

Insula and Inferior Frontal Gyrus' Activities Protect Memory Performance Against Alzheimer's Disease Pathology in Old Age

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Abstract. Apolipoprotein E (APOE) $\epsilon 4$ carriers and patients with amnesic mild cognitive impairment (MCI) have high risk of developing Alzheimer's disease (AD). The Scaffolding Theory of Aging and Cognition proposes that recruitment of additional frontal brain regions can protect cognition against aging. This thesis has yet to be fully tested in older adults at high risk for AD. In the present study, 75 older participants (mean age: 74 years) were included. Applying a voxel-wise approach, fractional amplitude of low-frequency fluctuations (fALFF) in resting-state functional neuroimaging data were analyzed as a function of APOE $\epsilon 4$ status (carrier versus noncarrier) and clinical status (healthy control [HC] versus MCI) using a 2×2 analysis of covariance (ANCOVA). Measures of cognition and cerebrospinal fluid levels of amyloid- β were also obtained. Three frontal regions were identified with significant interaction effects using ANCOVA (corrected $p < 0.01$): left-insula, left-inferior frontal gyrus (IFG), and right-precentral gyrus. The HC/APOE $\epsilon 4$ carrier group had significantly higher fALFF in all three regions than other groups. In the entire sample, for two regions (left insula and left IFG), a significant positive relationship between amyloid- β and memory was only observed among individuals with low fALFF. Our results suggest higher activity in frontal regions may explain being cognitively normal among a subgroup of APOE $\epsilon 4$ carriers and protect against the negative impact of AD-associated pathology on memory. This is an observation with potential implications for AD therapeutics.

Keywords: Amyloid- β , apolipoprotein E $\epsilon 4$, frontal cortex, memory, mild cognitive impairment, resting state functional MRI

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INTRODUCTION

Apolipoprotein E (APOE) $\epsilon 4$ carriers and individuals with amnesic mild cognitive impairment (MCI) have greater Alzheimer's disease (AD) pathology than their genetically or cognitively normal counterparts [1–3], but do not necessarily convert to dementia [4, 5]. A recent postmortem study suggests a discrepancy between clinically defined AD and brain pathological alterations [6].

Factors explaining the discrepancy are mainly behavioral. For example, higher cognitive reserve, indexed by higher levels of education, or activity engagement, helps protect cognitive performance against AD pathology [7, 8]. While this may be so, the underlying neural mechanism linking reserve to cognitive protection is not clear. The Scaffolding Theory of Aging and Cognition (STAC) posits that cognitive protection against aging or neurodegeneration is regulated through compensatory neural reconfigurations that rely heavily on recruitment of frontal regions [9]. The STAC has been widely tested in the normal aging process [10–12], but relatively few in the context of AD-associated neurodegeneration among older adults at high risk for AD [13, 14], or understanding the frontal regions' role in AD pathology, such as amyloid deposition [15].

The fractional amplitude of low-frequency fluctuations (fALFF) measures the power within a specific frequency range (0.01–0.08 Hz) divided by the total power in the entire detectable frequency range (0.009–0.25 Hz) of resting-state functional magnetic resonance imaging (rs-fMRI), reflecting selective brain regions' oscillatory activity [16]. fALFF is considered a sensitive index for detecting AD-associated neurodegeneration, such that MCI and AD patients have lower fALFF in multiple frontal brain regions [17, 18].

In the present study, we hypothesize that the activity of frontal circuits, indexed by relevant areas' fALFF, is critical in explaining the differential associations between AD pathology and cognition across older adults with high risk for AD. Two steps were conducted to test the hypothesis: first, we used a voxel-wise approach and employed a 2 (APOE $\epsilon 4$ status) \times 2 (clinical status) analysis of covariance (ANCOVA) to identify relevant frontal regions; and second, we examined whether fALFF in these regions would explain the differential associations between cognitive function (i.e., memory and executive function) and AD pathology (i.e., cerebrospinal fluid levels of amyloid- β and tau).

MATERIALS AND METHODS

ADNI data

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see <http://www.adni-info.org>.

