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Aβ-related hyperactivation in frontoparietal control regions in cognitively normal elderly

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ABSTRACT

The accumulation of amyloid-beta (Aβ) peptides, a pathologic hallmark of Alzheimer's disease, has been associated with functional alterations in cognitively normal elderly, most often in the context of episodic memory with a particular emphasis on the medial temporal lobes. The topography of Aβ deposition, however, highly overlaps with frontoparietal control (FPC) regions implicated in cognitive control/working memory. To examine Aβ-related functional alternations in the FPC regions during a working memory task, we imaged 42 young and 57 cognitively normal elderly using functional magnetic resonance imaging during a letter Sternberg task with varying load. Based on ^{18}F-florbetaben-positron emission tomography scan, we determined older subjects' amyloid positivity (Aβ+) status. Within brain regions commonly recruited by all subject groups during the delay period, age and Aβ deposition were independently associated with load-dependent frontoparietal hyperactivation, whereas additional compensatory Aβ-related hyperactivity was found beyond the FPC regions. The present results suggest that Aβ-related hyperactivation is not specific to the episodic memory system but occurs in the PFC regions as well.

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1. Introduction

Neuritic plaques of fibrillar amyloid-beta (Aβ) peptides are considered as one of the hallmark characteristics of Alzheimer's disease (AD) pathology (Braak and Braak, 1991; Hardy and Selkoe, 2002). With recent application of positron emission tomography (PET) with the radiotracer binding to Aβ plaques, it has been postulated that accumulation of Aβ appears more than a decade in advance before clinical symptoms in humans (Benzinger et al., 2013; Villemagne et al., 2013). Consistent with this view and autopsy findings, Aβ deposition is commonly found in clinically normal older people (Bennett et al., 2006; Mintun et al., 2006). It has been suggested that Aβ deposition leads to downstream neural changes, which is a more direct substrate of cognitive changes than initiating Aβ accumulation. Supporting this view, several neural changes in relation to Aβ deposition have been documented. Compared with healthy controls, patients with AD and mild cognitive impairment (MCI) exhibited significantly increased Aβ deposition and atrophy (Chetelat et al., 2010, 2011; Jack et al., 2008, 2009; Kemppainen et al., 2007). Greater Aβ deposition was further associated with increased brain atrophy or atrophy rate in AD (Archer et al., 2006; Becker et al., 2011) and MCI (Tosun et al., 2011). Consistent with known regional atrophy in AD and MCI, Aβ-related atrophy was notable in the medial temporal lobe (MTL), especially hippocampus, and other regions such as anterior/posterior cingulate, temporal cortices, precuneus, and frontal cortices (Braak and Braak, 1991; Csernansky et al., 2004; de Leon et al., 1989; Dickerson et al., 2009; Jack et al., 2008, 2009). Not only structural but also functional alterations due to Aβ deposition have been shown, particularly in a form of hypometabolism, reduced resting-state functional connectivity, and aberrant task-related hyperactivity across brain regions that are highly implicated in successful episodic memory (EM) (Buckner et al., 2005; Celone et al., 2006; Engler et al., 2006). Potentially mediated by these Aβ-related neural changes, patients with AD and MCI who present with increased levels of Aβ deposition showed greater clinical severity, worse EM, and a higher conversion rate to AD from MCI (Forsberg et al., 2008; Grimmer et al., 2009; Pike et al., 2007; Wolk et al., 2009).

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Aβ-related structural and functional changes have also been reported in cognitively intact normal elderly. Structural changes include gray-matter atrophy in hippocampal volume (Bourgeat et al., 2010; Chetelat et al., 2010; Mormino et al., 2009; Oh et al., 2014; Storandt et al., 2009), temporal pole, superior frontal cortex (Dickerson et al., 2009), and frontal and posterior association cortices (Becker et al., 2011; Oh et al., 2011). Cerebrospinal fluid Aβ was related to longitudinal changes in cortical thinning in lateral and medial frontal and temporal cortices and the posterior cingulate in cognitively intact older adults (Fjell et al., 2010) and also in reduced structural integrity of the default mode network (Spreng and Turner, 2013). Studies examining functional changes in relation to Aβ pathology in cognitively normal elderly have found alterations in resting-state functional connectivity and aberrant task-related hyperactivation in brain regions collectively known as default mode network that is largely overlapping with amyloid deposition (Buckner et al., 2005; Elman et al., 2014; Hedden et al., 2009; Mormino et al., 2011; Sperling et al., 2009). Task-related functional magnetic resonance imaging (fMRI) studies have further found that older adults with Aβ deposition (Aβ+) show greater brain activity in task-positive regions for EM performance equivalent to that of Aβ-negative (Aβ−) older adults (Huijbers et al., 2014; Mormino et al., 2012; Oh and Jagust, 2013; Sperling et al., 2009). In addition, a parametric increase in brain activity was shown to track memory strength in Aβ+ but not in Aβ− older adults (Elman et al., 2014). Together these results suggest that Aβ-related structural and functional alterations occur during the preclinical stage of AD pathology, although some of these changes would benefit EM functions in older adults in preclinical AD.

