

RESEARCH ARTICLE

A quadratic function of activation in individuals at risk of Alzheimer's disease

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Systematic review: The authors reviewed the literature.

Abstract

Introduction: Brain activation is hypothesized to form an inverse U-shape in prodromal Alzheimer's disease (AD), with hyperactivation in the early phase, followed by hypoactivation.

Methods: Using task-related functional magnetic resonance imaging (fMRI), we tested the inverse U-shape hypothesis with polynomial regressions and between-group comparisons in individuals with subjective cognitive decline plus (SCD⁺; smaller hippocampal volumes compared to a group of healthy controls without SCD and/or apolipoprotein E [APOE] ϵ 4 allele) or mild cognitive impairment (MCI).

Results: A quadratic function modeled the relationship between proxies of disease severity (neurodegeneration, memory performance) and left superior parietal activation. Linear negative functions modeled the relationship between neurodegeneration and left hippocampal/right inferior temporal activation. Group comparison indicated presence of hyperactivation in SCD⁺ and hypoactivation in MCI in the left superior parietal lobule, relative to healthy controls.

Discussion: These findings support the presence of an inverse U-shape model of activation and suggest that hyperactivation might represent a biomarker of the early AD stages.

KEYWORDS

Alzheimer's disease, associative memory, functional magnetic resonance imaging, hyperactivation, mild cognitive impairment, subjective cognitive decline

1 | INTRODUCTION

There has been growing interest in hyperactivation as an early signature of Alzheimer's disease (AD). This interest stems from the observation of higher task-related functional magnetic resonance imaging (fMRI) activation in individuals with mild cognitive impairment (MCI)

than in cognitively healthy controls (HC).¹⁻⁶ This contrasts the observation of lower level of activation, or hypoactivation, in individuals with dementia or in the late stage of MCI.⁷⁻⁹ Thus, the relationship between disease progression and brain activation in the continuum of AD appears to take the form of an inverse U-shape function, with an increase in activation early in the prodromal phase followed by

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hypoactivation as patients progress toward dementia.¹⁰ This suggests that hyperactivation may be an excellent candidate for an early signature of AD, although critical issues must be resolved.

An important question is whether activation with disease progression follows an inverse U-shape as this hypothesis has never been directly assessed with statistical modeling in a single group of individuals at risk of AD. This information would contribute to identifying the time point at which hyperactivation occurs and thus provide important information for early diagnosis. We used polynomial regressions in a group of individuals with either subjective cognitive decline plus (SCD⁺)^{11,12} or MCI to test whether a quadratic function models the relationship between proxies of disease severity and task-related brain activation. Individuals with SCD⁺ had reduced hippocampal volumes and/or an apolipoprotein E (APOE) $\epsilon 4$ allele, which are biomarkers that increase the likelihood of preclinical AD.^{12,13}

Another question is whether hyperactivation is present prior to the MCI phase. Group comparisons were used to assess the magnitude of activation during an associative memory task, which was dependent on regions that are sensitive to AD.^{14,15} The two clinical groups were assessed separately, in comparison to HC, to determine whether hyperactivation is present in individuals with SCD⁺ only, prior to the MCI phase.

2 | MATERIALS AND METHODS

2.1 | Participants

The study included data from the Consortium for the Early Identification of Alzheimer's disease-Quebec cohort (CIMA-Q <http://www.cima-q.ca/en/home/>).¹⁶ The main objective of CIMA-Q is to characterize a longitudinal observational cohort consisting of more than 350 community-dwelling older adults recruited via advertisements, electronic media, and memory clinics from three Canadian cities (Montreal, Sherbrooke, and Quebec City). Participants were either: (1) cognitively healthy, (2) exhibiting SCD, (3) suffering from MCI, or (4) diagnosed with dementia due to probable AD. CIMA-Q collects clinical, cognitive, biological, radiological, and pathological data from these participants to: (1) establish an early diagnosis of AD, (2) provide a well-characterized cohort to the scientific community, (3) identify new therapeutic targets to prevent or slow cognitive decline and AD, and (4) support new clinical studies on these targets. For this study, 108 CIMA-Q participants were included, who completed the fMRI memory examination at baseline.

