ARTICLE

Multiple pathways of reserve simultaneously present in cognitively normal older adults

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Abstract

Objective

To examine neural correlates of intellectual activity underlying multiple pathways imparting reserve by testing that higher intellectual activity is associated with lower brain amyloid pathology, greater gray matter (GM) volume, and differential task-evoked brain activation levels as a function of amyloid positivity status among clinically intact older adults.

Methods

Eighty-two cognitively normal older adults and 46 healthy young participants underwent fMRI during task switching. All older participants completed ^{18}F-florbetaben-PET and an individual's amyloid positivity status was determined. To assess GM volume, T1-weighted high-resolution structural images were processed using voxel-based morphometry. As lifestyle factors, intellectual activity was estimated by a composite score of vocabulary, reading ability, and years of education.

Results

Across all older participants, intellectual activity was associated with lower amyloid deposition in lateral and medial frontoparietal and temporal lobes but higher amyloid deposition in superior frontal and parietal cortices, larger GM volume across widespread brain regions, and reduced brain activation during task switching. These patterns of associations, however, differed by amyloid positivity status. While the patterns of associations remained similar among amyloid-negative older adults, among amyloid-positive older adults, intellectual activity was associated with increased amyloid deposition in frontoparietal cortices and increased activation during task.

Conclusions

Intellectual activity simultaneously exerts both neuroprotective and compensatory effects via multiple neural pathways that promote optimal brain aging and help maintain normal cognition during amyloid accumulation.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

Aβ = β-amyloid; **AMNART** = American version of the National Adult Reading Test; **CR** = cognitive reserve; **DRS** = Mattis Dementia Rating Scale; **GLM** = general linear model; **GM** = gray matter; **SUVR** = standardized uptake value ratio; **VBM** = voxel-based morphometry.

Several theoretical models have been proposed to explain the mechanisms relating lifestyle to disease status. The cognitive reserve (CR) hypothesis postulates that individual differences in the way people process tasks or in the neural networks underlying task performance allow some people to cope better with brain damage than others,[1,2] emphasizing the modulatory role of the individual difference factors. Several lifetime experience measures have been used as a proxy of CR, including premorbid IQ, education, occupation, and leisure activities.[3] Lifestyle variables, however, may directly exert influence on the brain itself or on brain pathology, in the form of neuroplasticity, which has been conceptualized as brain maintenance. Brain maintenance emphasizes the preservation of brain health in old age, focusing on the relative lack of senescent brain changes or absence of pathology.[4] Few studies have directly examined the interaction between neural correlates of multiple pathways imparting reserve during aging, particularly in relation to amyloid pathology.

In the present study, we examined whether and how intellectual activity relates to brain β-amyloid (Aβ) pathology, brain morphology, and function among cognitively normal older adults. Although conceptually related, the direct and modulatory accounts of reserve predict different neuromechanistic outcomes. We hypothesized that for the brain maintenance prediction, higher intellectual activity would be associated with lower amyloid pathology and increased gray matter (GM) volume. For the CR prediction, however, higher intellectual activity would relate to differential brain activation as a function of amyloid positivity status among cognitively normal older adults.

Methods

Participants

Eighty-two cognitively normal older adults (age range 60–70 years) and 46 healthy young adults (age range 20–30 years) were recruited using a random market mailing method to participate in the study. Participants were screened for dementia or mild cognitive impairment by the Mattis Dementia Rating Scale (DRS),[5] and any history of neurologic and psychiatric illnesses and major medical illness or medication that could affect cognition. All participants underwent fMRI using a task-switching paradigm and high-resolution structural MRI scans. All older participants additionally completed ^{18}F-florbetaben-PET and were classified as either amyloid-positive (Aβ+) or amyloid-negative (Aβ−) using previously reported cutoff values applied to the global amyloid deposition level[6] (for details on PET acquisition, see appendix e-1, links.lww.com/WNL/A40), resulting in 61 Aβ− and 21 Aβ+. A subgroup of the study participants was included in our previous report.[7]

Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional review board of the College of Physicians and Surgeons of Columbia University. All participants provided written informed consent.