Participants

The present study used data obtained in April 2015 from ADNI-GO and ADNI-2. Our sample included 75 adults aged 60 to 90 and who have rs-fMRI data with the same scanning parameters (details in *Rs-fMRI data acquisition and preprocessing* section), and compatible cognitive and AD pathology data (see Table 1 for the sample characteristics). The diagnosis of amnesic MCI was made by a psychiatrist or neurologist at each study site and reviewed by a Central Review Committee. Diagnoses were based on subjective memory complaints and performance on neurocognitive testing, including the Logical Memory II subscale of the Wechsler Memory Scale-Revised (score ≤ 8 , cut-off adjusted for education level), the Mini-Mental State Examination (MMSE; score 24–30), and the Clinical Dementia Rating (global score = 0.5). These subjects did not meet the NINCDS-ADRDA criteria for AD. The APOE $\epsilon 4$ positive classification was defined as having at least one APOE $\epsilon 4$ allele (by analyzing blood sample at the National Cell Repository for AD).

Measures

Memory and executive function were measured using two composite scores [19, 20]. The composite memory index was based on the memory-related domains of the MMSE, Alzheimer's Disease Assessment Scale-Cognition subscale, Rey Auditory Verbal Learning Test, and Logical Memory test. The composite executive function index was based on the Wechsler Memory Scale- Revised Digit Span Test,

Table 1
Baseline sample characteristics (n = 75)

	Diagnostic status			APOE ϵ 4 status		
	HC N = 26	MCI N = 49	t or χ^2 value, df, (p)	APOE ϵ 4 (-) N = 43	APOE ϵ 4 (+) N = 32	t or χ^2 value, df, (p)
APOE ϵ 4 (+), n (%)	10 (38.5)	22 (44.9)	0.28, 1 (0.59)	–	–	–
Age	75.19 (5.79)	73.82 (6.61)	0.89, 73 (0.37)	75.37 (6.89)	72.84 (5.25)	1.73, 73 (0.087)
Male, n (%)	10 (38.5)	30 (61.2)	3.54, 1 (0.060)	23 (53.5)	17 (53.1)	0.001, 1 (0.98)
White, n (%)	24 (92.3)	47 (95.9)	2.65, 1 (0.45)	40 (93.0)	31 (96.9)	1.56, 1 (0.67)
Years of education	16.12 (2.03)	15.94 (2.56)	0.30, 73 (0.76)	15.49 (2.20)	16.69 (2.47)	-2.22, 73 (0.03)
Amyloid- β	190.43 (57.34)	174.41 (56.69)	1.08, 65 (0.28)	202.98 (50.36)	149.13 (50.96)	4.31, 65 (<0.001)
Tau	72.17 (40.70)	92.70 (59.39)	-1.40, 61 (0.17)	66.15 (37.37)	114.69 (62.96)	-3.83, 61 (<0.001)
Memory	0.77 (0.44)	0.16 (0.44)	5.74, 73 (<0.001)	0.39 (0.55)	0.35 (0.49)	0.37, 73 (0.71)
Executive function	0.70 (0.61)	0.21 (0.78)	2.79, 73 (0.007)	15.49 (2.20)	16.69 (2.47)	-0.04, 73 (0.97)

Comparing the diagnostic and APOE ϵ 4 status between HC and MCI group. Independent t or χ^2 tests were used to determine the difference in demographic and health characteristics between subgroups.

Digit Span Backwards, Category Fluency, Trails A and B, and the Clock Drawing Test. Lower values in these composite scores indicated worse cognitive performance. Amyloid- β and tau in cerebrospinal fluid aliquots was analyzed using the multiplex xMAP Luminex platform (Luminex Corp., Austin, TX, USA) with immunoassay kit-based reagents (assay lot # 157353 and calibrator lot # 157379 INNO-BIA AlzBio3; Innogenetics, Ghent, Belgium). Demographic information, including age, sex, and years of formal education were obtained through interview during screening.

rs-fMRI data acquisition and preprocessing

The rs-fMRI data were collected on a 3T Philips MRI using an echo-planar imaging sequence (TR = 3000 ms, TE = 30 ms, slice thickness = 3.3 mm, matrix = 64 × 64, spatial resolution = 3 × 3 × 3 mm³, number of volumes = 140, number of slices = 48). Pre-processing was conducted using the Data Processing Assistant for Resting-State fMRI (DPARSF) based on SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) [21]. The first 10 volumes of each participant were excluded to avoid potential noise related to initial equilibration of the scanner and participant's adaptation to the scanning environment. The remaining 130 volumes were included in the slice timing correction, motion correction, normalization and Gaussian spatial smoothing (FWHM = 4 mm).

