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β-Amyloid Deposition Is Associated with Decreased Right Prefrontal Activation during Task Switching among Cognitively Normal Elderly

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The accumulation of β-amyloid (Aβ) peptides, a pathological hallmark of Alzheimer's disease (AD), has been associated with functional alterations, often in an episodic memory system with a particular emphasis on medial temporal lobe function. The topography of Aβ deposition, however, largely overlaps with frontoparietal control (FPC) regions implicated in cognitive control that has been shown to be impaired in early mild AD. To understand the neural mechanism underlying early changes in cognitive control with AD, we examined the impact of Aβ deposition on task-evoked FPC activation using functional magnetic resonance imaging (fMRI) in humans. Forty-three young and 62 cognitively normal older adults underwent an fMRI session during an executive contextual task in which task difficulty varied: single (either letter case or vowel/consonant judgment task) vs dual (switching between letter case and vowel/consonant decisions) task. Older subjects additionally completed ^{18}F-florbetaben positron emission tomography scans and were classified as either amyloid positive (Aβ+) or negative (Aβ−). Consistent with previous reports, age-related increases in brain activity were found in FPC regions commonly identified across groups. For both task conditions, Aβ-related increases in brain activity were found compared with baseline activity. For higher cognitive control load, however, Aβ+ elderly showed reduced task-switching activation in the right inferior frontal cortex. Our findings suggest that with Aβ deposition, brain activation in the cognitive control region reaches a maximum with lower control demand and decreases with higher control demand, which may underlie early impairment in cognitive control with AD progression.

Key words: amyloid PET; β-amyloid; cognitive control; cognitively normal older adults; fMRI; frontoparietal cortex

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Significance Statement

The accumulation of β-amyloid (Aβ) peptides, a pathological hallmark of Alzheimer's disease, spatially overlaps with frontoparietal control (FPC) regions implicated in cognitive control, but the impact of Aβ deposition on FPC regions is largely unknown. Using functional magnetic resonance imaging with a task-switching task, we found Aβ-related increases in FPC regions compared with baseline activity. For higher cognitive control load, however, Aβ-related hypoactivity was found in the right inferior frontal cortex, a region highly implicated in cognitive control. The findings suggest that with Aβ deposition, task-related brain activity may reach a plateau early and undergo downstream pathways of neural dysfunction, which may relate to the early impairment of cognitive control seen in the progression of Aβ pathology.

Introduction

Neuritic plaques of fibrillar β-amyloid (Aβ) peptides are hallmark characteristics of Alzheimer's disease (AD) pathology (Braak and Braak, 1991; Hardy and Selkoe, 2002). Studies using positron emission tomography (PET) with radioligands binding to fibrillar Aβ plaques have found that ~20–30% of cognitively normal older adults harbor Aβ deposition, consistent with autopsy findings (Bennett et al., 2006; Mintun et al., 2006). Even in cognitively normal elderly, the presence of elevated levels of Aβ deposition has been associated with abnormal changes in multiple biomarkers, including brain gray matter atrophy, aberrant glucose metabolism, and reduced resting-state functional connectivity (Hedden et al., 2009; Becker et al., 2011; Mormino et al.,

2011; Johnson et al., 2014; Lowe et al., 2014; Oh et al., 2014). Task-related functional magnetic resonance imaging (fMRI) studies have commonly found Aβ-related increases in brain activity during episodic memory (EM) performance (Sperling et al., 2009; Mormino et al., 2012; Oh and Jagust, 2013; Huijbers et al., 2014). In addition, this Aβ-related increase in activity was shown to track memory strength in older adults with Aβ deposition (Elman et al., 2014). Together these results suggest that Aβ-related changes in brain structure and function occur among cognitively normal elderly, which may herald behavioral trajectories of older adults in preclinical AD.

Aβ-related functional changes have often been examined in a context of EM, with a particular focus on the medial temporal lobe (MTL) function. Topography of Aβ deposition, however, is quite widespread across the brain. Therefore, it is highly likely that Aβ deposition also affects other functional networks. A few recent studies have examined the impact of Aβ deposition on neural systems beyond the EM network among cognitively normal elderly and early-stage probable AD subjects. Compared with normal controls, early-stage probable AD patients showed altered brain activation within the language system that was closely correlated with independently measured naming performance (Nelissen et al., 2007). In cognitively normal elderly, higher Aβ deposition was related to hyperactivity in posterior left middle temporal gyrus, a region involved in associative-semantic language processing (Adamczuk et al., 2016). Previously, we examined the relationship between Aβ deposition and working memory load-related brain activation in cognitively normal elderly and found Aβ-related increases in frontoparietal cortices with higher verbal working memory load (Oh et al., 2015). Therefore, emerging evidence seems to suggest that Aβ-related functional alterations are not specific to the EM network but occur in other functional networks as well.

The topography of Aβ deposition highly overlaps with regions known as frontoparietal control (FPC) regions that have been implicated in cognitive control, an ability to flexibly interact with the environment in accordance with an internal goal (Miller and Cohen, 2001; Braver et al., 2003; Brass and von Cramon, 2004; Badre and D'Esposito, 2007; Power et al., 2011; Cole et al., 2013; Waskom et al., 2014). Although Aβ-related and AD-related changes in cognition have often focused on EM, it is well documented that impairment of cognitive control is one of the early cognitive deficits observed in mild AD patients. Accumulating evidence further suggests that cognitive control impairment can be an early behavioral marker discriminating healthy aging from very mild AD dementia and predicting later conversion (Balota et al., 2010; Aschenbrenner et al., 2015). The neural mechanisms underlying cognitive control deficits in the early stage of AD, however, remain largely unknown. One hypothesized mechanism is that Aβ-related hyperactivation would reach a breakdown and fail to accommodate further cognitive processing demand, as postulated as neural reserve (Stern, 2009) and proposed by others (Jagust and Mormino, 2011). In the present study, we tested this hypothesis using an executive contextual task in which a level of cognitive control load varied. Specifically, we hypothesized that older adults with Aβ deposition (Aβ+), compared with older subjects without Aβ deposition (Aβ−), would show greater frontoparietal activation with lower control load, but decreased activity with higher control load. We further expected to observe age-related increases in frontoparietal activation as previously reported.