Neuropsychological tests

All participants were assessed by a comprehensive battery of neuropsychological tests (for details, see appendix e-2, links.lww.com/WNL/A40). For intellectual activity, we used mean *z* scores of 3 intellectual ability measures: education, accuracy of the American version of the National Adult Reading Test (AMNART), and vocabulary.[8] Although proxy measures we used reflect its hold nature rather than concurrent cognitive activity, we used the term intellectual activity to focus on intellectual exposure across the lifespan, rather than the outcome ability that may have resulted from these activities.[9–11] Cognitive measures selected as a proxy of reserve are composed of measures that capture crystalized knowledge that little changes with age, rather than fluid knowledge, such as executive function, as traditionally conceptualized. For cognitive assessment, we used scores in the domains of processing speed and memory, because these domains are most commonly affected by aging and early stage of Alzheimer disease. *z* Scores were computed based on 189 study participants who were enrolled in the cognitive aging study cohort.[12]

Assessing the relationship between intellectual activity and amyloid deposition

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) 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. For further details on analysis, see appendix e-1 (links.lww.com/WNL/A40).

fMRI experimental task

To assess a brain activation pattern in association with intellectual activity, we used a task-switching paradigm during fMRI, which was designed to capture executive control function.[7] Two task conditions (i.e., single task vs dual task)

were used, each representing an easier task and a more demanding one (for detailed description of the fMRI task, see appendix e-3, links.lww.com/WNL/A40). Response time of correct trials and accuracy rate 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 (Best, the Netherlands) Achieva System equipped with a standard quadrature head coil. Imaging measures for high-resolution T1-weighted magnetization-prepared rapid gradient echo scans and a T2*-weighted gradient-echo echoplanar image sequence for fMRI are provided in appendix e-4 (links.lww.com/WNL/A40).

Structural MRI processing

Voxel-wise GM volume was assessed by voxel-based morphometry (VBM) processing streams implemented in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) in relation to intellectual activity. For further details on VBM processing and analyses, see appendix e-5 (links.lww.com/WNL/A40).

fMRI processing and analysis

All fMRI analyses were performed with SPM8. Detailed description of fMRI data preprocessing and subject-level analysis can be found elsewhere.[7] Briefly, a subject-level design matrix was constructed using a GLM consisting of epochs representing each experimental task block: 2 single-task blocks, 2 dual-task blocks, and 2 rest blocks in each run, 6 functional runs in total. Task blocks in each run were convolved with the canonical hemodynamic response function provided by SPM8 for the block duration. For details on group-level analysis, see appendix e-6 (links.lww.com/WNL/A40).

For all voxel-wise analyses for all neuroimaging modalities, significant clusters were determined at $p < 0.05$ at cluster level with family-wise error correction and at $p < 0.05$ at voxel level (uncorrected). Cluster size >640 voxels was considered significant by 3dClustSim function provided by AFNI.

Nonimage data analysis

For statistical analyses on nonimage data, see appendix e-7 (links.lww.com/WNL/A40).

Results

Participant characteristics

Participant characteristics and behavioral performance for both neuropsychological composite scores and fMRI task are summarized in the table. Among older participants, Aβ+ vs Aβ− groups did not differ in age, sex, education, DRS scores,

Table Participant characteristics

	Young		β-Amyloid−		β-Amyloid+	
	Mean	SD	Mean	SD	Mean	SD
n	46		61		21	
Age, y	27.9	6.2	65.4	2.8	66.0	3.2
Female, n (%)	31 (67)		30 (49)		10 (48)	
Education, y	15.9	2.1	16.6	2.4	16.0	2.6
Global SUVR			1.15	0.1	1.35	0.1
Intellectual activity[a]	−0.1	0.7	0.3	0.7	0.2	0.8
AMNART (IQ)	114	7.6	118	9.7	120	7.9
DRS	140	2.2	140	2.9	140	2.2
NP-process	0.7	0.8	−0.2	0.6	−0.3	0.6
NP-memory	0.7	0.7	−0.2	0.9	−0.6	0.9
fMRI, single RT	0.8	0.1	0.9	0.1	1.0	0.2
fMRI, dual RT	1	0.2	1.2	0.2	1.2	0.2
fMRI, single Acc	0.95	0.1	0.95	0.1	0.94	0.1
fMRI, dual Acc	0.92	0.1	0.9	0.1	0.9	0.1

Abbreviations: Acc = accuracy rate; AMNART = American National Adult Reading Test; DRS = Mattis Dementia Rating Scale; dual = dual-task condition; NP-memory = neuropsychological composite scores for memory; NP-process = neuropsychological composite scores for processing speed; RT = response time, s; single = single-task condition; SUVR = standardized uptake value ratio.
[a] Composite scores of education, vocabulary, and AMNART.

cognitive composite scores of processing speed or memory, or AMNART. Intellectual activity scores and behavioral measures of the fMRI task did not differ between Aβ groups ($p > 0.1$). No association between intellectual activity and each measure of fMRI task performance was significant, controlling for age and sex ($p > 0.1$). Further details on behavioral results of fMRI task and cognitive composite scores and their association with intellectual activity are provided in appendix e-8 (links.lww.com/WNL/A40).