fALFF analysis

After preprocessing in DPARSF, the linear trend was removed, and fALFF analysis was conducted using Resting-State fMRI Data Analysis Toolkit

(REST, <http://www.restfmri.net>) [22]. For each voxel, the time course of the BOLD signal was converted to the frequency domain using the Fast Fourier Transform. Then the square root of the power spectrum was calculated and averaged across 0.01–0.08 Hz at each voxel. The fALFF was obtained using the ratio of power spectrum in a given frequency band (0.01–0.08 Hz) to the total power in the entire detectable frequency range (0.009–0.25 Hz) [16]. To reduce the global effects across participants, the fALFF value of each voxel was divided by the global mean value [16, 23].

To examine the interaction between diagnostic (MCI versus HC) and APOE ϵ 4 status (carrier versus noncarrier), a two-way ANCOVA analysis was conducted on the individual fALFF map in a whole-brain voxel-wise way controlling for age. A threshold of corrected $p < 0.01$ (synthesizing uncorrected individual $p < 0.005$ and cluster size > 216 mm³) was applied to all statistical maps. Correction for multiple comparisons was performed within the whole brain mask and determined by Monte Carlo simulations using the Analysis of Functional NeuroImages AlphaSim program (<http://afni.nih.gov/afni/docpdf/AlphaSim.pdf>) [24].

Additionally, we also calculated the functional connectivity based on the frontal brain regions found in fALFF analysis. The functional connectivity was calculated as the temporal correlation of the BOLD signal in different brain regions using the REST software.

Of note, for both fALFF and functional connectivity analyses, the following nuisance covariates were regressed out to exclude non-neuronal signals: six head motion parameters, white matter signal, and cerebrospinal fluid signal.

Other data analyses

Independent t or χ^2 tests were used to determine the difference in demographic and health characteristics between subgroups based on the categorization of diagnostic status or APOE status. As described in the *Rs-fMRI data* section, the frontal regions were determined using ANCOVA. After identifying the frontal regions, to examine the main and interaction effects of each involved region and AD pathology on cognition as the entire sample or within certain sample characteristics, a Generalized Linear Model (GLM) was used controlling for relevant covariates. This model involved a normally distributed outcome and identity link with each region's activity and amyloid deposition (and their interaction) as the main factors of interest. Region's activity here refers to relevant fALFF or functional connectivity. Exploratory analysis of the correlation between AD pathology and cognition within different levels of region activity involved Pearson correlations. The False discovery rate (FDR) was controlled at a q level of 0.05 when multiple brain regions were involved in the comparison.

RESULTS

fALFF in frontal regions responsive to both clinical and APOE ϵ 4 status

In the 2 (APOE ϵ 4 status) \times 2 (clinical status) ANCOVA controlling for age in a whole-brain voxel-wise way (AlphaSim: $p < 0.005$, cluster $> 216 \text{ mm}^3$, corrected $p < 0.01$), four brain regions were identified as having significantly different fALFF levels across groups. These included three frontal regions (Left [L]-insula, L-inferior frontal gyrus [IFG], Right [R]-precentral gyrus [PG]) and one posterior region (R-superior parietal lobe [SPL]) (see Fig. 1). Subsequent analyses focused on the three frontal regions. The HC/APOE ϵ 4(+) group had significantly higher fALFF in the L-insula ($F = 29.28$, $df_1 = 1$, $df_2 = 75$, $q < 0.001$) and R-PG ($F = 28.78$, $df_1 = 1$, $df_2 = 75$, $q < 0.001$) than all other groups, and higher fALFF in the L-IFG ($F = 25.86$, $df_1 = 1$, $df_2 = 75$, $q < 0.001$) than HC/APOE ϵ 4(-) and MCI/APOE ϵ 4(+) groups.

Of note, fALFF values in the three frontal regions were not associated with age, sex, education, amyloid- β , tau, or cognitive performance after examining Pearson or Spearman correlations with FDR-correction (data not shown).