Materials and Methods

Participants. Forty-three healthy young adults (age range, 20–30 years; 29 females) and 62 cognitively normal older adults (age range, 60–70 years; 33 females) participated in the study. Subjects were recruited using a market mailing procedure. To ensure that subjects did not have dementia or mild cognitive impairment (MCI), a score of ≥136 was required on the Mattis Dementia Rating Scale (DRS; Mattis, 1988). All subjects had no history of neurological and psychiatric illnesses and no major medical illness or medication that influenced cognition. Older subjects were classified as either amyloid positive (Aβ+O) or amyloid negative (Aβ−O) based on the criteria described below. All subjects provided informed consent in accordance with the Institutional Review Boards of the College of Physicians and Surgeons of Columbia University. Participants were paid for their participation in the study.

Neuropsychological tests. A comprehensive battery of neuropsychological (NP) tests were administered to all participants. Using a subset of NP tests, cognitive composite scores for processing speed/attention and EM were generated: for processing speed/attention (NP-process), the Wechsler Adult Intelligence Scale—Third Edition Digit Symbol subtest (Wechsler, 1997), the Trail Making Test Part A (Reitan, 1978; inversed value), and the Stroop Color Naming Test—Color Naming in 90 s (Golden, 1978) were included; for EM (NP-memory), scores from the Selective Reminding Test (SRT; Buschke and Fuld, 1974)—Long-Term Storage, SRT—Continued Recall, and SRT—Recall at the Last Trial were combined. The American National Adult Reading Test (AMNART; Grober and Sliwinski, 1991) was used as an estimate of IQ.

Experimental design. The executive contextual task used for fMRI was adapted from Koechlin et al. (2003). A schematic diagram of the task design is provided in Figure 1A. Subjects were presented a series of task blocks that comprised two single-task conditions and two identical dual-task conditions, each implemented in blocks. Each block lasted 33.5 s in which 12 letters were displayed sequentially. At the beginning of each block, an instruction page was shown for 4.7 s to inform subjects of the appropriate action for each stimulus. The single-task condition was either a vowel/consonant judgment task or a lower-case or upper-case judgment task that was determined based on colors of letters. In the vowel/consonant judgment task, either a green or a white letter appeared; a green letter was associated with the vowel/consonant task (left press for vowel, right press for consonant), while white letters required no action. In the lower/upper-case judgment task, a red letter signaled lower/upper-case judgment (left press for lower case; right press for upper case); with white letters, no action was required. In the dual-task condition, both green and red letters appeared together with white letters. White letters comprised one third of letter stimuli in each block (i.e., four letters). Each stimulus was shown for ≤2400 ms, but terminated following a response before that deadline. A blank screen was inserted between trials so that the stimulus-onset asynchrony was fixed as 2.4 s. In addition to the active task blocks, there was a resting-condition block, 33.5 s in duration, during which no stimuli was presented and no response was required. Each functional run consisted of four task (two single-task blocks and two dual-task blocks) and two resting-condition blocks; in total, the scan session was composed of six functional runs. Before scanning, subjects were given 36 block sessions for practice to stabilize their performance. The executive contextual task fMRI session lasted ~26 min.

Response time (RT) of correct trials and proportion correct for single-task and dual-task conditions were calculated for each individual and reported as behavioral measures.

MRI data acquisition. Participants underwent MRI using a 3T Philips Achieva System equipped with a standard quadrature headcoil. High-resolution T1-weighted magnetization-prepared rapid gradient echo scans were collected axially for each subject [TR = 6.6 ms; TE = 3 ms; flip angle, 8°; field of view (FOV), 256 × 256 mm; matrix size, 256 × 256 mm; slices, 165; voxel size, 1 × 1 × 1 mm^3]. For the executive context task scans, 111 volumes of functional images were acquired in each run (six runs in total) using a T2*-weighted gradient-echo echo planar image sequences (TR = 2000 ms; TE = 20 ms; flip angle, 72°; FOV, 224 × 224 mm; voxel size, 2 × 2 mm; slice thickness, 3 mm; duration, 3.5 min). Each functional volume consisted of 41 transverse slices per volume.

Four dummy volumes acquired at the beginning of each functional run were discarded from the dataset before image processing and analysis.

Structural MRI image processing. For each subject, a single structural T1 image was processed through FreeSurfer v5.1 to implement region-of-interest (ROI) labeling following the FreeSurfer processing pipeline (http://surfer.nmr.mgh.harvard.edu/). Briefly, structural images were bias field corrected, intensity normalized, and skull stripped using a watershed algorithm, followed by a white matter-based segmentation, defining gray/white matter and pial surfaces, and topology correction (Dale et al., 1999). Subcortical and cortical ROIs spanning the entire brain were defined in each subject's native space (Fischl et al., 2002).

18F-florbetaben-PET acquisition, image processing, and analysis. 18F-florbetaben was donated by Piramal (Piramal Pharma). PET scans were performed using a Siemens MCT PET/CT scanner in dynamic, three-dimensional acquisition mode. Dynamic acquisition frames were obtained over 20 min (4 × 5 min frames) beginning 50 min following the bolus injection of 10 mCi of 18F-florbetaben. An accompanying structural CT scan (in-plane resolution, 0.58 × 0.58 mm; slice thickness, 3 mm; FOV, 300 × 300 mm; number of slices, 75) was acquired and used for attenuation correction. PET data were reconstructed using a TrueX (HD-PET) algorithm. Images were smoothed with a 2 mm Gaussian kernel with scatter correction.