This study was approved by the CIMA-Q scientific committee and the *Comité mixte d'éthique de la recherche vieillissement-neuroimagerie* of the *Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal*, and all participants provided written informed consent to participate in the study.

Clinical diagnoses were made by expert consensus based on current clinical criteria. The criteria for SCD were based on the Subjective Cognitive Decline Initiative.^{11,12} Study participants: (1) expressed memory complaints and worries, (2) had normal education-adjusted scores on

HIGHLIGHTS

- A quadratic function described left parietal activation in a group at risk of Alzheimer's disease.
- Linear models rather described hippocampal and temporal activation.
- We found hyperactivation in individuals with subjective cognitive decline plus and hypoactivation in mild cognitive impairment relative to controls.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional scientific sources (eg, PubMed). It is proposed that increased activation, or hyperactivation, characterizes the early phase of Alzheimer's disease (AD), before diminishing in later stages (ie, hypoactivation). However, this inverse U-shape of activation remains to be statistically described in individuals at risk of AD.
2. Interpretation: A quadratic function best described the trajectory of brain activation in individuals with subjective cognitive decline plus (SCD⁺) and mild cognitive impairment (MCI), with hyperactivation in individuals with SCD⁺ and hypoactivation in people with MCI.
3. Future directions: Our findings provide empirical evidence for hyperactivation as a potential biomarker to detect individuals at risk of AD prior to the onset of objective cognitive symptoms. Future prospective and multimodal studies are required to determine the value of hyperactivation as a predictor of cognitive decline and better understand its role in the pathological cascade of AD.

the Logical Memory subtest of the Wechsler Memory Scale (WMS;¹⁷ score of ≥ 3 for 0 to 7 years of education, ≥ 5 for 8 to 15 years, and ≥ 9 for 16 or more years), (3) had scores of >26 on the Montreal Cognitive Assessment (MoCA),¹⁸ and (4) had a score of 0 on the Clinical Dementia Rating Scale (CDR).¹⁹ The SCD⁺ classification relied on the SCD⁺ criteria published in 2014,¹¹ which proposes to include APOE $\epsilon 4$ genotyping and/or biomarker evidence to increase the likelihood of preclinical AD. Participants met study criteria for SCD⁺ if they had smaller left or right hippocampal volumes (defined as one standard deviation below the mean of study HC without memory complaint, corrected for intracranial volume) and/or carried at least one APOE $\epsilon 4$ allele. Individuals with SCD that did not meet criteria for SCD⁺ ($N = 33$) were integrated into the HC group. Criteria for MCI were based on recommendations from the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA).²⁰ Participants met criteria for MCI if they:

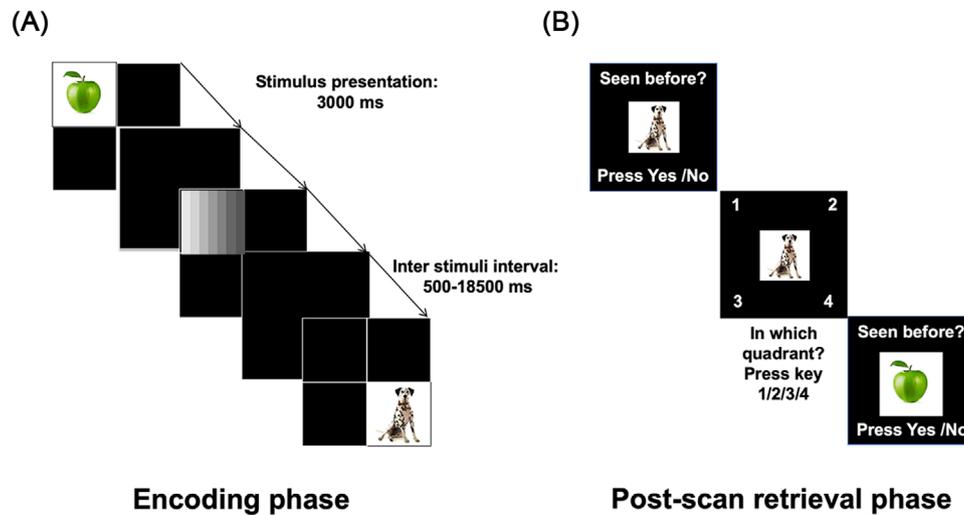


FIGURE 1 Functional magnetic resonance imaging memory task. A, In the encoding phase, target items consisted of pictures of common objects positioned in one of four quadrants and interspersed with gray squares (control stimuli). B, In the retrieval phase, 78 previously studied pictures and 39 new items were presented. Participants indicated whether the items were previously seen in the encoding phase, and were asked to remember their location

(1) expressed complaints about their memory, (2) showed objective memory impairment based the Logical Memory score (≥ 2 for 0 to 7 years of education, ≥ 4 for 8 to 15 years, and ≥ 8 for 16 or more years), (3) had a score between 20 and 25 on the MoCA, and (4) had a CDR score of 0.5. HC performed within normal ranges on clinical tests (see above for SCD), did not meet criteria for MCI or study criteria for SCD⁺, and were APOE $\epsilon 4$ negative. All participants met safety criteria for an MRI study and were right-handed. Fasting blood sampling was conducted to determine APOE genotype.

Participants were included if they were age 65 and over, lived in the community or residence of an independent person; had a score of 17 or higher on the telephone-Mini-Mental State Examination (T-MMSE);²¹ were able to understand, read, and write in either French or English; had sufficient auditory and visual acuity to participate in a neuropsychological assessment; and were willing to answer health-related questionnaires, undergo a physical and neuropsychological assessment, and have a blood test. Participants were excluded if they were planning on moving outside of Quebec in the next 3 years, or had a central nervous system disease (eg, subdural hematoma, active epilepsy, primary or metastatic brain cancer); intracranial brain surgery; a history of addiction to alcohol, drugs, or narcotics; a daily consumption of benzodiazepines (≥ 1 mg of lorazepam taken daily); and/or any illness or condition that could compromise their participation in the study.

2.2 | fMRI memory task and procedure

Brain activation was measured with a task designed to assess associative memory encoding (see Figure 1A,B). The encoding phase was done in the scanner. Participants were presented with a series of items placed in one of four quadrants of a grid (top left, top right, bottom left, bottom right). They were asked to memorize the target items,

which included 78 pictures of common objects belonging to one of six semantic categories (musical instruments, animals, fruits and vegetables, kitchen tools, sports gear, and food). Thirty-nine gray squares were used as control stimuli. Participants were instructed to remember the pictures and their position on the grid, and pay attention to the gray squares without having to remember their position. They were asked to press a key on a remote control whenever a stimulus occurred, whether a picture or a gray square. Stimuli were presented on a black background of a computer screen. They were presented for 3 seconds with a 500- to 18,500-millisecond inter-stimulus interval. Instructions were displayed on the screen prior to the task. This phase lasted about 10 minutes.

After the encoding phase, participants left the scanner and were invited to a separate room for the retrieval phase. The 78 studied pictures and 39 new ones were presented one at a time in the center of a computer screen. Studied and new items were presented in a random order. Participants were asked to determine whether an item had been studied during the encoding phase by pressing the Yes/No response key. When an item was identified as having been studied, participants were asked to determine where it was located on the grid by pressing the corresponding key on a different keypad. Participants had an unlimited amount of time to respond. The retrieval phase lasted approximately 10 minutes.

2.3 | Neuroimaging data acquisition

The core CIMA-Q protocol is referred to as the Canadian Dementia Imaging Protocol (www.cdip-pcid.ca). All brain images were acquired from either Siemens Healthcare (TrioTim and Prisma Fit) or Philips Medical Systems (Achieva and Ingenia) scanners with a magnetic field of 3 Tesla (more details about the acquisition parameters can be found

in supporting information). The protocol sequences for image acquisition were harmonized between manufacturers/software configurations to optimize commonality, and quality control procedures were performed monthly to ensure across-scan comparability (see Duchesne et al.²²).