Association between intellectual activity and amyloid deposition

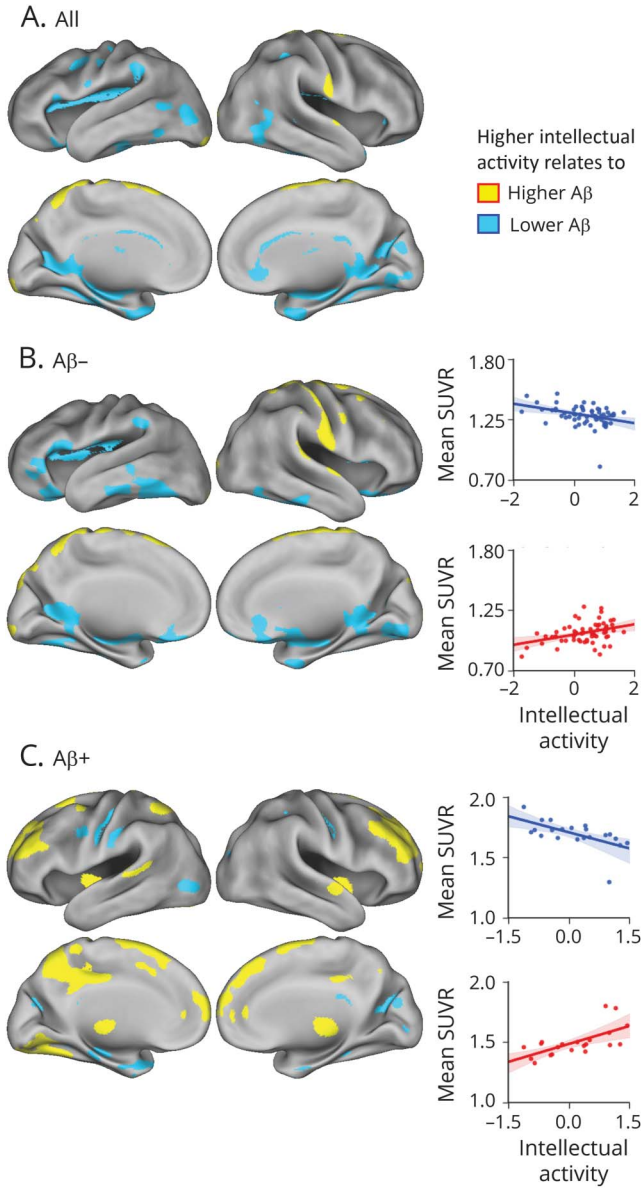
In the whole-brain voxel-wise analysis, we found regionally distinctive associations between intellectual activity and amyloid deposition across all older adults showing higher intellectual activity with lower amyloid deposition in inferior temporal and medial temporal lobes and left lateral frontal cortex but higher amyloid deposition in superior frontal and parietal cortex (figure 1A). In order to explore whether this relationship differs by amyloid positivity status, we additionally conducted a whole-brain voxel-wise analysis separately by group. Among Aβ− participants, a similar pattern of the relationship between intellectual activity and voxel-wise Aβ deposition was found (figure 1B). Among Aβ+ participants, however, intellectual activity was associated with higher Aβ deposition in the lateral and medial frontal cortex bilaterally and medial and lateral parietal cortex, while a level of Aβ deposition in medial temporal lobes and primary motor and sensory cortices decreased with higher intellectual activity (figure 1C). These results were unchanged when we added NP-memory scores as a covariate (figure e-1, links.lww.com/WNL/A39).

When we assessed the interaction effect between intellectual activity and amyloid positivity status on mean cortical standardized uptake value ratios (SUVRs) that constituted a global index of amyloid deposition, controlling for age and sex, we found a main effect of amyloid group ($F_{1,76} = 92.3$, $p < 0.001$), as expected, but neither main effect of intellectual activity ($F_{1,76} = 1.2$, $p = 0.3$) nor interaction between amyloid group and intellectual activity ($F = 3.14$, $p = 0.1$) (figure e-2, links.lww.com/WNL/A39).

Association between intellectual activity and gray matter volume

Across all older adults, we found increased GM volume with higher intellectual activity scores throughout the brain including posterior cingulate cortex, hippocampus, and lateral temporoparietal cortex, insular cortex, and primary sensory and motor cortex (figure 2A). In order to explore a differential relationship between intellectual activity and GM volume by amyloid positivity status, we assessed the relationship separately by amyloid group. Among Aβ− participants, a regional distribution of the intellectual activity and GM volume relationship was similar to that observed across all older adults (figure 2B). Within Aβ+ participants, however, an extent of the relationship between higher intellectual activity and increased GM volume was more regionally restricted (figure 2C).