Dynamic PET frames (four scans) were aligned to the first frame using rigid-body registration and a static PET image was obtained by averaging the four registered frames. The static PET and CT images were coregistered and merged to generate a composite image in the PET static space. Each individual's structural T1 image in FreeSurfer space was also registered to the participant's merged image to transfer ROIs (see below) and the cerebellar gray matter from FreeSurfer space to static PET image space. These ROIs in static PET space were used to extract the regional PET data.

The standardized uptake value (SUV) was calculated at selected cortical regions that have been also adopted for the processing stream of the Alzheimer's Disease Neuroimaging Initiative (adni.loni.usc.edu; Landau et al., 2013, 2015). The SUV was then normalized to gray matter cerebellum to derive the SUV ratio (SUVR). The selected regions included the following: the frontal (all frontal regions anterior to the precentral sulcus), the temporal (superior and middle temporal gyri), the parietal (superior and inferior parietal cortices, supramarginal gyrus, and precuneus), and the anterior/posterior cingulate cortices. Mean SUVR values from these large ROIs constituted a global amyloid index for each subject.

Amyloid positivity of elderly subjects was determined using a k-means clustering method as previously reported (Oh et al., 2015). Twelve older subjects were classified as Aβ+; 50 older subjects were classified as Aβ−. The proportion of Aβ+ subjects in our sample is comparable to the reports from other studies (Mormino, 2014).

fMRI image processing and analysis. All fMRI analyses were performed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing steps included slice timing, motion correction, coregistration of the T1-weighted anatomical image and the mean functional image, spatial normalization to the Montreal Neurological Institute template, and smoothing with an isotropic Gaussian kernel of 8 mm full-width half-maximum.

For the whole-brain analysis of the executive contextual task, a block-based analysis was performed for each participant. A subject-level design
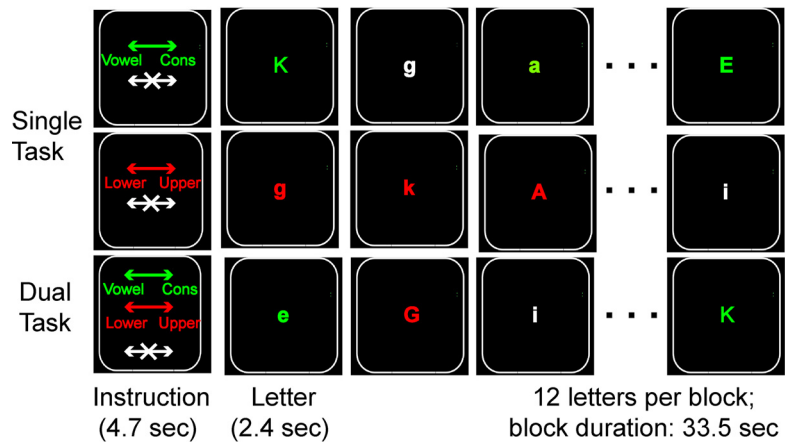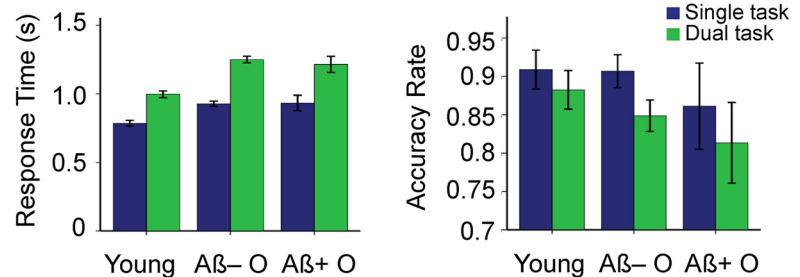

Figure 1. fMRI task design and behavioral performance. *A*, A schematic diagram of single-task and dual-task conditions. The single-task condition was either a vowel/consonant judgment or a lower-case or upper-case judgment task, while the dual-task condition involved task switching between the two tasks. A green letter was associated with the vowel/consonant task (left press for vowel, right press for consonant); a red letter signaled lower/upper-case judgment (left press for lower case, right press for upper case); with white letters, no action was required. Each block started with instruction (4.7 s), and the time interval between the onsets of each letter trial was fixed at 2.4 s. For simplicity, the interstimulus interval blank screen and rest block were not shown in the figure. *B*, Behavioral data of RT and accuracy rate.

matrix was constructed using a GLM consisting of epochs representing each experimental task block: two single-task blocks, two dual-task blocks, and two rest blocks in each run, six functional runs in total. Task blocks in each run were convolved with the canonical hemodynamic response function in SPM8 (i.e., a double-gamma function) for the block duration. In addition to the task block regressors, time-series BOLD signals were high-pass filtered (1/128 Hz) to remove low-frequency drifts. Because the fMRI data were analyzed as a block design, we did not separately model motion-related parameters (i.e., six rigid-body translation and rotation parameters) that did not show any group differences across three subject groups (Johnstone et al., 2006). To identify brain regions that show task-related activity common across groups, three group maps were created by comparing single task versus baseline and dual task versus baseline, and contrasting single task versus dual task collapsing across groups at the group-level analysis, by applying a one-sample t test, controlling for the age group. The whole-brain family-wise error was cluster-corrected to $p < 0.05$ (two-sided) using a cluster-forming threshold of $p < 0.05$. Thresholded statistical maps were projected onto inflated atlases for display purposes using Caret v5.65 software. To assess the effect of age and Aβ deposition on task-related activity in single-task and dual-task conditions and activity difference between dual-task versus single-task conditions, ROI analyses were conducted by extracting mean contrast values from all suprathreshold voxels of task-positive and task-negative brain regions from each group map using the MarsBar Matlab toolbox (Brett et al., 2002; http://marsbar.sourceforge.net). Extracted mean contrast values were averaged for task-positive and task-negative regions separately. These values were then used in ANOVA to assess group differences using SPSS v.22. Age and sex were controlled in all analyses when only older subjects were included.

