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Both hyper- and hypo-activation to cognitive challenge are associated with increased beta-amyloid deposition in healthy aging: A nonlinear effect

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ABSTRACT

Beta-amyloid (Aβ) positive individuals hyper-activate brain regions compared to those not at-risk; however, hyperactivation is then thought to diminish as Alzheimer's disease symptomatology begins, evidencing eventual hypoactivation. It remains unclear when in the disease staging this transition occurs. We hypothesized that differential levels of amyloid burden would be associated with both increased and decreased activation (i.e., a quadratic trajectory) in cognitively-normal adults. Participants ($N = 62$; aged 51–94) underwent an fMRI spatial distance-judgment task and Amyvid-PET scanning. Voxelwise regression modeled age, linear-Aβ, and quadratic-Aβ as predictors of BOLD activation to difficult spatial distance-judgments. A significant quadratic-Aβ effect on BOLD response explained differential activation in bilateral angular/temporal and medial prefrontal cortices, such that individuals with slightly elevated Aβ burden exhibited hyperactivation whereas even higher Aβ burden was then associated with hypoactivation. Importantly, in high-Aβ individuals, Aβ load moderated the effect of BOLD activation on behavioral task performance, where in lower-elevation, greater deactivation was associated with better accuracy, but in higher-elevation, greater deactivation was associated with poorer accuracy during the task. This study reveals a dose-response, quadratic relationship between increasing Aβ burden and alterations in BOLD activation to cognitive challenge in cognitively-normal individuals that suggests 1) the shift from hyper-to hypo-activation may begin early in disease staging, 2) depends, in part, on degree of Aβ burden, and 3) tracks cognitive performance.

Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disorder for which a precise diagnosis in living persons remains elusive. Despite this limitation, there has been general agreement on several biomarkers, as well as the staging of these biomarkers, such that individuals at-risk for transitioning to AD can be identified in pre-clinical, asymptomatic states (Albert et al., 2011; Dubois et al., 2016; Jack et al., 2010, 2013; Sperling et al., 2011). Increased beta-amyloid (Aβ) deposition is thought to be the earliest biomarker for AD, followed by tau deposition and brain atrophy (Jack et al., 2010, 2013), with Aβ deposition occurring 15–30 years before the onset of AD symptoms (Dubois et al., 2016; Jansen et al., 2015; Rowe et al., 2010). Importantly, while Aβ is a necessary component of AD pathology, individuals have been identified with clinically significant Aβ burden who exhibit no AD behavioral symptomatology (Delaère et al., 1993). However, evidence suggests that within cognitively normal aging, elevated Aβ burden may alter patterns of functional brain activation.

In clinically-normal older adults performing cognitive (typically episodic memory) tasks during scanning, those with measurable Aβ burden tend to show increased brain activation (i.e., hyperactivation) in select brain regions such as the hippocampus, parietal cortex, precuneus, posterior cingulate, and temporal cortex, compared to older adults without Aβ burden (e.g., Elman et al., 2014; Huijbers et al., 2014; Leal et al., 2017; Mormino et al., 2012; Oh et al., 2015; Oh et al., 2016; Sperling et al., 2009). Similarly, older adults diagnosed with mild cognitive impairment (MCI) also exhibit functional hyperactivation (for review see Sperling et al., 2011), although this phenomenon is likely limited to individuals at the earliest identifiable stage of MCI (e.g., Celone et al., 2006; Dickerson et al., 2005; Foster et al., 2016). Furthermore, longitudinal research following early MCI individuals with hyperactivation at baseline suggests that these individuals may experience more rapid cognitive decline than their non-hyperactivating MCI peers (e.g., Dickerson et al., 2004; Miller et al., 2008; O'Brien et al., 2010; Sperling et al., 2010). Thus, it appears that hyperactivation may be a specific marker for individuals in the earlier phases of AD development (i.e., early MCI) and a predictor of poorer cognitive outcomes. While the

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mechanism driving Aβ-related hyperactivation is still unclear, hyperactivation occurs in regions that activate or deactivate in response to cognitive tasks (e.g., Huijbers et al., 2014; Oh et al., 2015, 2016; Sperling et al., 2009). These results suggest that a similar mechanism, likely reduced inhibition (Sperling et al., 2014), underlies hyperactivation regardless of the region or direction of activation.