Figure 1 Relationships between β-amyloid (Aβ) accumulation and intellectual activity

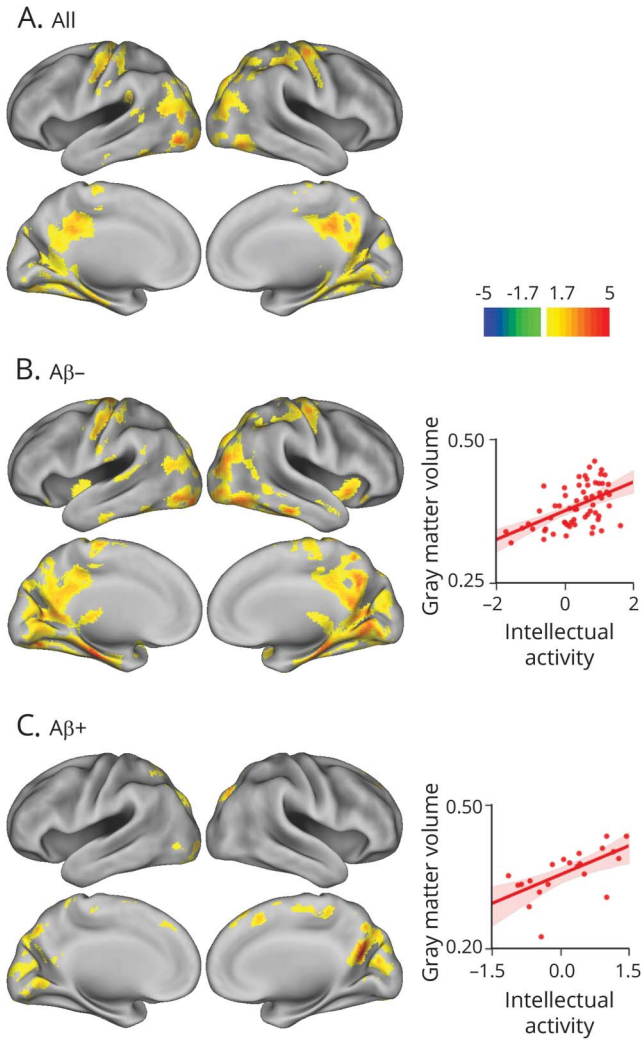


Brain regions demonstrating positive (warm-colored) and negative (cool-colored) relationships between amyloid accumulation and intellectual activity are overlaid on lateral and medial views of semi-inflated brain surfaces for all older adults (A), Aβ− older adults (B), and Aβ+ older adults (C). For Aβ− and Aβ+ old groups, upper (cool-colored) and lower (warm-colored) plots show the correlation between intellectual activity and mean standardized uptake value ratios (SUVRs) from regions showing negative (cool-colored) and positive (warm-colored) associations, respectively. Results are thresholded at $p < 0.05$ at cluster level with family-wise error correction and at $p < 0.05$ at voxel level (uncorrected).

Differential association between intellectual activity and task-switching brain activation as a function of amyloid positivity status

In order to examine brain activation differences in relation to intellectual activity, we used a task-switching paradigm during fMRI and determined brain regions that are task-positive and task-negative commonly across young and older participants.

Figure 2 Higher intellectual activity is associated with larger gray matter (GM) volume in cognitively normal older adults