Table 1. Subject characteristics

	Young		All old		Aβ−0		Aβ+0	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
N	43		62		50		12	
Age (years)	26.6	4.9	64.6	3	64.7	2.9	64.2	3.5
Female [N (%)]	29 (67%)		33 (53%)		27 (54%)		6 (50%)	
Education[a] (years)	15.6	1.9	16.7	2.4	16.9	2.4	16.8	2.3
Global SUVR					1.15	0.05	1.37	0.12
Mattis DRS score	140	2.3	139.8	2.5	139.4	2.8	140.4	2.3
AMNART score	29.9	7.7	33.7	9.7	33.5	9.7	35.5	8.2
NP-process composite score	0.5	1.3	−0.1	3.2	−0.1	3.5	−0.2	0.9
NP-memory composite score[b]	0.9	2.4	−0.4	1.7	−0.5	1.9	−0.4	0.6

[a]Older subjects were more educated than young subjects ($p < 0.01$).

[b]Young subjects performed better than older subjects ($p < 0.005$).

To assess Aβ-related differences in task-related activity with a finer grain, we additionally performed direct voxelwise group comparisons between Aβ+ and Aβ− groups in three activation maps: single-task versus baseline, dual-task versus baseline, and single-task versus dual-task contrast maps. These whole-brain voxelwise comparisons would complement ROI analyses that are more robust to multiple-comparison corrections, while detecting the brain regions most robustly representing the association with Aβ deposition.

Results

Subject characteristics

Subject data are summarized in Table 1. Older subjects were more educated than young subjects ($T_{(103)} = -2.8$, $p < 0.01$). Aβ+O vs Aβ−O groups did not differ in age, gender, education, DRS scores, or AMNART scores. With composite NP test scores, young subjects, compared with Aβ−O subjects, showed significantly higher NP-memory scores, while no other group differences were found for both NP-memory and NP-process composite scores.

Behavioral results of executive contextual task

With RT, a 2 × 3 ANOVA with task condition (single-task vs dual-task conditions) and group (young, Aβ−O, and Aβ+O) being independent variables revealed significant main effects of task condition and group: for task condition, $F_{(1,200)} = 106.96$, $p < 0.001$; for group, $F_{(2,200)} = 38.85$, $p < 0.001$. *Post hoc* analyses revealed that young subjects were significantly faster than older subject groups across all conditions (p's < 0.05). An interaction effect between task condition and group approached significance ($F_{(2,200)} = 2.87$, $p = 0.06$). With accuracy rate, assessed by a 2 × 3 ANOVA, neither main nor interaction effect was significant (p's > 0.1), indicating that accuracy measures (i.e., proportion correct) were not different across groups (p's > 0.1). Aβ+O and Aβ−O groups did not differ in any behavioral measures of the fMRI task. The results are shown in Figure 1B.

Age-related increases in single-task and dual-task activations compared with baseline

To assess a differential effect of age and Aβ deposition on brain activity in frontoparietal regions implicated in cognitive control, we first examined the effect of age on brain activity during the executive contextual task by comparing healthy young and Aβ−O subjects. Age-related brain activity patterns were examined in single-task and dual-task conditions compared with baseline and a contrast of dual-task versus single-task conditions (i.e., parametric increases or decreases due to executive control load) separately. Task-related activation (task-positive) was found
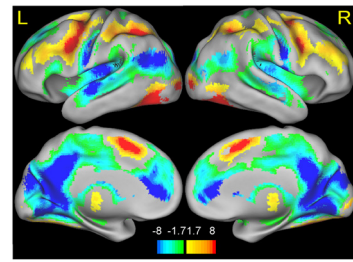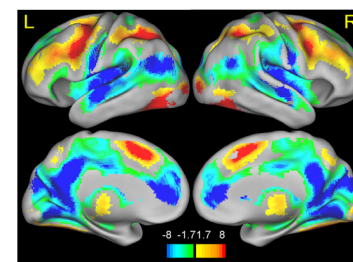

Figure 2. Single-task and task-switching fMRI results by group. *A*, Brain activation during the single-task condition compared with baseline shows an age-related increase in task-positive regions, independent of Aβ deposition. Plots display mean contrast values of significant clusters showing task-related activation (i.e., warm-colored regions in the left panel) and deactivation (i.e., cool-colored regions in the left panel) for each group. *B*, Brain activation during the dual task compared with baseline shows an age-related increase in task-positive regions, independent of Aβ deposition. Plots display mean contrast values of significant clusters showing task-related activation (i.e., warm-colored regions in the left panel) and deactivation (i.e., cool-colored regions in the left panel) for each group. Brain activation maps are thresholded at $p < 0.05$, cluster corrected for multiple comparisons. Scales represent T values. L, Left hemisphere; R, right hemisphere. Error bars in the bar charts represent SEM. *$p < 0.05$; **$p < 0.01$.

throughout the lateral frontal and parietal cortices, the superior medial frontal cortex, and the lateral temporo-occipital cortices bilaterally in the single-task condition compared with baseline (Fig. 2). Task-related deactivation (task-negative) was found in the lateral temporal and temporoparietal cortices bilaterally, and in the medial frontal and parietal cortices. Compared with young subjects, older subjects, independent of Aβ status, showed greater activity in task-positive regions, while no Aβ-related difference was found in task-positive regions ($p > 0.05$; Fig. 2A, bar charts). In task-negative regions, no group difference was found. Similar topography of task-related activation and deactivation was found in the dual-task condition compared with baseline activity (Fig. 2B). In addition, a significant age effect was found such that independent of Aβ deposition, older subjects showed increased task-positive activation compared with young subjects, while no group difference was found in task-negative activation. None of these activations was correlated with RT or accuracy measures collapsing all subject groups.