The effect of AD pathology on cognitive performance modified by fALFF in frontal regions

We next fit GLM (with normal outcome and identity link) examining the main effect and interaction between the fALFF in frontal regions and AD pathology as independent variables, for the dependent variable of cognitive performance. For each region, fALFF was coded as high versus low using a median split. The L-insula (Wald $\chi^2 = 5.43$, $p = 0.020$) and L-IFG (Wald $\chi^2 = 6.03$, $p = 0.014$) showed an interaction with amyloid- β with respect to memory, in a model containing main effects of brain regions and AD pathology, as well as age, sex, education, APOE ϵ 4, and clinical status (see Table 2). Further, there was a significant positive relationship between amyloid- β and memory among individuals with low levels of fALFF in the L-insula ($r = 0.41$, $p = 0.014$) or L-IFG ($r = 0.34$, $p = 0.047$), but not among those with high levels of fALFF (see Fig. 2).

Additionally, the functional connectivity between L-insula and L-IFG was calculated, and divided into high versus low levels using a median split. A similar interaction effect was found between the connectivity and amyloid- β on memory with the same sets of covariates ($B = -0.006$, $SE = 0.002$, Wald $\chi^2 = 12.92$, $p < 0.001$). There was also a positive correlation between amyloid- β and memory but only among individuals with low connectivity ($r = 0.37$, $p = 0.036$), not among those with high connectivity.

We did not find an interaction effect of any of the three brain regions with amyloid- β on executive functioning (all FDR-corrected $p > 0.05$).

Secondary subgroup analysis for the interaction between fALFF in frontal regions and the effect of amyloid- β on memory

We repeated the GLM analysis for the L-insula, L-IFG, and their functional connectivity by factors that were controlled in the main analysis (age, sex, education, APOE ϵ 4, and clinical status). We did not adjust for multiple comparisons for the secondary analysis, as it was intended to be exploratory and hypothesis generating. To control for the potential difference in age, sex, and education, these factors were controlled when examining APOE ϵ 4 and clinical status. The significant interaction effect was more evident if a subject was a young (< 75 years) female APOE non-carrier in the HC group with higher levels of education (> 16 years) (see Table 3).