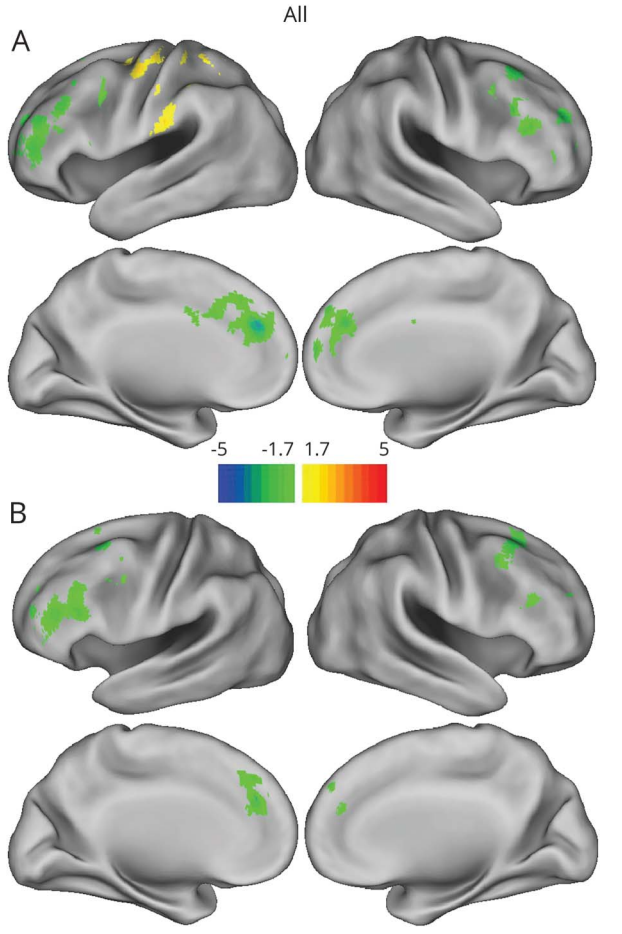


Brain regions demonstrating relationships between voxel-wise GM volume and intellectual activity are overlaid on lateral and medial views of semi-inflated brain surfaces for all older adults (A), β-amyloid (Aβ)− older adults (B), and Aβ+ older adults (C). Results are thresholded at $p < 0.05$ at cluster level with family-wise error correction and at $p < 0.05$ at voxel level (uncorrected). Warm and cool colors indicate GM volume increases and decreases in relation to intellectual activity. Plots show the correlation between intellectual activity and GM volume from regions showing a positive association (warm-colored regions) for each group. Scales represent *t* values.

Brain activation patterns were extracted from 3 activation comparisons: single-task vs baseline, dual-task vs baseline, and dual-task vs single-task conditions (for common activation patterns across all participants, see figure e-3, links.lww.com/WNL/A39). Using GLM, we regressed brain activation for each comparison to intellectual activity across all older participants, controlling for age and sex. For single-task condition, we found a relationship between higher intellectual activity and lower brain activation in lateral and medial frontal cortex, indicating less activation for equal performance, with a brain activation increase with higher intellectual activity in the primary motor cortex (figure 3A). For the dual-task condition, a similar pattern of association was found showing less activation in the lateral and medial frontal cortex (figure 3B). For brain activation difference between dual-task vs single-task conditions, which represents brain activation with increased executive control demand, no brain activation difference was found in association with intellectual activity.

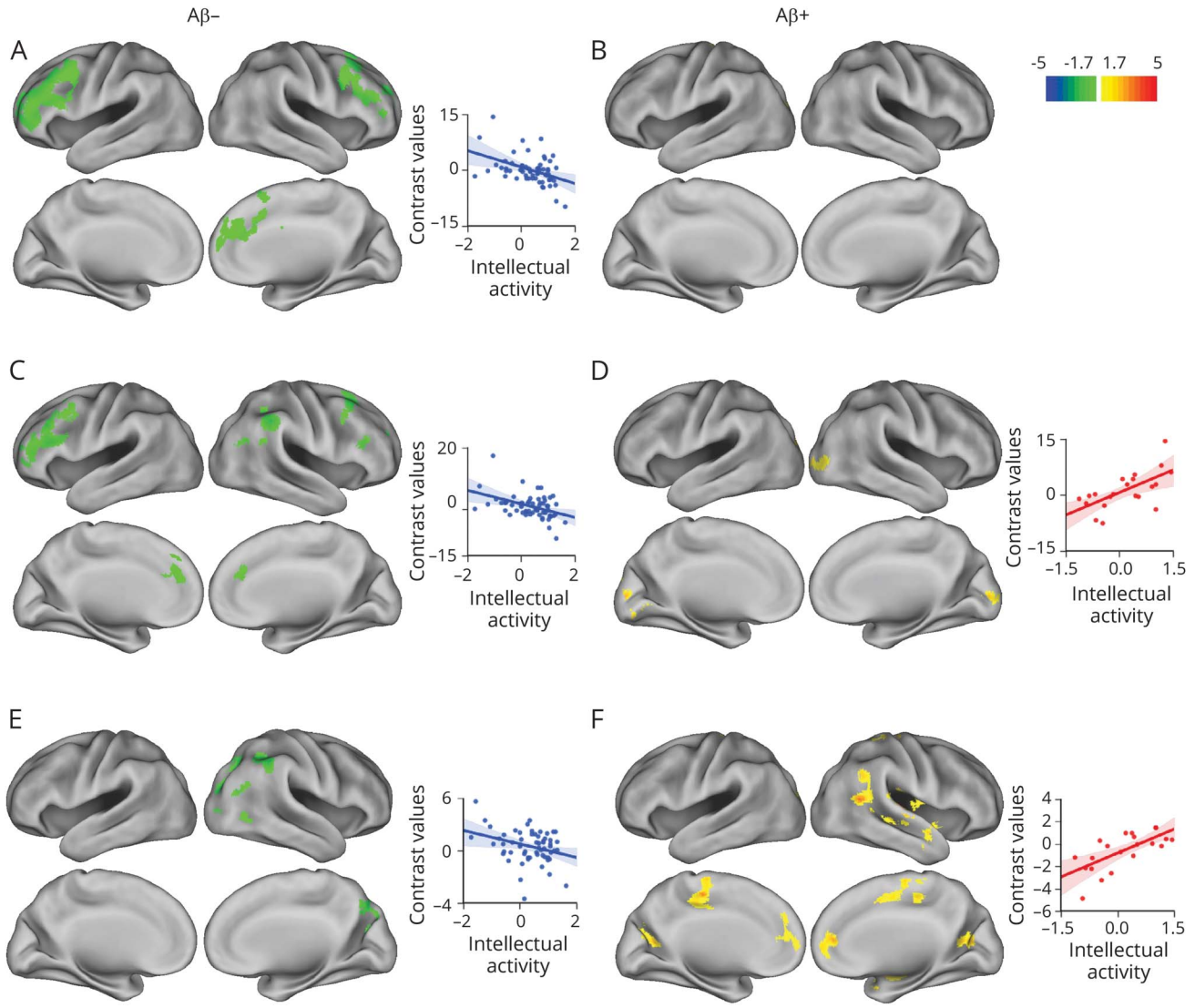
We further tested whether the brain activation patterns differ by amyloid positivity status. Among Aβ– participants, activation patterns in relation to intellectual activity were similarly found for both single-task and dual-task conditions (figure 4, A and C). In the dual-task and single-task activation