Aβ-related increases in single-task and dual-task activations compared with baseline

To further assess Aβ-related differences in brain activity supporting executive control with higher resolution that might have been missed in our ROI analyses, we directly compared Aβ+O and Aβ−O groups in brain activation obtained from three contrast

A Aβ+ O > Aβ- O in Single task vs. Baseline

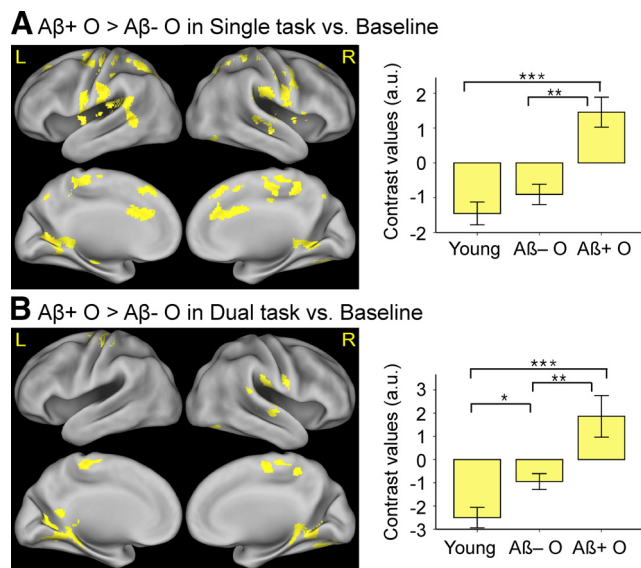**B** Aβ+ O > Aβ- O in Dual task vs. Baseline

Figure 3. Aβ deposition is associated with increased brain activity in subregions that deactivate commonly across all subjects during the executive contextual task conditions. **A**, Aβ-related increases in brain activity for the single task compared with baseline. **B**, Aβ-related increases in brain activity for the dual task compared with baseline. These regions mostly overlap with task-related deactivation regions common across all subjects as shown in Figure 2 A, B. The whole-brain voxelwise contrast maps between Aβ+ and Aβ− groups are thresholded at p < 0.05, cluster corrected for multiple comparisons. Scales represent T values. L, Left hemisphere; R, right hemisphere. Plots display mean contrast values of significant clusters showing Aβ-related increases in brain activation for each group. Contrast values of young subjects from the suprathreshold clusters are displayed for comparison purposes. Error bars in the bar charts represent SEM. *p < 0.05; **p < 0.01; ***p < 0.001.

maps: single task versus baseline; dual task versus baseline; and a contrast of dual-task versus single-task conditions. These whole-brain voxelwise analyses revealed that in single-task compared with baseline activity, Aβ-related increases in activity were found in the anterior cingulate cortex, the posterior hippocampus, the superior medial frontal cortex, the lateral temporal cortex, the superior parietal cortex, the primary sensory and motor cortex, and the insular cortex (Fig. 3A). Aβ-related increases in activity in dual-task compared with baseline activity were found, although less extensive, in the right temporal cortex, the posterior hippocampus, and the primary sensorimotor cortex (Fig. 3B). When we restricted these Aβ-related activation patterns within the common control regions identified across all subject groups, Aβ-related increases were more prominent in task-negative regions (Fig. 3A, B). No significant voxel was found in the opposite contrasts (i.e., greater activity for Aβ−O than Aβ+O). As expected, young subjects showed task-negative activation within regions showing Aβ-related increases in activity, which was significantly greater than that in Aβ+ older subjects for the single-task condition and those in both Aβ+O and Aβ−O groups for the dual-task condition (Fig. 3A, B, bar charts). The categorical differences in brain activity between Aβ+O and Aβ−O groups were further confirmed by significant associations between brain activity and global amyloid indices treated as a continuous variable, controlling for age and sex (single-task vs baseline activity: $\beta = 0.26$, $p < 0.05$; dual-task vs baseline activity: $\beta = 0.26$, $p < 0.05$). When frontal and parietal cortical SUVRs were associated with brain activity in these regions, the results remained similar to those obtained from global amyloid indices with a stronger trend with parietal than frontal cortical SUVRs (for single task vs baseline: frontal SUVR: $\beta = 0.23$, $p = 0.07$; parietal SUVR: $\beta = 0.29$, $p <$

0.05; for dual task vs baseline: frontal SUVR: $\beta = 0.24$, $p = 0.06$; parietal SUVR: $\beta = 0.31$, $p < 0.05$).

Age-related increases but Aβ-related decreases in brain activity in task-positive regions with increased demand of cognitive control

To assess parametric changes in brain activity related to cognitive control load (i.e., dual-task vs single-task conditions), we first identified brain regions that showed parametric increases and decreases commonly across young, Aβ−O, and Aβ+O groups, controlling for age group and performance (Fig. 4A). Load-related parametric increases in activity common across groups were found in lateral frontal and lateral parietal cortices bilaterally, the medial parietal cortex, the inferior temporal cortex, and the precuneus. Parametric decreases related to cognitive control load were found in the medial frontal cortex, the lateral temporo-parietal cortices, the insular cortex, and the left hippocampus. To assess age-related and Aβ-related changes in parametric modulation in activity due to cognitive control load, we extracted contrast values from the suprathreshold clusters identified as cognitive control-related parametric increases and decreases in activity and compared them between groups. Compared with young subjects, Aβ−O subjects showed greater load-related parametric increases in the identified brain regions (Fig. 4B, upper bar chart). The Aβ+O group, however, did not differ from the Aβ−O group in parametric increases in activity collapsing across the identified task-positive regions, controlling for age and sex. In brain regions showing parametric decreases in activity in association with cognitive control load, no group difference was observed (Fig. 4B, lower bar chart).