Aβ-related functional changes have most often been examined in a context of EM, with a particular focus on the MTL function. This might be because of the relevance of Aβ deposition to AD and the most detrimentally affected cognitive function in AD patients being EM/long-term memory (LTM). The topography of Aβ deposition, however, is rather widespread across the brain and highly overlaps with regions known as a frontoparietal control (FPC) network that has been implicated in cognitive control tasks such as working memory (WM) (Niendam et al., 2012; Salami et al., 2012). In addition, neurocognitive research has consistently shown that successful LTM is achieved by several cognitive mechanisms and a coordination of multiple brain regions, part of which consists of FPC regions (Salami et al., 2012; St-Laurent et al., 2011). In line with this view, even with much emphasis placed on Aβ-related LTM deficits in both clinical and preclinical older adults, WM has been shown to deteriorate to a greater extent than LTM in preclinical older adults with AD pathology identified at autopsy (Monsell et al., 2014). In a recent meta-analysis examining the relationship between Aβ deposition and cognition among cognitively normal elderly, executive functions were shown to be negatively associated with brain Aβ in preclinical older adults (Hedden et al., 2013). Therefore, it is possible that not only the MTL structures but also the frontoparietal cortices may undergo Aβ-related changes in the early stage of AD pathology. These changes, however, are less understood and investigated than those in the MTL function.

In the present study, we examined the impact of Aβ deposition on FPC regions while subjects were engaged in a WM task. Based on the previous findings of Aβ-related hyperactivation during a cognitive task, we hypothesized that compared with Aβ− older subjects, Aβ+ older adults would show greater brain activity in FPC regions for WM performance equated to the level of Aβ− older subjects. In addition, we examined age-related changes in neural activity by comparing young and Aβ− older adults accounting for a potential confounding effect of Aβ-related hyperactivation.

2. Materials and methods

2.1. Participants

Forty-two healthy young (age range: 20–30 years and 30 females) and 57 cognitively normal older adults (age range: 60–70 years and 31 females) participated in the study. Subjects were recruited using a market mailing procedure. To ensure that subjects did not have dementia or MCI, a score of at least 136 was required on the Mattis Dementia Rating Scale (Mattis, 1988). All subjects had no history of neurologic 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.

2.2. Neuropsychological tests

A comprehensive battery of neuropsychological (NP) tests were administered to all the participants. Using a subset of NP tests, cognitive composite scores for processing speed/attention and EM were generated; for processing speed/attention (“NP process”), Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), Digit Symbol Subtest (Wechsler, 1997), Trail Making Test Part A (Reitan, 1978) (inversed value), and Stroop Color Naming Test-Color Naming in 90 seconds (Golden, 1978) were included; and for EM (“NP memory”), scores from 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 (Grober and Sliwinski, 1991) was used as an estimate of IQ.

2.3. Experimental design

During the fMRI acquisition, participants performed the letter Sternberg task. Details of this task have been described previously (Zarahn et al., 2007). Briefly, the letter Sternberg task consisted of a total of 3 runs of 30 trials each. Each trial consisted of 3-second study, 7-second retention, and 3-second probe phases followed by a 3-second intertrial interval. Seventy 2-second “blank” periods were appended to the intertrial interval period at random to increase subject alertness by varying the time between trials and also to increase the sensitivity of statistical tests. The study component consisted of the simultaneous presentation for 3 seconds of 1, 3, or 6 uppercase letters (10 of each trial type per run) arranged in a 2×3 grid. After a retention interval (7 seconds), a single lowercase letter was presented in the center of the screen for 3 seconds. During this period, subjects pressed one of 2 keys indicating whether this probe was part of the study set.

Response time (RT), proportion correct, and *d*’ scores (i.e., a discriminability index correcting for false alarm rates) (Snodgrass and Corwin, 1988) for each load condition were calculated for each individual. In addition, a slope of RT across 3 load conditions was calculated as each subject’s behavioral measure.