Figure 3 Task-evoked brain activation in association with intellectual activity across all older adults



Among all older adults, task-related increases and decreases in relation to intellectual activity are overlaid on lateral and medial views of semi-inflated brain surfaces for task conditions vs baseline comparisons (A, B), while no suprathreshold voxels were found for the dual-task vs single-task contrast (not shown). Results are thresholded at $p < 0.05$ at cluster level with family-wise error correction and at $p < 0.05$ at voxel level (uncorrected). Warm colors indicate activation increases in relation to intellectual activity in single and dual tasks compared to baseline (A, B). Cool colors indicate activation decreases in relation to intellectual activity in single and dual tasks compared to baseline (A, B). Scales represent *t* values.

Figure 4 Differential relationship between intellectual activity and task-evoked brain activation by amyloid positivity status



(A–F) Brain regions demonstrating task-related activation differences in relation to intellectual activity are overlaid on lateral and medial views of semi-inflated brain surfaces by amyloid group. Scatterplots visualize a relationship between intellectual activity and β values averaged across the suprathreshold voxels. Among β-amyloid (Aβ)− older adults, a degree of task-related increases was reduced with higher intellectual activity for single-task or dual-task conditions compared with baseline activity (A, C) and for a more cognitively strenuous condition (E; activation difference between dual-task and single-task conditions). Among Aβ+ older adults, only activation increases in relation to intellectual activity were found in the dual-task condition (D) and with increased task difficulty (F; activation difference between dual-task and single-task conditions). Results are thresholded at $p < 0.05$ at cluster level with family-wise error correction and at $p < 0.05$ at voxel level (uncorrected).

difference, a significant association of lower brain activation with higher intellectual activity was found in lateral and medial parietal cortex (figure 4E). Within Aβ+ participants, no significant suprathreshold regions were found during the single-task condition (figure 4B). In the dual-task condition, a significant relationship of higher intellectual activity and increased brain activation was found only in the visual cortex (figure 4D). An association of higher intellectual activity with increased brain activation was more pronounced in the dual-task vs single-task contrast in brain regions including lateral temporoparietal cortex, medial frontal cortex, and posterior cingulate/retrosplenial cortices, which mostly comprised task-negative regions (figure 4F). All results remained unchanged when we additionally covaried out behavioral performance (i.e., accuracy rate).

Discussion

In this study, we examined neural correlates of direct and modulatory effects of intellectual activity on the aging brain by assessing fibrillar Aβ pathology, GM atrophy, and task-evoked brain activation among cognitively normal older adults. Higher intellectual activity was mainly related to lower amyloid accumulation across the brain with some increased

amyloid deposition in selective brain regions among all older adults. Within Aβ+ adults, however, higher intellectual activity was associated with increased amyloid deposition in lateral and medial frontoparietal cortices. Greater intellectual activity was associated with larger GM volume regardless of amyloid positivity status. Furthermore, while higher intellectual activity was associated with less brain activation in frontoparietal cortices during executive control performance among Aβ− adults, Aβ+ adults showed increased brain activation in multiple areas. The directionality of voxel-wise association between intellectual activity and multiple imaging measures remained similar when we used education, instead of a composite measure of intellectual activity, although the regional extent was reduced (figures e-4–e-7, links.lww.com/WNL/A39). Our findings provide novel insights into associations between intellectual activity, amyloid level, and brain activation among cognitively normal older adults by examining these measures in the same study.