To further assess which task-related activity derived the observed group differences in parametric activity slope, we masked the brain activation maps for the single-task vs baseline activity and dual-task vs baseline activity with the task-positive and task-negative network maps derived from the dual-task vs single-task contrast common across all three groups (i.e., Fig. 4A). Extracted mean activity values for the single-task and dual-task conditions compared with baseline activity from these masked regions are plotted by subject groups (Fig. 4C). The line charts in Figure 4C demonstrate that task-positive activity for both single-task and dual-task conditions compared with baseline increase with age and Aβ deposition, while the activity difference between dual-task and single-task conditions was the greatest in the Aβ−O group.

To further determine age-related and Aβ-related activity differences in cognitive control with higher resolution, we conducted a whole-brain voxelwise analysis by directly comparing Aβ−O and Aβ+O groups in control load-related brain activity. This analysis revealed that, compared with the Aβ−O group, the Aβ+O group showed parametric decreases in activity for cognitive control in the right prefrontal cortex and the right insular cortex (Fig. 5). Plots displaying mean contrast values of significant clusters are provided to better visualize load-related parametric decreases in activity in Aβ+O compared with Aβ−O subjects (Fig. 5). By treating global amyloid indices as a continuous variable, we found a similar association between Aβ deposition and right prefrontal activation ($\beta = -0.34$, $p = 0.005$). The results remained the same when we assessed the relationships using frontal and parietal cortical SUVRs (frontal SUVR: $\beta = -0.32$, $p < 0.01$; parietal SUVR: $\beta = -0.31$, $p < 0.05$). Brain regions showing Aβ-related decreases in cognitive control activity also showed an age-related difference such that, compared
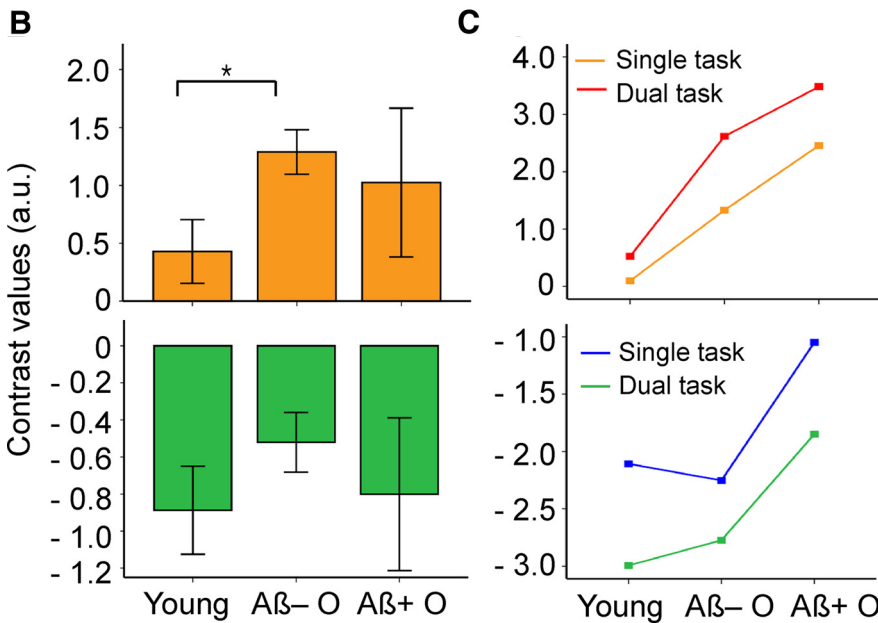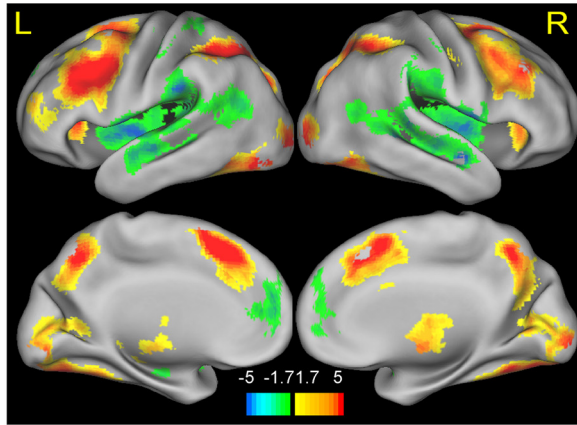
A   Dual vs. Single task

Figure 4. Age is associated with increased brain activity with higher cognitive control load compared with lower cognitive control load conditions. ***A***, Brain regions demonstrating activation and deactivation in relation to higher cognitive control load commonly across all subject groups. Brain activation maps are thresholded at $p < 0.05$, cluster corrected for multiple comparisons. Scales represent T values. L, Left hemisphere; R, right hemisphere. ***B***, Age is associated with greater increases with a higher cognitive control load in task-positive activation in the cognitive control regions common across all subjects. Plots display mean contrast values of significant clusters showing parametric increases with cognitive control load (i.e., yellow/red-colored regions in ***A***; task-positive regions) and parametric decreases with cognitive control load (i.e., green/blue-colored regions in ***A***; task-negative regions) for each group. Error bars represent SEM. *$p < 0.05$. ***C***, Line charts represent mean contrast weights compared with baseline within cognitive control load-related task-positive and task-negative regions by cognitive control load condition and group. Red line: Dual-task, task-positive regions; orange line: single-task, task-positive regions; green line: dual-task, task-negative regions; blue line: single-task, task-negative regions.

with young subjects, Aβ−O subjects showed increased activity for cognitive control.

To assess which task activity derived the observed group differences in parametric activity slope within these regions, we extracted mean contrast values from the suprathreshold clusters for the single-task versus baseline activity and dual-task vs baseline activity separately and plotted them by group. Line charts in Figure 5C demonstrate that for the single task, activity continues to increase with age and Aβ deposition, while for the dual task, activity increases with age, followed by decreases with Aβ deposition. Within the Aβ+ group, right inferior frontal cortex activation was further significantly correlated with RT difference between dual-task and single-task conditions, indicating that

longer RT for the dual-task compared with single-task conditions relates to greater activation in right inferior frontal cortex ($\beta = 0.8$, $p < 0.01$).