2.4. MRI data acquisition

Participants underwent MRI using a 3-T 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 (repetition time: 6.6 ms, echo time: 3 ms, flip angle: 8°, field of view [FOV]: 256×256 mm, matrix

size: 256 × 256 mm, slices: 165, and voxel size: 1 × 1 × 1 mm^3). For the letter Sternberg task scans, 314 volumes of functional images were acquired in each run using a T2*-weighted gradient-echo echo-planar image sequences (repetition time: 2000 ms, echo time: 20 ms, flip angle: 72°, FOV: 224 × 224 mm, voxel size: 2 × 2 mm, slice thickness: 3 mm, and duration: 10.5 minutes). Each functional volume consisted of 36 transverse slices. Four dummy volumes were acquired at the beginning of each functional run and discarded from the data set before image processing and analysis.

2.5. Structural MRI image processing

For all subjects, a single structural T1 image was processed through FreeSurfer, version 5.1, 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 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).

2.6. ^{18}F-florbetaben-PET acquisition, image processing, and analysis

^{18}F-florbetaben was donated by Piramal (Piramal Pharma, Inc.). PET scans were performed using a Siemens MCT PET/CT scanner in dynamic, 3-dimensional acquisition mode. Dynamic acquisition frames were obtained over 20 minutes (4 × 5 minutes frames) beginning 50 minutes after the bolus injection of 10 mCi of ^{18}F-florbetaben. An accompanying structural CT scan (in-plane resolution: 0.58 × 0.58 mm, slice thickness: 3 mm, FOV: 300 × 300 mm, and number of slice: 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 (4 scans) were aligned to the first frame using rigid-body registration, and a static PET image was obtained by averaging the 4 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 was calculated at selected regions that have been also adopted for the processing stream of Alzheimer's Disease Neuroimaging Initiative (adni.loni.usc.edu) (Landau et al., 2013, 2015). The standardized uptake value was then normalized to gray-matter cerebellum to derive the standardized uptake value ratio (SUVR). The selected regions included frontal (all frontal regions anterior to the precentral sulcus), temporal (superior and middle temporal gyri), parietal (superior and inferior parietal cortices, supramarginal gyrus, and precuneus), and 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 2 clustering methods applied to log-transformed global SUVRs: K-means clustering and 2-step clustering. Twelve and 16 older subjects were classified as "Aβ+" by each clustering method, respectively (note that all 12 subjects classified as Aβ+ by K-means clustering were classified as Aβ+ by the 2-step clustering method). To be more conservative in classifying older adults as Aβ+, main results are reported based on 12 Aβ+ and 41 Aβ− subjects with 4 older subjects undetermined. The results, however, remained identical when we included 16 subjects as Aβ+.

2.7. 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 anatomic image and the mean functional image, spatial normalization to the Montreal Neurological Institute template, and smoothing with an isotropic 8-mm full-width half-maximum Gaussian kernel.

For the whole-brain analysis of the letter Sternberg task, we used the general linear model (GLM) to construct a design matrix for each individual data set. fMRI trials were classified into a combination of 3 load conditions and accuracy (i.e., correct vs. incorrect). Each event vector defined as the onset times of study, delay, and probe was convolved with a canonical hemodynamic response function with duration of 3 seconds, 7 seconds, and RT, respectively, for each trial. A linear contrast was formed to assess parametric changes by load for each stimulus presentation, delay, and probe period. This resulted in a linear contrast of [load 6 > load 3 > load 1] and an opposite pattern of contrast for each subject for each event. Only correct trials were included.

Estimated parameters (beta values) of each condition/event were derived for each individual using the GLM described earlier (i.e., first-level analysis). To identify brain regions that show load-related parametric increases and decreases in delay-period activity common across young and older subjects, a group map was created by applying a 1-sample *t* test to delay-period activity slopes (e.g., linear contrast of [load 6 > load 3 > load 1]) collapsing all groups at the group level, controlling for age group and individual differences in performance (i.e., RT slope). In other words, contrast images (i.e., contrast values) submitted to *t* tests represent a degree of linear increases or decreases across 3 load conditions. To examine the effect of age and Aβ deposition on parametric changes across 3 load conditions, we extracted mean contrast values from suprathreshold voxels of brain regions showing significant load-related parametric effects commonly across all subjects using the Mars-Bar Matlab toolbox (Brett et al., 2002) (http://marsbar.sourceforge.net). These values were entered into a 1-way analysis of variance with the group as an independent factor. To assess a relationship between activity slope and NP test scores, the same mean contrast values from suprathreshold voxels were entered into multiple regressions as an independent measure with NP composite scores as a dependent measure. For comparison purposes, 1-sample *t* tests were applied to activity slopes during the stimulus presentation and probe periods, separately. In addition to our ROI analyses, we further conducted a whole-brain voxel-wise analysis by directly contrasting groups on load-dependent activity slope contrast maps during the delay period to determine the effects of age and Aβ deposition with a higher resolution. To do so, we inclusively masked the group activation slope difference with regions showing load-dependent activity increases commonly across groups, followed by multiple comparison correction within the mask. We added RT slope as a covariate in all voxel-wise analyses and age when only older adults were included in the analyses.