Brain aging is commonly associated with poorer cognitive performance, although significant individual differences exist.[13,14] Striking evidence of these individual differences is the discrepancy between the degree of clinical symptoms and the amount of neuropathology. The concept of CR has been proposed in order to explain this phenomenon.[1,3,4] The CR hypothesis emphasizes a modulatory role of lifetime exposures; higher CR, therefore, is related with (1) less cognitive decline and clinical severity in the given amount of neurodegeneration or pathology or (2) equated clinical severity accompanied by greater amount of AD pathology or neurodegeneration.[15–17] In contrast, brain maintenance explicates a direct effect of lifetime exposures on neuropathologic and neuromorphologic aspects of the brain.[4,18,19] Our results suggest that these conceptual frameworks are not mutually exclusive; instead, multiple pathways reflected in these conceptual frameworks may occur simultaneously, through different neural markers. This may explain, in part, inconsistent findings on the relationship between lifestyle variables and several neuropathologic and morphologic markers across studies.[3,9,20–22]

The present study complements previous studies while providing novel findings. Consistent with some studies,[9,20] we did not find any significant relationship between intellectual activity and a global Aβ index across all older participants. The whole brain voxel-wise approach, however, revealed a relationship of higher intellectual activity with lower amyloid deposition, which is consistent with other reports[22] and was more pronounced among Aβ− adults. These conflicting results using a global Aβ index vs whole brain voxel-wise analyses may stem from the fact that our mean cortical SUVRs are the averaged value encompassing much larger areas than brain regions showing a significant relationship between intellectual activity and voxel-wise Aβ. It is important to note that the different relationships as a function of amyloid positivity status are based on separate analyses by group and that we did not find any significant group by intellectual activity interaction on voxel-wise or mean cortical SUVR values.

Although the present study cannot address a causal relationship between intellectual activity and amyloid pathology as implied by the brain maintenance hypothesis, the present findings are in line with the possibility of a protective role of intellectual activity for amyloid accumulation, potentially via increased functional connectivity and increased neural plasticity markers.[18,23,24] Synaptic preservation reflected in increased functional connectivity is compromised with Aβ deposition, which may result in compensatory increases in regional neural activity that further lead to increased Aβ secretion. Brain regions showing decreased Aβ deposition with higher intellectual activity largely overlap with the language processing network that captures crystalized knowledge such as vocabulary and semantic processing.[25] In contrast, the relationship of higher intellectual activity and increased amyloid deposition seen in Aβ+ adults provides further support for the modulatory role of intellectual activity imparting reserve: individuals with higher CR could tolerate more amyloid burden and still meet entry criteria into the study. It is intriguing that higher intellectual activity in Aβ+ adults relates to higher Aβ deposition in particular in frontal and parietal cortical regions. Although speculative, findings of increased brain activation in these regions, possibly reflecting neural compensation or additional cognitive work, in presymptomatic familial AD[26] and *APOE4* carriers in young adulthood[27] may explain this regional specificity.

Our results also indicate that intellectual activity is associated with larger GM volume regardless of amyloid positivity status, while the magnitude of the beneficial effect is reduced with Aβ deposition. Larger GM volume in superior temporal gyrus and insular cortex with higher intellectual activity, in particular, among Aβ− adults has been reported in other studies.[23] Our results of larger GM volume with higher intellectual activity, however, are mostly in more posterior brain regions including medial temporal lobes, possibly reflecting better semantic processing. Our post hoc power analyses revealed that the regionally restricted pattern of association in Aβ+ adults was not due to a lack of power. Therefore, although speculative, a reduced beneficial effect of intellectual ability on GM volume among Aβ+ adults may be due to Aβ-related atrophy that might have been already occurring in these individuals.[28–32] Despite this reduced beneficial effect in Aβ+ adults, intellectual activity is, in overall, associated with greater GM volume, which may further serve as brain reserve in older age.[21,33]

One of the central motivations of the present study was to elucidate functional implementation of CR in the face of brain aging and Aβ deposition. As possible mechanisms, a recent model of CR proposes neural efficiency and neural compensation.[1] Neural efficiency refers to the reduced neural recruitment of brain regions implicated in a given

task with the same level of cognitive performance. Neural compensation refers to the recruitment of brain regions that are not typically implicated in accomplishing a given task, as shown in cognitive aging studies.[34–37] Our findings of decreases in activation in frontal and parietal cortices in relation to intellectual activity among Aβ−O adults support neural efficiency in brain regions that play a critical role in executive control function. Considering that older adults typically show increased brain activation compared with young adults, decreased brain activation with higher intellectual activity among these older adults may indicate that intellectual activity promotes more youth-like brain function among older adults.[4] On the other hand, increased activation in right retrosplenial cortex, posterior cingulate cortex, and medial frontal cortex, which constitute a part of the default mode network,[38] as a function of intellectual attainment in Aβ+ adults may reflect neural compensation for cognitive processes, such as retrieving a task rule or a stimulus-response mapping, that would help successful task switching in our fMRI paradigm. This interpretation is consistent with findings showing that Aβ-related hyperactivity reflects neural compensation that helps cognitive performance.[39]