Interestingly, hyperactivation appears to eventually transition to decreased activation (i.e., hypoactivation) in those individuals farther along the AD spectrum, such as in late MCI or probable AD (e.g., Bosch et al., 2010; Celone et al., 2006; Dickerson et al., 2005; Sperling, 2011; Sperling et al., 2010), suggesting a quadratic trajectory of functional brain activation changes across the AD continuum: preclinical AD to MCI/prodromal AD (hyperactivation) and prodromal AD/MCI to probable AD (hypoactivation). While the transition to hypo-from hyperactivation has previously been thought to occur after the onset of AD symptomatology (e.g., Celone et al., 2006; Dickerson et al., 2005), there is also evidence that hypoactivation may occur in older, cognitively-normal individuals with significant Aβ burden (Kennedy et al., 2012), suggesting that the effect of Aβ on brain activation is complex, likely quadratic, and that the transition between these states may occur earlier than previously thought.

To assess whether Aβ is associated with a quadratic change in activation within a sample of cognitively healthy middle-aged and older adults, we utilized a spatial distance-judgment task with three levels of difficulty (Rieck et al., 2017). This task affords the ability to investigate the dynamic range over which the brain responds (or modulates) to task difficulty; however, in the current study we compare the hardest level of the task to the control condition, optimizing the potential to find Aβ-related changes in functional brain activation in healthy aging. We hypothesized that differential levels of Aβ burden would be associated with both increases and decreases (i.e., nonlinearity) in activation to a cognitively challenging spatial distance-judgment task. Further, we hypothesized that Aβ burden-related activation would be associated with task performance.

Methods

Participants

Participants included 62 healthy adults (mean age = 67.73 ± 10.21; age range 51–94 years) who were drawn from a larger study of 181, of whom 73 had both fMRI and amyloid-PET data. Eighteen participants were deemed to have elevated Aβ burden using a standardized uptake value ratio (SUVR) cutoff of 1.11 (Clark et al., 2011; see Table 1). A sample of 42 younger adults (mean age = 27.45 ± 4.40; age range 20–35) were also included to provide visual estimates of task-related activity as a reference, however these individuals were not included in the Aβ analysis and did not undergo amyloid-PET data collection. All participants were recruited from the Dallas-Fort Worth metroplex and screened to ensure they were right-handed, fluent English speakers, with normal or corrected-to-normal vision. When required, MRI-compatible glasses were used during scanning. Participants were also screened against a history of metabolic, neurological or psychiatric conditions, head trauma, drug or alcohol problems, significant cardiovascular disease, depression (Center for Epidemiological Study - Depression < 16; Radloff, 1977), and to be cognitively intact (Mini Mental State Exam ≥ 26; Folstein et al., 1975). Twenty-two participants in the current sample self-reported a diagnosis of hypertension. PET scanning took place on average within a year of MRI acquisition (M = 12.16, SD = 5.24 months).

Eleven of the initial 73 participants were excluded from analysis due to MRI acquisition issues: excessive in-scanner motion (n = 4); poor functional image acquisition (n = 2); no response on greater than 15% of trials (n = 1); or < 70% accuracy on the control condition (n = 4). The 11 excluded participants did not differ significantly from the included participants, respectively, in age ($t(71) = -1.20$, $p = 0.24$; 71.91 ± 13.74 SD vs 67.73 ± 10.21), education ($t(71) = 0.58$, $p = 0.56$; 15.09 ± 3.27 vs 15.60 ± 2.54), MMSE ($t(71) = 1.66$, $p = 0.10$; 28.45 ± 0.69 vs 28.87 ± 0.78), or CESD ($t(71) = 0.03$, $p = 0.98$; 3.73 ± 3.32 vs 3.76 ± 3.77). One excluded participant was amyloid positive.

Table 1
Participant demographics and task performance.