To detect brain regions that show an association with Aβ deposition but not at the group level, multiple regressions treating a global SUVR as a continuous variable were applied at the group level to identify voxels that show parametric increases and decreases in the delay-related activity as a function of a global amyloid index. Age and RT slope were included as covariates in the voxel-wise multiple regression model. Mean contrast values were extracted from suprathreshold voxels of the multiple regression GLM map and plotted for visualization purposes.

The whole-brain analysis results were cluster corrected to $p < .05$ (2 sided) using a voxel threshold of $p < .05$. Thresholded

statistical maps were projected on to inflated atlases using Caret, version 5.65, software. Non–image-based analyses were conducted using SPSS, version 22. For non–image-based analyses, age and sex were controlled in both analysis of variance and regression models when only older subjects were included. Linear and nonlinear regressions and bootstrap resampling were conducted to assess the correlations between load-related activation increases and NP test performance.

3. Results

3.1. Subject characteristics

Subject data are summarized in Table 1. Aβ+ O versus Aβ− O groups did not differ in age, gender, education, Dementia Rating Scale, cognitive composite scores, or American National Adult Reading Test. For the letter Sternberg task, young subjects were significantly faster than older subject groups across all load conditions (p's $< .05$), whereas accuracy measures (i.e., proportion correct and d' scores) were not different across groups (p's $> .1$). For RT slope, Aβ+ O subjects showed a significantly steeper slope than young subjects ($p < .05$), whereas no other group difference was found. Aβ+ O and Aβ− O groups did not differ in any behavioral measures of the fMRI task.

3.2. Age and Aβ deposition are associated with load-dependent hyperactivation in the FPC regions

To assess parametric changes in delay-period brain activity related to WM load, 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. 1). Load-related parametric increases in activity common across groups were found in lateral frontal and lateral parietal cortices bilaterally, medial parietal cortex, and inferior temporal cortex. Parametric decreases related to load were found in posterior cingulate and left temporoparietal cortices (Fig. 1B).

Table 1
Subject characteristics

Group	Young		All old		Aβ− O		Aβ+ O	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
n	42		57		41		12	
Age, y	26.6	4.9	64.6	3	64.7	2.9	64.2	3.4
F, *n* (%)	30 (71)		31 (54)		23 (54)		8 (57)	
Education	15.6	1.9	16.7	2.4	16.7	2.5	16.8	2.2
Global SUVR					1.144	0.045	1.368	0.121
Mattis DRS	140	2.3	139.8	2.5	139.5	2.6	140.4	2.3
AMNART	29.9	7.7	33.7	9.7	33.5	9.7	35.5	8.2
Letter Sternberg task								
RT								
Load 1	0.95	0.25	1.13	0.26	1.13	0.26	1.12	0.28
Load 3	1.12	0.27	1.32	0.28	1.31	0.27	1.31	0.34
Load 6	1.3	0.3	1.56	0.3	1.54	0.28	1.6	0.37
RT slope	0.2	0.18	0.29	0.15	0.28	0.14	0.33	0.14
Accuracy								
Load 1	0.96	0.05	0.93	0.14	0.92	0.16	0.95	0.09
Load 3	0.96	0.06	0.93	0.13	0.93	0.15	0.93	0.09
Load 6	0.91	0.09	0.89	0.14	0.88	0.14	0.86	0.12
d'								
Load 1	2.43	0.61	2.22	0.9	2.2	0.96	2.33	0.74
Load 3	2.35	0.58	2.21	0.8	2.26	0.85	2.04	0.67
Load 6	2.04	0.74	1.78	0.8	1.78	0.8	1.64	0.83

Key: AMNART, American National Adult Reading Test; Aβ+ O, amyloid-positive older subjects; Aβ− O, amyloid-negative older subjects; DRS, Dementia Rating Scale; F, female; RT, response time; SD, standard deviation; SUVR, standardized uptake value ratio.

To assess age- and Aβ-related changes in parametric modulation in activity due to WM load, we extracted contrast values from the suprathreshold clusters identified as load-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. 1B, upper bar chart). Compared with Aβ− O subjects, Aβ+ O subjects showed stronger parametric increases in relation to WM load (Fig. 1B, upper bar chart), controlling for age and sex. In brain regions showing parametric decreases in activity in relation to WM load, no group difference was observed, although there was a trend for parametric modulation in these regions to be relatively smaller in Aβ+ O compared with Aβ− O and young subjects (Fig. 1B, lower bar chart).

