Supplemental Data

Appendices

Appendix e-1

^{18}F-Florbetaben-PET acquisition, image processing and analysis

^{18}F-Florbetaben was donated by Piramal (Piramal Pharma Inc.). Detailed information on ^{18}F-Florbetaben PET data acquisition and image processing can be found in our previous report [1]. Briefly, scans were performed on a Siemens MCT PET/CT scanner in dynamic, three-dimensional acquisition mode over 20 minutes (4 X 5 min frames) beginning 50 min following 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 = 3mm, FOV = 300 X 300 mm, 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.

For all participants, 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 tissue-based segmentation, defining gray/white matter and pial surfaces, and topology correction [2]. Subcortical and cortical ROIs spanning the entire brain were defined in each subject's native space [3].

Dynamic PET frames (4 scans) were aligned and averaged to form a mean PET image that was coregistered and merged to the CT image. Each individual's structural T1 image in FreeSurfer space was also registered to the participant's merged image to obtain region of interest (ROI) values as described next. The standardized uptake value ratio (SUVR) was calculated for selected cortical regions

encompassing frontal, temporal, parietal, and anterior/posterior cingulate cortices with cerebellar gray matter as a reference region [4, 5]. Mean SUVR values from these lobar ROIs constituted a global amyloid index for each subject. To determine amyloid positivity of elderly participants, we used a K-means clustering method as previously reported [6]. Twenty-one and 61 older participants were classified as Aβ+ and Aβ− participants, respectively. The proportion of Aβ+ participants in our sample is comparable to the reports from other studies [7].

For whole brain voxel-wise analyses, SUVR images on native space were warped into MNI template space using symmetric diffeomorphic non-linear registration implemented in the advanced normalization tools (ANTS) software package (http://picsl.upenn.edu/software/ants/). A relatively small step size (0.25 mm) is used for higher accuracy with mutual information as a cost function and regularization is done by Gaussian kernel with FWHM=3 mm. In order to assess the relationship between intellectual activity and Aβ deposition, we performed 2 analyses: (1) multiple regression model using a mean cortical Aβ measure as a dependent variable and intellectual activity as an independent variable, and (2) the whole-brain voxel-wise analysis using general linear model (GLM) treating voxel-wise Aβ level as a dependent measure and intellectual activity as an independent measure. Age and sex were controlled in all analyses, because these variables may relate to dependent measures of interest beyond intellectual activity. For all voxel-wise analyses, the whole brain family-wise error was cluster corrected to $p<0.05$ (two-sided) using a cluster forming threshold of $p<0.05$ (cluster size>640 voxels). Thresholded statistical maps were projected on to inflated atlases for display purposes using Caret v5.65 software.

Appendix e-2

Neuropsychological tests

A comprehensive battery of neuropsychological (NP) tests was administered to all the participants. Using a subset of NP tests, we computed two cognitive composite scores: processing speed/attention (NP-process) and episodic memory (NP-memory). For NP-process, we included scores of Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol subtest [8], Trail Making Test Part A [9](inversed value), and Stroop Color Naming test-Color naming [10]. For NP-memory, we combined scores from Selective Reminding Test (SRT)[11]: long term storage, SRT-continued recall, and SRT-recall at the last trial.

Appendix e-3

Task-switching fMRI task

The detailed description of the fMRI task is provided in our previous report [1]. Briefly, the fMRI task was designed to assess executive control function in a block-design, in which either single or dual task condition was assigned. During fMRI scans, a letter in either red or green appeared on the screen and participants were asked to make a vowel/consonant judgment for green letters and a lower/upper-case judgment for red letters. For a single task condition, letters in only one of the two colors appeared throughout the entire block so that participants had to do the same type during the task block. For a dual task condition, color of letters changed between green and red so that participants had to switch between vowel/consonant judgment and lower- or upper-case judgment within a task block accordingly. Each letter stimulus was shown for a maximum of 2400 msec, but terminated following a response before that deadline. Twelve letters were presented within each block that was 33.5 sec in duration. Intermixed with letters in red or green, a one third of letters in a block appeared in white, for which no response was required. In addition to the active task blocks, there were resting condition blocks, 33.5 sec in duration, during which no stimuli were presented and no response was required. Each functional run consisted of

four task (2 single-task blocks and 2 dual-task blocks) and 2 resting condition blocks; in total, the scan session was composed of 6 functional runs. Prior to scanning, participants were given 36 block sessions for practice to stabilize their performance. The task fMRI session lasted approximately 26 min.

Appendix e-4

MRI data acquisition

Imaging parameters for high-resolution T1-weighted magnetization-prepared rapid gradient echo (MPPAGE) scans were as follows: TR = 6.6 ms, TE = 3 ms, field of view (FOV) = 256 X 256 mm, flip angle = 8°, matrix size = 256 X 256 mm, voxel size = 1 X 1 X 1 mm^3, 165 slices, voxel size = 1 X 1 X 1 mm^3. Whole-brain fMRI was collected using a T2*-weighted gradient-echo echo planar images (EPI) sequence (TR = 2000 ms; TE = 20 ms; FOV = 224 X 224 mm; flip angle = 72°; voxel size = 2 X 2 X 3 mm^3; 41 slices). Each functional run consisted of 111 volumes of functional images, with 6 runs in total.