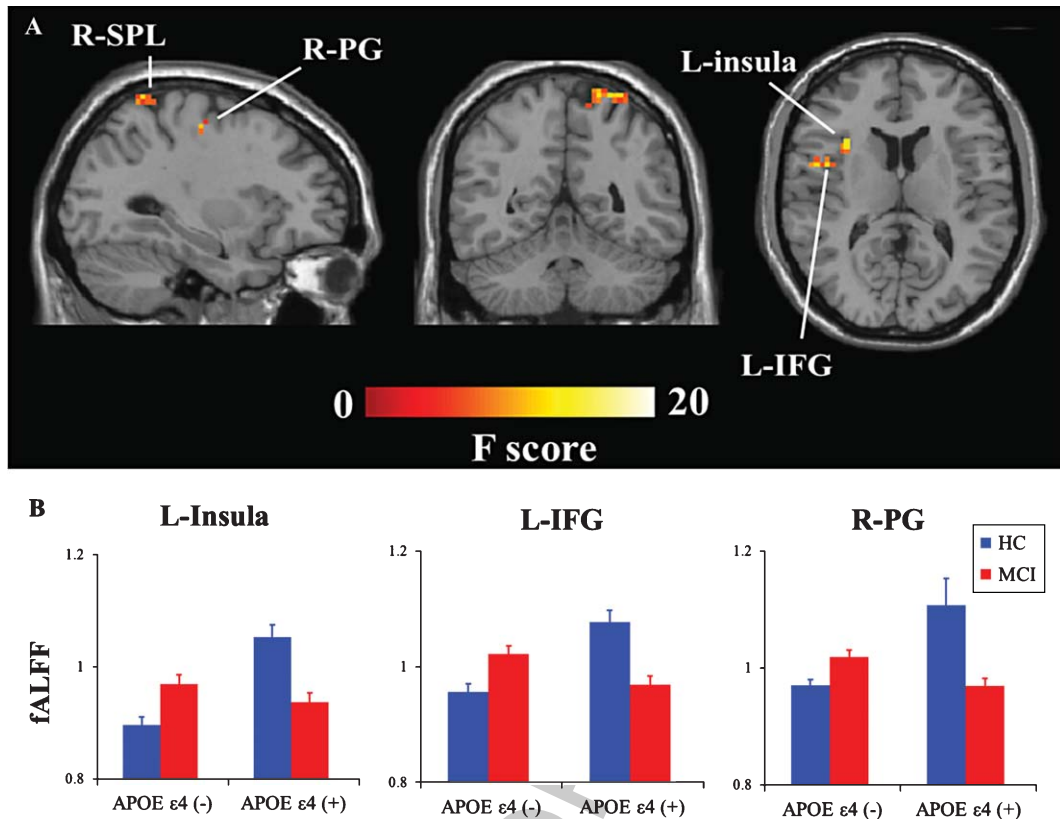


Fig. 1. Interaction between diagnostic status (MCI versus HC) and APOE status (APOEε4+ versus -) in fALFF. A) The active regions were obtained by using two-way ANCOVA analysis in a voxel-wise way controlling for age, with individual $p < 0.005$ and cluster size $> 216 \text{ mm}^3$ (corrected $p < 0.01$, Alphasim correction). B) The average ALFF values extracted from the three regions (the L-insula, L-IFG, and R-PG) were different between HC (blue) and MCI (red) patients in APOEε4+ and APOEε4- group, separately. IFG, inferior frontal gyrus; PG, precentral gyrus; SPL, superior parietal lobe; L, left; R, right.

Table 2
Generalized linear model of effects of amyloid-β and brain function on memory

	Amyloid-β		Brain Region [#]		Amyloid-β × Brain Region [#]	
	B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula	0.003 (0.002)	4.25 (0.039) [^]	0.70 (0.35)	3.93 (0.048)	-0.004 (0.002)	5.43 (0.020) [^]
L-IFG	0.003 (0.002)	4.07 (0.044)	0.85 (0.35)	5.76 (0.016) [^]	-0.005 (0.002)	6.03 (0.014) [^]
R-PG	0.001 (0.002)	1.82 (0.18)	0.26 (0.37)	0.46 (0.50)	-0.001 (0.002)	0.52 (0.47)

Controlled for age, sex, education, clinical status, and APOE ε4 status. [#]lower level as reference; [^]significant level remained after FDR-correction.

DISCUSSION

The present study tested the STAC model in a group of older adults at high risk for AD. There are two main findings: first, higher activity within three frontal regions (the L-insula, L-IFG, and R-PG) differentiated the HC/APOEε4(+) group from other groups; second, higher activity and stronger functional connectivity seen in the L-insula and L-IFG might reduce the impact of amyloid-β on memory in older adults. Additionally, this effect was particularly evi-

dent in those who were in the HC group, APOEε4 non-carriers, relatively younger (<75 years), female, and had higher levels of education (≥ 16 years). Our findings further one of the central hypotheses of the STAC regarding the protective role that recruitment of frontal regions appears to play against AD pathology.

We found that higher fALFF in the insula and IFG occurred in the group with genetic risk of AD but who also showed cognitively intact status (HC/APOEε4(+)), relative to other groups. Fur-