To assess whether age- and Aβ-related changes in parametric modulation in activity are specific to the delay period activity or general to other WM components, we examined load-related increases and decreases in activity during the stimulus presentation and probe periods (Fig. 1A and C). Collapsing all groups, a set of brain regions showed parametric increases and decreases in activity during the stimulus presentation period (Fig. 1A), whereas, during the probe period, only parametric decreases in activity were identified (Fig. 1C). None of these parametric changes, however, showed age- or Aβ-related differences ($ps > .05$).

To examine whether greater slope of load-related activity during the delay period in Aβ+ O subjects has functional significance in other cognitive functions beyond the task given, we assessed an association between delay-period activity slope of Aβ+ O subjects and NP composite scores of processing speed ("NP process") and EM ("NP memory"). Controlling for age and sex, significant quadratic relationships (in an inverted U shape) were found between activity slope and NP test performance (both NP-process and NP-memory scores). These initial analyses, however, seemed to be mostly driven by one subject who just did not meet the outlier criteria (3 standard deviation away from the mean activity slope). With subsequent 1000 bootstrap sampling and analyses excluding the extreme subject, the quadratic relationships did not remain significant (95% confidence interval for regression coefficients: NP process, −0.28 to 0.07 and NP memory, −0.59 to 0.003).

To further determine whether the significant difference due to age and Aβ deposition in load-dependent activity slope during the delay period is driven by any particular area within these common regions, we directly contrasted groups (young vs. Aβ− O and Aβ− O vs. Aβ+ O) on voxel-wise contrast maps with an inclusive mask of common regions. This analysis revealed that age- and Aβ-related hyperactivity was more regionally restricted within the regions commonly recruited across groups (Fig. 2). Note that these results are complementary to our ROI-based results that are more robust because of no need of multiple comparison correction as applied to voxel-based analyses. No regions showed greater load-dependent activity slope for the young compared with Aβ− O groups and for the Aβ− O compared with Aβ+ O groups.

3.3. Aβ deposition relates to compensatory recruitment of additional brain regions

We conducted an exploratory whole-brain analysis to identify brain regions that might not have been detected by the group contrast analysis but exhibit Aβ-related changes in load-dependent parametric modulation during the delay period. Additional brain regions were identified showing Aβ-related parametric increases across 3 load conditions including superior medial frontal cortex, posterior cingulate, and posterior hippocampus (Fig. 3A). Plots displaying mean contrast values of significant clusters are provided to better visualize load-related parametric increases in activity in Aβ+ O compared with Aβ− O