Discussion

In this study, we examined the association between fibrillar Aβ deposition and task-related frontoparietal activation during cognitive control among cognitively normal elderly. Several key findings emerged: (1) we replicated age-related frontoparietal hyperactivation during cognitive control, independent of Aβ deposition; (2) while providing additional support for Aβ-related hyperactivation in cognitively normal elderly, we showed that Aβ-related hyperactivation is not restricted to the EM system but also occurs in the cognitive control brain regions; (3) Aβ-related activity in the right prefrontal cortex, which was thought to be critical in cognitive control, decreased with higher cognitive control load, while overall being greater compared with baseline activity.

Approximately 20∼30% of cognitively normal elders harbor elevated accumulation of Aβ, which has been considered as a cause of downstream pathological events during the progression of AD (Selkoe, 2003). Because of the relevance of Aβ deposition to AD and the most detrimentally affected cognitive function in AD patients being EM, studies investigating the relationship of Aβ deposition with other neural markers have focused primarily on the brain systems supporting EM, with a particular focus on MTL, including the hippocampus and more directly anatomically connected regions. The topographical distribution of Aβ deposition, however, is quite widespread across the brain and overlaps highly with brain regions supporting cognitive control, such as the prefrontal and parietal cortices (Braak and Braak, 1991). Therefore, it is highly likely that Aβ deposition also affects other cognitive and memory-related networks.

It is well established that the prefrontal cortex is involved in the executive/cognitive control process. Cognitive control refers to an ability to flexibly interact with the environment by adopting task-relevant behavior while ignoring task-irrelevant one and has been considered to underlie several higher cognitive processes. Lesion, electrophysiological, and fMRI studies in humans and nonhuman primates have shown that the prefrontal cortex, and the lateral frontal cortex in particular, is a critical neural substrate subserving this process. With the damage or reduced brain activation in the prefrontal cortex, subjects' performance in cognitive control function was undermined. The lateral parietal cortex is also thought to be commonly involved in control by showing task-related increases in brain activity as measured in fMRI (Braver et
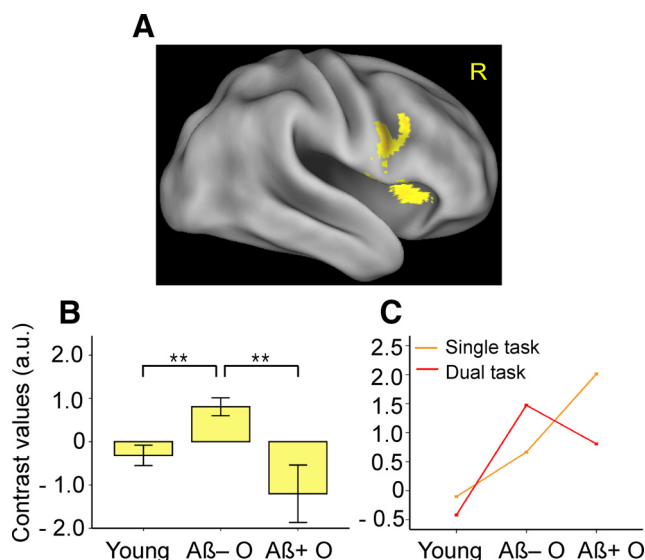
A

B

C

Figure 5. Aβ deposition is associated with decreased brain activity in the right prefrontal and insular cortices with higher cognitive control load compared with lower cognitive control load. **A**, Aβ-related decreases in brain activity for the dual-task compared with single-task conditions. These regions mostly overlap with task-related activation regions common across all subjects as shown in Figure 4A. The whole-brain voxelwise contrast maps between Aβ+ and Aβ− groups are thresholded at $p < 0.05$, cluster corrected for multiple comparisons. **B**, Plots display mean contrast values of significant clusters showing Aβ-related decreases in brain activation for each group. Contrast values of young subjects from the suprathreshold clusters are displayed for comparison purposes. Error bars in the bar charts represent SEM. ** $p < 0.01$. **C**, Line charts represent mean contrast weights compared with baseline within regions showing Aβ-related decreases in brain activation by cognitive control load condition and group. Red line: Dual-task, task-positive regions; orange line: single-task, task-positive regions.

al., 2003; Brass and von Cramon, 2004; Badre and D'Esposito, 2007). Studies of resting-state and task-based connectivity analyses (Power et al., 2011; Cole et al., 2013) further suggest that control is supported in part by a distributed frontoparietal network centered on the inferior frontal sulcus and intraparietal sulcus (Waskom et al., 2014), highlighting a critical role of inferior frontal and parietal cortices in cognitive control.

Although Aβ-related and AD-related changes in cognition have been often focused on EM, it is well documented that impairment of cognitive control is one of early cognitive deficits observed in mild AD patients. Accumulating evidence further suggests that cognitive control impairment can be an early behavioral marker discriminating healthy aging from very mild AD dementia and predicting later conversion (Balota et al., 2010). Even in cognitively normal elderly, well designed cognitive control measures have been associated with AD biomarkers, such as brain amyloid deposition measured by Pittsburgh Compound B PET and CSF measures, including tau, phosphorylated tau (p-tau), and Aβ42, and AD risk factors, such as *apolipoprotein E4* *(APOE4)* genotypes (Aschenbrenner et al., 2015). These findings from both clinical and cognitive/experimental studies, therefore, clearly indicate that cognitive control impairment occurs early in the progression of AD and may be indicative of a presymptomatic stage of AD. Our results provide evidence at the neural level supporting these previous behavioral findings.