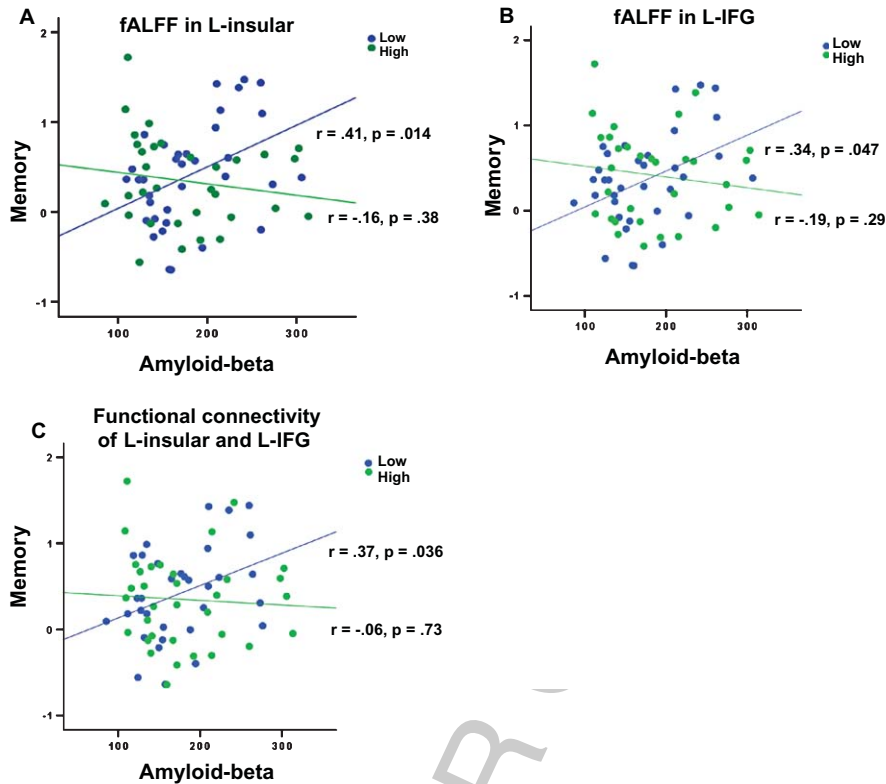


Fig. 2. The interaction between brain function (fALFF in L-insular (A), fALFF in L-IFG (B), and functional connectivity between L-insular and L-IFG (C)) and amyloid- β on memory. The fALFF and functional connectivity was subdivided into high versus low groups using the median value, respectively. The results were adjusted for age, sex, education, APOE ϵ 4, and clinical status.

thermore, regardless of clinical, APOE ϵ 4 status, or demographic characteristics, the significant effect of amyloid- β deposition on memory was only found among individuals with low fALFF or functional connectivity of the insula and IFG. These two lines of findings suggest that greater activation or additional recruitment of frontal regions may provide protection against the neural challenges arising from AD pathology (genetic risk or amyloid- β deposition, which are highly correlated). There is a known positive link between cerebrospinal fluid amyloid- β deposition and memory performance in AD-related neurodegeneration [15, 25]. Noticeably, executive functioning was not affected in the process although frontal regions, in general, are known to attend the regulation. A potential explanation may be further validated; that is, APOE ϵ 4 that was used in brain region identification was AD-neurodegeneration related. Executive functioning is known to be more relevant to other genetic risk, such as TOMM40 [26].

An expansion of the STAC model might consider how the insula or IFG may counteract amyloid-

β deposition. This might result through multiple pathways. The IFG is known to participate in the maintenance of memory [27, 28]. In a recent longitudinal study, older adults with more IFG activity tended to succeed in the memory task regardless of brain volume or white matter integrity [29]. In parallel, the insula is known to direct the regulation of cerebral circulation, which in turn helps with the maintenance of memory [30]. It is also noteworthy that the left lateral aspect of the frontal regions seemed to be more relevant for neural protection. Previous studies found neural disruptions of both regions to be pronounced in the right side in AD-associated neurodegeneration [31, 32], suggesting that the recruitment of homologous regions in the contralateral (left) hemisphere may act as a compensatory mechanism [33, 34].

Although the protective effect of the IFG and the insula was found among older adults across various clinical and APOE ϵ 4 statuses, the effect seemed more robust in females who were healthier, younger, and more educated. Of note, we did not find a direct relationship between the function of frontal regions and

Table 3
Subgroup analysis of generalized linear model of effects of amyloid-β and brain function[#] on memory

<i>Clinical status (controlled for age, sex, and education)</i>		HC (n = 26)		MCI (n = 49)	
		B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula		-0.01 (0.003)	11.95 (0.001)	-0.002 (0.002)	0.95 (0.33)
L-IFG		-0.01 (0.003)	10.81 (0.001)	-0.003 (0.002)	0.83 (0.36)
Connectivity		-0.006 (0.003)	4.04 (0.044)	-0.005 (0.002)	8.61 (0.003)
<i>APOE ε4 status (controlled for age, sex, and education)</i>		Carrier (n = 43)		Noncarrier (n = 32)	
		B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula		0.001 (0.006)	0.03 (0.87)	-0.005 (0.003)	2.42 (0.12)
L-IFG		0.007 (0.007)	0.92 (0.34)	-0.007 (0.004)	4.62 (0.032)
Connectivity		-0.002 (0.004)	0.29 (0.59)	-0.003 (0.004)	0.68 (0.41)
<i>Age</i>		<75 years (n = 38)		≥75 years (n = 37)	
		B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula		-0.009 (0.002)	15.32 (<0.001)	-0.003 (0.004)	0.68 (0.41)
L-IFG		-0.006 (0.003)	6.04 (0.014)	-0.004 (0.004)	1.34 (0.25)
Connectivity		-0.005 (0.003)	3.91 (0.048)	-0.002 (0.004)	0.29 (0.59)
<i>Sex</i>		Male (n = 40)		Female (n = 35)	
		B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula		-0.005 (0.003)	3.05 (0.081)	-0.005 (0.003)	2.72 (0.099)
L-IFG		-0.002 (0.003)	0.23 (0.63)	-0.009 (0.003)	10.86 (0.001)
Connectivity		-0.005 (0.003)	2.36 (0.12)	-0.006 (0.003)	4.28 (0.039)
<i>Years of Education</i>		<16 years (n = 23)		≥16 years (n = 52)	
		B (SE)	Wald χ^2 (p)	B (SE)	Wald χ^2 (p)
L-insula		-0.006 (0.004)	2.70 (0.10)	-0.005 (0.003)	3.37 (0.066)
L-IFG		-0.004 (0.004)	0.92 (0.34)	-0.005 (0.003)	3.43 (0.064)
Connectivity		-0.005 (0.004)	2.04 (0.15)	-0.006 (0.003)	4.02 (0.045)