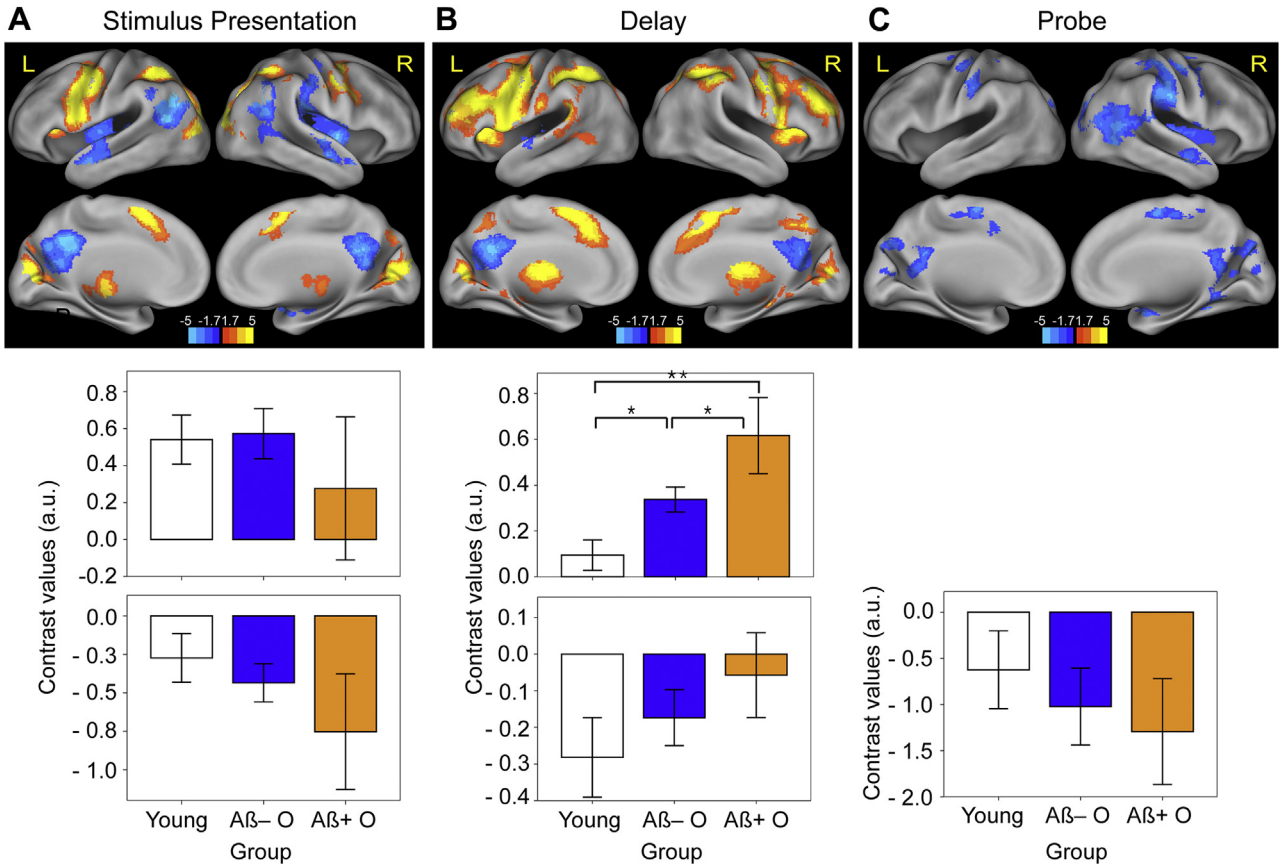

Fig. 1. Age and amyloid-beta deposition are associated with greater parametric increases in delay-period activation in a verbal working memory (WM) brain network common across all subjects. Brain regions demonstrating activation and deactivation in relation to WM load (1, 3, or 6 letters) during a stimulus presentation (A), delay (B), and probe (C) phase of the letter Sternberg task. Warm colors indicate load-dependent increases in activation, and cool colors indicate load-dependent decreases in activation (i.e., deactivation). Results are thresholded at $p < .05$, cluster corrected for multiple comparisons. Scales represent T values. Within each task phase, upper plots display mean contrast values of significant clusters showing load-related increases in activation (i.e., warm-colored regions in lateral and medial views of semi-inflated brain surfaces) for each group. Lower plots display mean contrast values of significant clusters showing load-related increases in deactivation (i.e., cool-colored regions in lateral and medial views of semi-inflated brain surfaces) for each group. For the probe phase, significant parametric changes occurred only in deactivation. Error bars represent standard error of the mean. $^{*}p < .05$ and $^{**}p < .01$. Abbreviations: a.u., arbitrary units; Aβ+ O, amyloid-positive older subjects; Aβ− O, amyloid-negative older subjects; L, left hemisphere; R, right hemisphere. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

subjects (Fig. 3B). When we assessed the relationship between activity slope and Aβ deposition separately for each Aβ group, however, a regression coefficient for each group was not significant, controlling for age and sex.

4. Discussion

In this study, we examined whether fibrillar Aβ deposition affects task-related activity in frontoparietal cortices during a WM

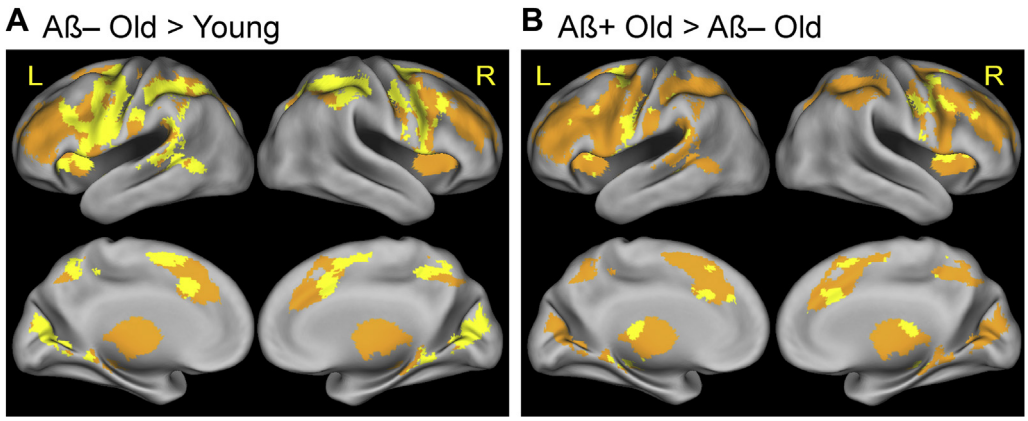

Fig. 2. Voxel-wise comparisons between young and amyloid-negative older (Aβ− O) subjects and between amyloid-positive older (Aβ+ O) and Aβ− O subjects in load-dependent delay activity slope within the frontoparietal control regions. Brain regions showing greater load-dependent activity slope for Aβ− O compared with young subjects and Aβ+ compared with Aβ− O (yellow, $p < .05$, cluster size corrected for multiple comparisons) are overlaid on regions showing a common load-dependent parametric increase in the delay period activity across all groups (orange), which are shown in Fig. 1B (warm colors). Abbreviations: L, left hemisphere; R, right hemisphere. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

