentiation Measures: We computed the asymmetry index (AI) as the hemispheric laterality of the mean activation in each region. We calculated the asymmetry index using the equation: $AI = \frac{L-R}{abs(L)+abs(R)}$, where L (left) and R (right) are the mean activation values of a given region of interest in the left and right hemisphere, respectively [16]. The equation yields a value between -1 and 1, where 0 represents symmetric activation between the hemispheres, and a negative or positive AI indicates right or left hemispheric dominant activation, respectively. In addition, absolute AI (abs_AI) was used to quantify dedifferentiation with a measure of non-

directional laterality. Smaller abs_AI indicates greater dedifferentiation (i.e., greater symmetric activation). We also measured dedifferentiation with the spread of activation within each region [17]. For all participants, we identified the peak activation voxels in each, then generated a series of spheres with radii ranging from 1 voxel to 25 voxels centered around peak activation, where we calculated the average activation within each sphere. We plotted the mean activation with respect to different radii with radii being on the horizontal axis and mean activation on the vertical axis. We used a linear interpolation method to estimate the neural activity decline and took the radius where the activation value was half of the observed peak activation as the spread of the activation (e.g., full width half maximum). Greater full width half maximum (FWHM) indicates greater spread (or dedifferentiation).

Statistical Analyses: We conducted eight multivariate linear regressions in R to investigate the association between measures of dedifferentiation (as outcome variables: AI and abs_AI for two regions, and spread for each hemisphere and each region) and AD related factors (PiB status, global cerebral glucose metabolism, and APOE E4 status). To test the relationship between the two dedifferentiation measures, we conducted four linear regressions to investigate the association between spread of activation (each hemisphere of two regions) and asymmetry of corresponding region. We also conducted 10 multivariate linear regressions to investigate the association between cognitive domains (five domains) and both measures of dedifferentiation (asymmetry and spread measures separately). Other AD related factors were included as predictor variables. All models controlled for demographic factors (age, education, sex, and race), and post-scan recognition accuracy was included as a covariate to predict cognitive function.

RESULTS

Among our eight multivariate linear regressions, two models showed marginal significance: absolute hippocampus AI ($F_{(7,53)} = 1.95$, $R^2 = 0.205$, $p = 0.08$) and spread of activation in the left hippocampus ($F_{(7,53)} = 2.07$, $R^2 = 0.215$, $p = 0.063$). PiB positive individuals (11/66) showed

greater asymmetric activation in the hippocampus (ß = 0.33, p = 0.024, Figure 2a). PiB positive individuals showed lower spread of activation in the left hippocampus (ß = -4.18, p = 0.019, Figure 2b). DLPFC dedifferentiation measures were not associated with any AD related factors. (**Figure 2 Here**). Individuals with lower activation spread in the left hippocampus had greater asymmetry of hippocampal activation ($F_{(1,82)}$ = 12.14, R^2 = 0.129, p = 0.001; ß = -4.33, p = 0.001). Out of the five cognitive domains, lower executive attention domain score was significantly associated with PiB positive status in the models which included abs_AI ($F_{(10, 50)}$ = 2.68, R^2 = 0.349, p = 0.01; ß = -0.53, p = 0.016) and spread ($F_{(12, 48)}$ = 3.39, R^2 = 0.459, p = 0.001; ß = -0.61, p = 0.004) as predictors, but none of the cognitive domain scores were associated with markers of dedifferentiation.

DISCUSSION

Contrary to our hypothesis, we found that PiB positive individuals had greater hippocampal asymmetry and lower spread of activation in the left hippocampus. There were no associations with DLPFC asymmetry or spread of activation. Greater asymmetry in preclinical AD may be a mechanism of either greater recruitment of activation in the right hippocampus or reduced activation of the left hippocampus. We found that lower left hippocampal spread of activation was associated with greater hippocampal activation asymmetry. One interpretation is that Aß deposition may be overwhelming compensatory mechanisms in the left hippocampus and hindering neuronal recruitment, hence greater asymmetry among cognitively normal older adults. PiB positive individuals who are cognitively normal may also have greater cognitive reserve, which enables them to compensate for greater pathology to maintain cognitive function. Therefore, the association between PiB positive individuals and greater asymmetry and less spread may be indicative of the individual differences of greater cognitive reserve, which may help to maintain normal cognitive function despite pathology.