	Low SUVR	High SUVR	Total
N (% Female)	44 (66)	18 (39)	62 (58.07)
Mean Age (SD)	65.36 (10.21)*	73.50 (7.14)	67.73 (10.21)
Mean Education (SD)	15.30 (2.53)	16.33 (2.50)	15.60 (2.54)
Mean MMSE (SD)	28.86 (0.82)	28.89 (0.68)	28.87 (0.78)
Mean CESD (SD)	3.68 (3.79)	3.94 (3.83)	3.76 (3.77)
fMRI Task Accuracy			
Control (SD)	97.47 (5.71)	95.53 (7.73)	96.91 (6.36)
Easy (SD)	95.24 (7.72)	93.57 (9.49)	94.76 (8.23)
Medium (SD)	87.25 (15.02)	86.22 (15.95)	86.95 (15.17)
Hard (SD)	71.69 (20.85)	76.18 (17.46)	72.99 (19.89)
fMRI Task RT (sec)			
Control (SD)	0.71 (0.18)	0.67 (0.10)	0.70 (0.16)
Easy (SD)	0.86 (0.16)	0.82 (0.12)	0.85 (0.15)
Medium (SD)	0.93 (0.18)	0.87 (0.12)	0.92 (0.16)
Hard (SD)	1.07 (0.24)	0.97 (0.17)	1.04 (0.22)

Note: Low SUVR – less than 1.11 standardized uptake value ratio; High SUVR – greater than or equal to 1.11 standardized uptake value ratio; There were no significant group differences on any measure (p's > 0.146) other than age ($t(60) = -3.080$, $p = 0.003$). MMSE - Mini Mental State Exam; CESD – Center for Epidemiologic Study-Depression; Accuracy reported as mean percent accuracy; Response time (RT) reported as a mean of medians in seconds; SD – standard deviation; *$p < 0.05$.

Imaging protocol

PET acquisition

On a separate session, participants were scanned on a single Siemens ECAT HR PET scanner at UT Southwestern Medical School. All participants were injected with 370 MBq (10 mCi) of ^{18}F-Florbetapir (Avid Radiopharmaceuticals/Eli Lilly). Approximately 30 min post-injection, participants were placed on the imaging table and foam wedges were used to secure the participant's head. A 2-min scout was acquired to ensure the brain was within the field of view. Fifty minutes post-injection, an internal rod source transmission scan was acquired for 7 min immediately followed by a 2-frame by 5 min each dynamic emission acquisition. The transmission image was reconstructed using back-projection with a 6-mm full-width at half-maximum (FWHM) Gaussian filter. Emission images were processed by iterative reconstruction, 4 iterations and 14 subsets with a 3-mm FWHM ramp filter.

PET data processing

Each participant's PET scan was first registered to their T1-weighted image with a rigid affine registration using Advanced Normalization Tools (ANTs) (Avants et al., 2009) scripts and visually inspected for registration quality. Freesurfer (Fischl, 2012) parcellations of interest that correspond to the traditionally used 7 ROIs for amyloid deposition (i.e., anterior cingulate, posterior cingulate, precuneus, lateral temporal, lateral parietal, middle frontal, and inferior frontal) were also registered to each subject's T1 image. Using methods outlined in Rodrigue et al. (2012), uptake counts were extracted from each ROI and normalized to whole cerebellar counts to yield standardized uptake value ratios (SUVRs) for each ROI. All ROIs were averaged to form mean cortical amyloid index.

MRI acquisition

Participants were scanned on a single Philips Achieva 3T whole-body scanner equipped with a 32-channel head coil. High-resolution anatomical images were collected with a T1-weighted MP-RAGE sequence with the following parameters: 160 sagittal slices, 1 × 1 × 1 mm^3 voxels; FOV = 256 mm × 204 mm x 160 mm, FOV = 256 mm, TE = 3.8 ms, TR = 8.3 ms, FA = 12°. Blood Oxygenation Level Dependent (BOLD) fMRI data were acquired using a T2*-weighted echo planar imaging sequence in 29 interleaved axial slices parallel to