2.4 | Neuroimaging data processing and analysis

2.4.1 | Task-related fMRI

Functional data was processed using Statistical Parametric Mapping version 12 software (SPM12) implemented in MATLAB 9.4. The first four volumes were discarded for every participant to avoid artefact contamination. All functional images were first converted into analyze format and unwarped. They were then realigned to the median image acquired in the session, and a mean image was created. Realigned volumes were co-registered to their corresponding T₁-MRI image, corrected for within-run movement, normalized into the Montreal Neurological Institute (MNI) stereotaxic space with a voxel size of 3 mm³, and spatially smoothed with an 8 mm full-width at half-maximum Gaussian kernel. Images were high-passed filtered (128 seconds) to remove low-frequency signal drifts.

fMRI data was analyzed in an event-related design and only participants with a minimum of 12 events per contrast were considered. Within-group voxel-wise comparisons were performed for all three groups for the associative memory contrast, which consisted of the subtraction of activation associated with the control items (gray squares) from those associated with the successful encoding of an item and its position. This was done with a family-wise correction (FWE) set at $P < 0.05$ at the cluster and peak levels. Analyses focused on both hippocampi and regions from the cortical signature of AD.²³ Masks were built using the PickAtlas toolbox,²⁴ and subject-wise beta values were extracted using MarsBar²⁵ implemented in MATLAB.

2.4.2 | Anatomical MRI

Cortical reconstruction and volumetric segmentations were performed using FreeSurfer 5.3 (<http://freesurfer.net>).²⁶ Two types of data were obtained: (1) raw hippocampal volumes (used to define SCD⁺), and (2) normative morphological data (hippocampal volumes, cortical thickness). These latter types of data were obtained by comparing them to large-scale normative cohorts and converted into Z scores correcting for age, sex, estimated total intracranial volume, scanner manufacturer, magnetic field strength, and interactions between these terms, as per the normative data and procedure defined by Potvin et al.^{27,28} (used for regression analyses).

Data on white matter lesions (WML) were also obtained and used as covariates, as white matter damage has been shown to cause blood-oxygen-level-dependant (BOLD) signal alterations unrelated to true change in neuronal activity (for a review, see D'Esposito et al.²⁹). WML were derived from the segmentation of the T₁-weighted and

fluid-attenuated inversion recovery (FLAIR) volumes using a patch-based method³⁰ implemented in volbrain (<http://volbrain.upv.es/>) and expressed as the percentage of total brain volume.

2.5 | Statistical analyses

Statistical analyses were conducted with R software packages (<http://www.R-project.org>). Participants whose T₁ ($n = 5$) or fMRI activation images ($n = 4$) failed quality control based on visual inspection of motion artefacts in the brain activations by an image analyst (SM) and the first author (NCL) were excluded from analyses. There were a few outliers identified when examining performance on the associative memory test ($n = 2$) and left superior parietal lobule fMRI activity ($n = 1$). Because these observations accounted for less than 5% of total observations, the winsorization procedure was applied.³¹ Kolmogorov-Smirnov tests were then conducted for normality for each variable included in the analyses. All variables of interest were normally distributed and showed appropriate residual distribution, except for the associative memory score ($P = 0.01$), which revealed a slightly positive asymmetric distribution. Hence, a non-parametrical test was used to compare groups on this score. All analyses involved scanning site, age, sex, and WML as covariates of nuisance.

2.5.1 | Behavioral analysis

An associative memory score was computed as follows: *correct source* (*wrong source* + *false alarm*), in which *correct source* refers to the number of responses in which both the item and its position were correctly identified. *Wrong source* refers to the number of responses for which the item was recognized but not its position, and *false alarm* refers to the number of responses in which a new image was falsely recognized.

Group differences on associative memory were assessed using a Kruskal-Wallis one-way analysis of variance (ANOVA) with group (HC, SCD⁺, MCI) as a between-subject factor and the associative memory score as the dependent variable. Post hoc comparisons were performed using the Mann-Whitney U-test.