In the clinical stages of AD, functional changes such as asymmetric cerebral hypometabolism are associated with asymmetric Aß deposition [6]. Further, Aβ positive status in AD is associated with leftward lateralization of glucose metabolism decline [9]. Our results indicate that early pathological Aß in the brain is associated with greater asymmetry in preclinical stages of AD, which is in agreement with previous studies that have associated asymmetry with AD, but hints toward an earlier neurodegenerative effect of Aß deposition. We found no associations between dedifferentiation measurements and cognitive function, as these compensatory mechanisms may help to maintain cognitive function. On the other hand, greater Aβ was associated with lower executive attention. These may suggest that Aß is a predictor of the higher order cognitive function regardless of dedifferentiation patterns among cognitively normal individuals or that a functional MRI task that engages executive function may be a better potential functional marker (i.e., face-name task is primarily memory encoding).

There are several limitations to this study – primarily, the associations between dedifferentiation measures and Aß should be validated in other samples and in studies that utilize longitudinal designs to observe changes in activation spread and symmetry in relation to changes in Aß deposition. These results show correlations and do not imply causation of Aß on functional brain activity. There were a limited number of PiB positive individuals (11 out of 66) and future studies should enrich for PiB positive individuals to better understand these associations. This study did utilize a fairly large cross-sectional sample with both functional imaging and intricate PET imaging, which is a strength.

CONCLUSION

We used two measurements (e.g., functional asymmetry and spread of activation) to quantify the extent of neuronal dedifferentiation as a tool to assess the association with Alzheimer's disease pathology in preclinical AD. We identified significant differences in markers of neural activity associated with the presence of AD risk factors in the hippocampus. We did not find associations

between DLPFC with any AD risk factors. We speculate that AD risk factors such as significant Aß deposition may limit the spread of activation in the left hippocampus which affects functional asymmetry.

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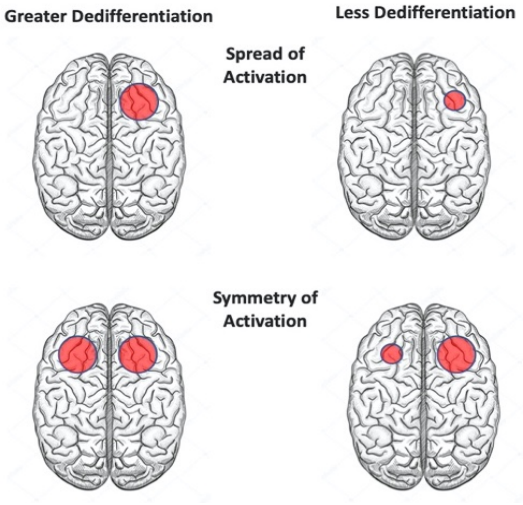

Figure 1. A schematic representation of two forms of dedifferentiation. Greater dedifferentiation may be indicated by greater spread (upper image) and greater symmetry (lower image) of activation due to greater recruitment of neural resource locally and laterally during a given task.

Table 1.

Demographics and Summary of Cognitive Domain Scores

Variable	PiB Positive (N = 11)	PiB Negative (N = 55)	95% CI for Mean Difference	Test Statistic (df)	p Value
	Mean (SD) N (%)				
Age (years)	79 (5)	74 (6)	(0.49, 8.84)	t(63) = 2.25	**0.03***
Sex	4 (36%)	17 (31%)	N/A	x (1) = 0	1.00
Race (White)	9 (82%)	46 (84%)	N/A	x (2) = 5.14	0.08
Education (years)	14 (2.5)	15(2.3)	(-2.71, 0.42)	t(63) = -1.47	0.15
Global PiB (SUVR)	2.53 (0.65)	1.34 (0.11)	(1.02, 1.38)	N/A	N/A
APOE Allele (+)	4 (36%)	11 (20%)	N/A	x(1) = 0.42	0.52
FDG	1.61 (0.11)	1.63 (0.13)	(-0.11, 0.06)	t(63) = -0.51	0.61
Memory Learning	-0.15 (0.84)	0.07 (0.64)	(-0.68, 0.22)	t(63) = -1.02	0.31
Memory Retrieval	-0.30 (0.96)	0.08 (0.63)	(-0.83, 0.09)	t(63) = -1.62	0.11
Visuospatial	-0.01 (0.94)	0.01 (0.67)	(-0.49, 0.46)	t(63) = -0.06	0.95
Language	-0.10 (0.90)	0.07 (0.76)	(-0.69, 0.34)	t(63) = -0.67	0.50
Executive Attention	-0.32 (0.53)	0.09 (0.60)	(-0.81, -0.02)	t(63) = -2.12	**0.03***
Task accuracy	0.64 (0.1)	0.69 (0.12)	(-0.12, 0.03)	t(63) = -1.26	0.21

Note: *$p < 0.05$. We did not conduct a statistical test on Global PiB (SUVR) since this is how these groups were defined.

Figure 2. PiB positive group showed significantly greater asymmetric hippocampal activation (a) and less spread of activation in the left hippocampus (indexed by FWHM) (b) during a memory encoding task compared to the PiB negative group.