Taken together, our results support the implementation of multiple pathways of reserve such that intellectual activity simultaneously exerts a neuroprotective role in brain aging and a mitigating role for cognitive change in the face of Aβ pathology. Potentially as a direct effect, intellectual activity is associated with lower Aβ deposition and larger GM volume in widespread regions among cognitively normal older adults, although a causal relationship cannot be tested in our cross-sectional data. As a modulatory effect, intellectual activity is associated with more efficient neural activity among older adults without Aβ deposition but compensatory activation increases among older adults with higher Aβ deposition. Among Aβ+ adults, intellectual activity is related to increased Aβ deposition, further reflecting its modulatory role. Our findings corroborate, in part, a recent proposal suggesting that the neuroprotective and compensatory pathways underlying the effect of intellectual activity might manifest as a gradient where protection occurs mainly early and compensation later as the disease progresses, while not in an exclusive manner.[40] Longitudinal assessment with a larger sample is warranted to elucidate how the multiple pathways of reserve play a role within an individual over time.

Author contributions

Hwamee Oh: study concept and design, drafting/revising the manuscript, analysis and interpretation of the data, accepts responsibility for conduct of research and final approval, statistical analysis. Qolamreza R. Razlighi: revising the manuscript, analysis of the data, accepts responsibility for conduct of research and final approval. Yaakov Stern: revising the manuscript, interpretation of data, accepts responsibility for conduct of research and final approval.

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Disclosure

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Multiple pathways of reserve simultaneously present in cognitively normal older adults

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Study question

How does intellectual activity exert neuroprotective or compensatory effects in cognitively normal older adults as measured by the morphology, function, and β-amyloid (Aβ) pathology of the brain?

Summary answer

During Aβ accumulation, intellectual activity exerts neuroprotective and compensatory effects by larger gray matter volume and increased brain activation that promote brain maintenance and normal cognition.

What is known and what this article adds

Intellectual activity may promote cognitive reserve or brain maintenance, although it remains unresolved whether and how this relates to Aβ deposition. This study provides evidence that both brain maintenance and cognitive reserve occur together and may help older adults with Aβ pathology remain cognitively normal.

Participants and setting

The study involved 82 cognitively normal older adults (ages 60–70 years) and 46 healthy young adults (ages 20–30 years).

Design, size, and duration

All participants underwent neuropsychological assessments for intellectual activity, fMRI scanning during a task-switching paradigm, and structural MRI scans. The older adults also underwent ^{18}F-florbetaben PET.

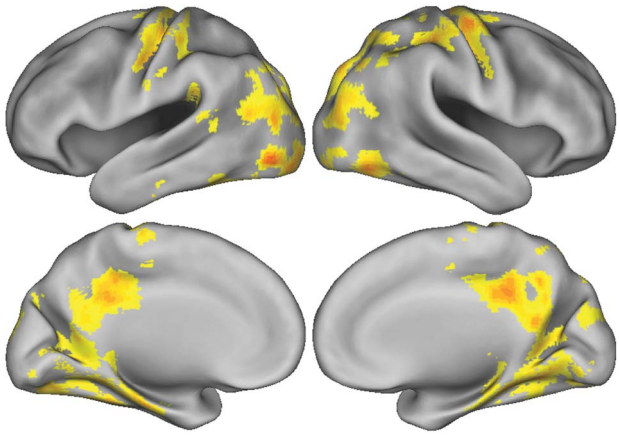
Primary outcomes

The primary outcomes were global and voxel-wise amyloid deposition, gray matter volume, and task-evoked brain activation measured by ^{18}F-florbetaben PET, MRI, and fMRI.

Main results and the role of chance

Among older participants, the amyloid-positive (n = 21) and amyloid-negative (n = 61) groups did not significantly differ in intellectual activity scores or fMRI task performance scores (p > 0.1 for all). In older adults, intellectual activity levels were associated with regionally distinctive amyloid deposition patterns and positively associated with gray matter volumes throughout the brain. During task-switching fMRI task, greater intellectual activity levels were mostly associated with decreased brain activation. Among older adults with Aβ deposition, however, greater intellectual activity levels were associated with increases in Aβ deposition and brain activation.

Figure Gray matter volumes and intellectual activity levels in older adults. Warm colors indicate positive associations between intellectual activity levels and gray matter volumes.



Bias, confounding, and other reasons for caution

This study could not establish causal relationships between intellectual activity and amyloid pathologies or regional brain activation patterns. Longitudinal cohort studies are necessary to examine how intellectual activity affects brain aging and amyloid pathology within individuals over time.

Generalizability to other populations

The study examined cognitively normal adults, so the results may not be generalizable to persons with cognitive abnormalities or neurologic disorders.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