Controlled for amyloid-β and relevant brain region's main effect. [#]lower level as reference.

demographic and health characteristics. The more efficient protection of the IFG and insula among those displaying better health, more education, relatively less advanced age, and who are women may be due to various mechanisms. For example, there may be a nonlinear relationship between age and amyloid-β deposition such that in individuals 70 years and older (especially in APOEε4 carriers) a steeper increase in amyloid-β deposition might be expected. This could, in turn, make it difficult for frontal regions to achieve their compensatory role [35, 36]. Additionally, even among individuals without evident amyloid pathology, APOEε4 carriers still tend to have more neural functional disruption related to memory than noncarriers [37]. Also, the cognitive reserve that is typically found in those with higher levels of education may interact with this process [38]. However, such findings need to be interpreted cautiously due to the relatively small sample size of the subgroups, and these proposed mechanisms will clearly require further direct testing.

Additionally, our findings of similarly low levels of fALFF in frontal regions in both the HC/APOEε4(-) and the MCI/APOEε4(+) groups, relative to the other two groups, are intriguing and perhaps could be considered counterintuitive. However, a key feature of successful aging is, *prima facie*, the absence of age-related pathology. As such, one might well predict relatively minimal additional frontal brain activation in the healthy normal brain [39], as observed here in the HC/APOEε4(-) group. On the other hand, in the group with both genetic and clinical predisposition (i.e., MCI/APOEε4[+]), one would expect accelerated amyloid-β deposition, which could in turn lead to premature interruption of the recruitment of compensatory frontal processes, consistent with the relatively low frontal activation patterns observed here [36]. Along with the subgroup analysis of clinical status in the compensatory frontal processes, these findings together suggests that the compensatory frontal mechanism may be more effective in the very early stage of neurodegeneration-those

with genetic risk but being cognitively intact. Therefore, compensation may be a strategy worthwhile for emphasis in maintaining cognitively healthy aging against genetic risk for AD.

Several limitations need to be acknowledged. First, although the literature has consistently identified patients with MCI or AD as having low fALFF values in frontal regions, a clinically meaningful cut-off score for fALFF values is not available. For the present analysis, we used the median score from the sample, which may not be applicable to samples with other demographic characteristics. Second, due to the nature of a dementia study, we have a relatively high prevalence of APOE ϵ 4(+) (42.7%) compared to the general population with similar ancestry characteristics [40]. This may affect the generalization of the conclusion. Third, the relatively small sample size in the secondary subgroup analysis clearly limits interpretation of these findings, which are solely intended to generate avenues for follow-up work and will require further validation. Finally, fALFF and functional connectivity of the frontal regions may relate to other variables that may positively impact cognitive performance but were not measured in the present study.

In conclusion, frontal regions play a critical role in protecting against the negative impact of neurodegeneration among people at risk for AD. The left insula and IFG may be particularly important in the maintenance of memory performance in the face of AD-related pathology, at least in the very early stage. Future studies should focus on the development of relevant modification strategies to enhance compensatory scaffolding and ultimately cognitive function.

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Informed consent was obtained from all individual participants originally enrolled in the ADNI study. The present study did not contain any direct involvement of identifiable human participants.

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