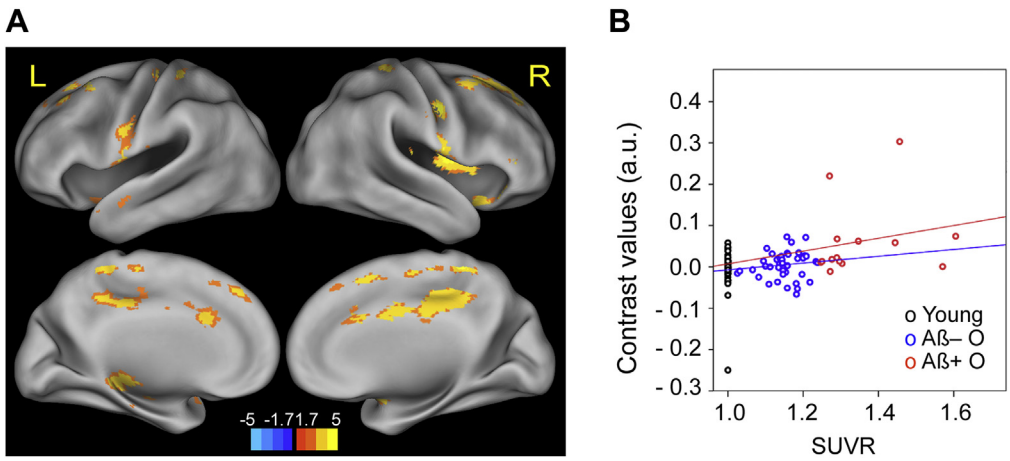

Fig. 3. Parametric activity increases for working memory load relate to amyloid-beta (Aβ) deposition as a continuous measure. (A) Warm colors indicate regions showing a positive relationship between load-related linear increases of activity and global standardized uptake value ratio (SUVR). These regions mostly do not overlap with regions common across all subjects. Results are thresholded at $p < .05$, cluster corrected for multiple comparisons. Scales represent T values. (B) Scatterplots visualize that greater parametric increases are positively related to the amount of amyloid deposition as measured by global SUVR. Contrast values of young subjects are displayed on the left for comparison purposes. Abbreviations: a.u., arbitrary unit; L, left hemisphere; R, right hemisphere. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

and cognitive control task in cognitively normal elderly. Several key findings emerged as follows: (1) we replicated findings of age-related activity increases in brain regions implicated in cognitive control and WM, independent of Aβ deposition (Cabeza et al., 2004; Zarahn et al., 2007); (2) older adults with fibrillar Aβ deposition showed greater parametric increases in frontoparietal activation during the delay period with higher WM load; and (3) with Aβ deposition, additional brain regions showed greater parametric increases beyond the WM control regions.

Approximately 20%–30% of cognitively normal elders harbor elevated level of accumulation of Aβ that, an oligomeric form of Aβ peptides in particular, has been considered as a cause of downstream pathologic events during the procession of AD including synaptic disruption, neuronal death, and eventually severe cognitive deficits (Selkoe, 2003). Studies have further suggested that several mechanisms intervening the Aβ-related downstream pathways such as neuroinflammation, tau-related neurofibrillary tangles, mitochondrial dysfunction, and abnormal regulation of ions may initiate and drive AD (Querfurth and LaFerla, 2010). Although a whole picture has not been emerged yet, studies collectively suggest that Aβ deposition present in cognitively normal elderly indicates an increased risk for developing AD.

Even in cognitively normal older adults, studies have found several functional changes in association with elevated Aβ deposition. Using fMRI, Aβ-related changes in network connectivity during the resting state were found in both within and between networks particularly in the heteromodal association areas (Elman et al., 2014; Hedden et al., 2009). While performing cognitive tasks of episodic encoding, Aβ+ older adults showed increased activation compared with Aβ− older adults in task-positive and -negative regions (Huijbers et al., 2014; Mormino et al., 2012; Oh and Jagust, 2013; Sperling et al., 2009). This Aβ-related hyperactivation in cognitively normal elderly is consistent with the findings showing hyperactivity in hippocampus in amnesic MCI patients (Bakker et al., 2012; Celone et al., 2006; Dickerson et al., 2005) and young presymptomatic individuals who carry the presenilin-1 (PS1) genetic mutation (Quiroz et al., 2010) and APOE ε4 allele (Filippini et al., 2009).