The significance of detecting early changes in cognitive control and underlying neural correlates may depend on its relevance to other neurocognitive systems that may become more critical to the disease progression with advanced AD pathology. The cognitive psychology and neuroscience literature has consistently shown that cognitive control is a critical and even prerequisite

cognitive component for declarative memory (Jacoby, 1991). Consistent with this view, previous work of cognitive neuroscience of memory using the whole-brain analysis with fMRI commonly showed brain activation beyond the MTLs during EM encoding and retrieval tasks. Not surprisingly, studies assessing functional changes in relation to an AD risk factor, such as *APOE4* genotypes, found brain activation changes in cognitive control regions defined during *n*-back working memory tasks. Wishart et al. (2006) showed that *APOE4* carriers demonstrated greater activity during verbal *n*-back working memory tasks. Chen et al. (2013) further found that *APOE4* carriers showed a greater increase in activation than *APOE4* noncarriers during low working memory-load tasks compared with baseline activity, while less increases in activation than *APOE4* noncarriers during higher working memory-load tasks compared with lower working memory-load tasks. Our findings of Aβ-related activation decreases in higher cognitive control load, therefore, are in line with these previous reports while providing direct evidence of the impact of brain Aβ deposition on brain activation in frontoparietal cognitive control regions. Future studies linking Aβ-related abnormal activity in frontoparietal cognitive control regions and EM deficits will be warranted to elucidate this hypothesized mechanism during the progression of AD pathology.

Aβ-related functional alterations in cognitively normal elderly have been often found in a form of hyperactivation given a similar level of cognitive performance in EM (Sperling et al., 2009; Mormino et al., 2012; Oh and Jagust, 2013; Huijbers et al., 2014). This Aβ-related hyperactivation in cognitively normal elderly is consistent with findings showing hippocampal hyperactivity in amnesic MCI patients (Dickerson et al., 2005; Celone et al., 2006; Bakker et al., 2012) and young presymptomatic individuals who carry the presenilin-1 genetic mutation (Quiroz et al., 2010) and the *APOE ε4* allele (Wishart et al., 2006; Filippini et al., 2009; Chen et al., 2013). A recent study by Gordon et al. (2015), however, examined task-evoked fMRI activations using semantic judgment (i.e., animacy) and Stroop tasks in association with several AD biomarkers in cognitively normal elderly and found a significant association of task-related activation with CSF tau and p-tau for both types of tasks, but not with CSF Aβ42/amyloid PET measures. Although behavioral ceiling effects and block-level modulations (e.g., incongruent and congruent trials combined) in this study may, in part, explain some inconsistencies between results of Gordon et al.'s study and the present study, it is also possible that other AD biomarkers, such as tau pathology, may affect cognitive control brain regions. Furthermore, it is well recognized that brain regions collectively known as the default mode network (DMN) undergo Aβ-related neural dysfunction as manifested by reduced functional synchrony across the network (Hedden et al., 2009) as well as aberrant increases in deactivation (Sperling et al., 2009). Together, our results of Aβ-related hyperactivation during the single-task and dual-task conditions compared with baseline activity, which topographically overlap with the DMN, corroborate previous findings, while providing novel data showing Aβ-related hyperactivation reaches a breakdown with higher cognitive demands and begins to decrease in the cognitive control regions.

Independent of Aβ deposition, we found age-related increases in frontoparietal activation during task switching. These results are highly consistent with previous findings showing age-related hyperactivation in frontoparietal cortices during working memory tasks compared with young adults with an equivalent level of behavioral performance (Cappell et al., 2010; Oh et al., 2015). Age-related hyperactivation within the common brain regions

involved in task switching supports the view that age is influencing the efficiency of this network, as proposed by our previous work on neural reserve (Stern, 2009) and as suggested by the compensation-related utilization of neural circuits hypothesis (Reuter-Lorenz and Cappell, 2008). Thus all groups can perform comparably on the task, but the network has to be activated to a greater degree in aging because network efficiency is reduced. This age-related reduction in network efficiency and resulting hyperactivity may continue and even increase with Aβ deposition until it reaches a breakdown when higher cognitive demand can no longer be accommodated by the neural system critical for the process.

Several limitations of the current study need to be addressed. First, while block-based analyses of the fMRI task allowed us to identify brain regions robustly activated in response to cognitive control demand, we could not pinpoint subprocesses supporting task switching with a finer grain. Considering that cognitive control, as demonstrated in task switching, is thought to be achieved by a combination of multiple cognitive processes, including representation of abstract rules for task context and response–stimulus association, decision making, and action selection, future studies will need to address whether and how subcomponents of cognitive control are more susceptible to age and Aβ deposition. Second, our data were analyzed cross-sectionally, thereby limiting our ability to predict longitudinal outcomes associated with Aβ-related decreases in right prefrontal activation. Although studies collectively suggest that Aβ deposition present in cognitively normal elderly indicates an increased risk for developing AD, a longitudinal assessment of the relationship between fMRI activation and cognitive trajectories will be warranted to fully evaluate the utility of task-related brain activation measures as an early biomarker of AD. Last, studies have consistently shown that the brain activation and cognition relationship is moderated by individual difference factors, such as life experience, education, and exercise, collectively conceptualized as cognitive reserve (Stern, 2009). Because of the relatively small sample size (Aβ+ older subjects in particular), the current study could not directly examine the effect of these modifying factors on age-related and Aβ-related brain activation changes during task switching. Future studies with a larger sample size will be warranted to address neural consequences of reserve on brain activation during task switching, which will allow us to finely tune in to age-related and Aβ-related changes in task-switching activation accounting for reserve-related activation differences.

In summary, we report a novel finding that with Aβ deposition, older adults show greater activation in the frontoparietal control regions recruited during cognitive control. However, activity in the right prefrontal cortex, which is critical for cognitive control, decreases with increased cognitive control demand in cognitively normal elderly with Aβ deposition. Independent of Aβ deposition, age is associated with greater frontoparietal activation during task switching. Dynamic Aβ-related changes in frontoparietal activation with different cognitive control demand may indicate crucial early functional mechanisms during the progression of Aβ pathology.

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