Appendix e-5

Structural MRI image processing

To assess voxel-wise gray matter (GM) volume, we applied voxel-based morphometry (VBM) processing streams implemented in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK), using a single structural T1 image as previously reported [9]. In the whole-brain voxel-wise analysis, we assessed the relationship between intellectual activity and GM volume using a GLM treating voxel-wise GM volume as a dependent measure and intellectual activity as an independent measure. Age, sex, and total intracranial volume (TIV) were controlled in the analyses.

Appendix e-6

fMRI task group-level analysis

To identify brain regions that show changes in task-related activity in relation to intellectual activity, we first identified task-positive and task-negative regions that were common across young and older participants in three comparison/contrasts: single-task condition compared with baseline, dual-task condition compared with baseline, and dual vs. single task contrast. Using GLMs, each comparison/contrast-related activity was regressed on intellectual activity scores among older adults, with age and sex as covariates of no interest. 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 on to inflated atlases for display purposes using Caret v5.65 software.

Appendix e-7

Non-image data analysis

We used one-way analysis of variance (ANOVA) and chi-square to assess group differences across the 3 groups (i.e., young, Aβ−O, and Aβ+O groups) in demographics and behavioral measures. Group differences among older groups were assessed by analysis of covariance (ANCOVA), controlling for age and sex. We conducted multiple regression to assess the relationship between intellectual activity and a mean cortical Aβ measure, cognitive composite scores, and fMRI executive control task performance (i.e.., RT and accuracy rate). We also used multiple regression to assess an interaction between intellectual acitivy and amyloid positivity status on a mean cortical Aβ measure, controlling for age and sex.

Appendix e-8

Behavioral results of fMRI task and neuropsychological composite scores

Compared with older adults, young participants showed significantly higher scores in both NP-memory and NP-process than older participants (*ps* < 0.001). Aβ−O group showed a significantly higher intellectual activity compared with young participants ($p < 0.05$).

For response time, a 2 X 3 ANOVA with task condition (single 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, 249) = 184.42, $p < 0.001$; For group, F (2, 249) = 43.05, $p < 0.001$. Post-hoc analyses revealed that the dual task condition took longer than the single task condition across the three subject groups and young participants were significantly faster than older subject groups across all conditions (*p*s < 0.001). An interaction effect between task condition and group approached significance (F (2, 249) = 2.67, $p = 0.07$). When accuracy rate was assessed by a 2 X 3 ANOVA, there was a significant main effect of task condition, F (1, 249) = 14.96, $p < 0.001$, showing that the single task condition yielded higher proportion correct than the dual task condition. Neither a main effect of group nor an age by group interaction was found, indicating that there was no accuracy difference between groups. When we assessed fMRI task performance only within older participants, Aβ+O and Aβ−O groups did not differ in any behavioral measures of the fMRI task (*ps* > 0.1). The results are summarized in Table 1.

Among older adults, the relationship between intellectual activity and each measure of fMRI task performance was assessed by separate multiple regressions with intellectual activity as an independent measure and proportion correct and RT for each fMRI task condition (i.e., single and dual task conditions) as dependent measures. No significant relationship was found, controlling for age and sex (*ps* > 0.1).

e-References

1. Oh H, Steffener J, Razlighi QR, Habeck C, Stern Y. beta-Amyloid Deposition Is Associated with Decreased Right Prefrontal Activation during Task Switching among Cognitively Normal Elderly. J Neurosci 2016;36:1962-1970.

2. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999;9:179-194.

3. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341-355.

4. Landau SM, Breault C, Joshi AD, et al. Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med 2013;54:70-77.

5. Landau SM, Fero A, Baker SL, et al. Measurement of Longitudinal beta-Amyloid Change with 18F-Florbetapir PET and Standardized Uptake Value Ratios. J Nucl Med 2015;56:567-574.

6. Oh H, Steffener J, Razlighi QR, et al. Abeta-related hyperactivation in frontoparietal control regions in cognitively normal elderly. Neurobiol Aging 2015;36:3247-3254.

7. Mormino EC. The relevance of beta-amyloid on markers of Alzheimer's disease in clinically normal individuals and factors that influence these associations. Neuropsychology review 2014;24:300-312.

8. Wechsler D. Wechsler Adult Intelligence Scale - III. San Antonio, TX: Psychological Corporation, 1997.

9. Reitan R. Manual for Administration of Neuropsychological Test Batteries for Adults and Children. Tucson, AZ: Reitan Neuropsychology Laboratories, Inc, 1978.

10. Golden CJ. Stroop Color and Word Test. Chicago, IL: Stolting, 1978.

11. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24:1019-1025.