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 functional changes to the accumulation of Aβ have focused primarily on the brain systems supporting EM, with a particular focus on MTL including hippocampus and more directly anatomically connected regions. The topographical distribution of Aβ deposition, however, overlaps highly with frontoparietal cortices, whereas MTL is relatively devoid of Aβ deposition in the early stage of Aβ pathology (Braak and Braak, 1991). Thus, although supporting Aβ-related hyperactivation previously observed in cognitively normal elderly, the present results provide the novel finding of Aβ-related hyperactivation beyond the MTL-based EM network. These results are consistent with a growing field of research examining the impact of known risk factors in prodromal AD, such as ApoE4 allele, to frontoparietal function and cognitive control (Chen et al., 2013; Wishart et al., 2006).

At the behavioral level, WM refers to the maintenance of a limited amount of information over a short period of time. It involves the integration of several subprocesses via attention to task-relevant information while resisting to task-irrelevant information, which is collectively termed as cognitive control (Baddeley, 1986; D'Esposito and Postle, 2015). Studies examining a neural basis of WM have consistently found the recruitment of prefrontal and parietal cortices as top-down control signals, attributed to for the integrated representations of task contingencies and rules and further biasing signals in other brain regions underlying WM performance (D'Esposito and Postle, 2015; D'Esposito et al., 2000; Habeck et al., 2005; Koechlin et al., 2003; Miller and Cohen, 2001; Smith and Jonides, 1999). In the cognitive aging literature, older adults showed greater activation in frontoparietal cortices during WM tasks compared with young adults with an equivalent level of behavioral performance (Cappell et al., 2010). Because previous studies are highly likely to have included older subjects with Aβ deposition, the results may have been driven by both Aβ− and Aβ+ older adults. In the present study, we provide evidence supporting an age-related parametric increase in frontoparietal activation with WM load increases, independent of Aβ deposition, whereas a load-related increase in activation was greatest in Aβ+ elders.

It is important to note that cognitive functions supported by frontoparietal cortices are not limited to WM, but rather generally applied to multiple cognitive processes including autobiographical memory, semantic memory, and EM (Salami et al., 2012;

St-Laurent et al., 2011). For EM, both memory encoding and retrieval processes recruit frontoparietal cortical activation (Salami et al., 2012; Sambataro et al., 2012). These neuroimaging results confirm that cognitive control processes subserved by FPC regions are involved in multiple cognitive functions and further suggest that functional changes in these regions may affect not only WM but also other cognitive processes such as EM. When we assessed an association of frontoparietal parametric increases with processing speed and EM in the present study, however, the association was not significant, possibly because of a small sample size of Aβ+ subjects. Future studies with a larger sample and longitudinal investigation will be warranted to test the relationship between frontoparietal brain activation and NP tests measuring global cognitive control and EM performance.

One possible interpretation of the present findings that both age- and Aβ-related hyperactivation were observed in the same brain network used by young adults is that both age and amyloid are influencing the efficiency of this network. Thus, all groups can perform comparably on the task, but the network has to be activated to a greater degree in aging and even more so in the presence of amyloid because network efficiency is reduced. This observation is compatible with our previous work on neural reserve (Stern, 2006) and with the Compensation-Related Utilization of Neural Circuits Hypothesis (Reuter-Lorenz and Cappell, 2008).

Additional brain regions identified showing greater parametric increases in relation to a global amyloid index as a continuous measure further suggest that with Aβ deposition, older adults recruit more brain regions to perform WM equivalently to Aβ− older adults. That is, in addition to reducing the efficiency of typically used networks, there is Aβ-related compensatory recruitment of neural resources that are needed to maintain cognitive performance. Although the exact nature of this Aβ-related compensatory recruitment of additional brain regions is unclear, the finding is concordant with age-related functional reorganization that is behaviorally beneficial, as conceptualized as a mechanism of neural compensation (Stern, 2006).

In summary, we report the novel finding that with Aβ deposition, older adults show greater load-dependent activation increases in FPC regions recruited during WM that also show age-related parametric increases in activity. With Aβ deposition, additional brain regions showed greater parametric increases beyond the frontoparietal regions, which may reflect compensatory recruitment of neural resources for an equivalent level of WM performance. Taken together, Aβ-related hyperactivation in FPC regions underlying WM and over-recruitment of additional brain regions can potentially be an early biomarker of AD and may harbinger an imminent cognitive decline in the progression of Aβ pathology.

Disclosure statement

The authors have no conflicts of interest to disclose.

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