2.5.2 | Polynomial analyses

Polynomial regression analyses were computed in a single group combining individuals with SCD⁺ and MCI. Within-group linear and quadratic regression models were assessed with intercept, mean-centered measures of neurodegeneration (ie, linear) and their squared term (ie, quadratic) as independent variables, and task-related activation as the dependent variable. When both the linear and quadratic models were found to be significant based on the F statistic, the Akaike information criterion (AIC) was used to determine which model better fit the data, where a smaller AIC indicated a better fit. A difference of >2 in the AIC was deemed to reflect a significant difference between models. The AIC was chosen because it provides a relative

TABLE 1 Demographic, clinical, genetic and behavioral characteristics of participants

	HC	SCD ⁺	MCI	P-values
Participants, N	54	28	26	–
Age (SD)	71.54 (4.56)	73.23 (5.21)	75.73 (5.01)	<i>P</i> = .002
Sex, M/F	14, 40	15, 13	12, 14	<i>P</i> = .031
Education (SD)	15.11 (3.14)	15.46 (3.70)	15.20 (3.27)	<i>P</i> = .900
MoCA (SD)	28.17 (1.40)	27.68 (1.33)	24.96 (2.25)	<i>P</i> = 2.03 ⁻¹²
Logical memory delayed recall (SD)	13.69 (4.99)	12.68 (3.69)	11.00 (4.51)	<i>P</i> = .028
APOE ε4 carriers (%)	0 (0)	10 (35.71)	11 (42.31)	–
WML	0.57 (0.79)	0.64 (1.04)	0.4 (0.47)	<i>P</i> = .52
Associative memory score	2.59 (1.63)	2.18 (1.46)	1.62 (1.56)	<i>P</i> = .014

Abbreviations: APOE, apolipoprotein E; HC, healthy controls; SCD⁺, subjective cognitive decline plus; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; SD, standard deviation; WML, white matter lesions.

balance of model fit and parsimony while penalizing for the number of parameters in the model. Measures of neurodegeneration included a composite score derived from mean thickness values in the cortical signature of AD²³ and left and right hippocampal volumes. Beta values extracted from region of interest (ROI) analyses were used as measures of task-related activation. Of note, normative Z-scores were used as measures of neurodegeneration for these analyses (see Potvin et al.²⁸ and D'Esposito et al.²⁹) in order to reduce the impact of the measures used for the definition of SCD⁺ (raw hippocampal volumes corrected for intracranial volume).

A similar procedure was used to examine the function modeling the relationship between memory performance and brain activation. An intercept, mean-centered associative memory performance score (ie, linear) and its squared term (ie, quadratic) were entered in the models as independent variables with task-related activation (beta values) as the dependent variable.

2.5.3 | Task-related activation analysis

Task-related activation group differences during the associative contrast were then performed by conducting one-way ANOVAs with group (SCD⁺, MCI, HC) as a between-subject factor on beta values derived from functional ROIs, and a Tukey test for post hoc comparisons.

3 | RESULTS

3.1 | Clinical and demographic characterization

Demographic and clinical data are shown in Table 1. All groups had similar education levels. However, there were proportionally more females in the HC group compared to the SCD⁺ and MCI groups, and participants with MCI were significantly older than HC. MCI individuals had lower MoCA scores than both HC and SCD⁺, and lower Logical Memory scores than HC but not SCD⁺.

3.2 | Behavioral performance

Analysis of post-scan memory performance revealed a group effect on the associative memory score. Participants with MCI performed more poorly than HC, whereas SCD⁺ did not differ from HC or MCI (see Table 1).

3.3 | Polynomial regressions

A significant quadratic function was found for the relationship between cortical thickness in the AD signature regions and activation in the left superior parietal lobule (see Figure 2C and Table 2), whereas the linear model was not significant. A linear model was found to be significant when examining the relationship between left hippocampal volume and activation of the left hippocampus, where smaller volume was associated with higher activation. In this case, the quadratic model was not significant. Both the linear and quadratic models were found to be significant to describe the relationship between left hippocampal volume and activation of the right inferior temporal lobule. The difference in AIC was <2 between the two models, indicating that they were statistically indistinguishable from each other. Therefore, the more parsimonious model was retained, that is, the linear model. Here again, smaller volume was associated with higher activation.

The analyses of the relationship between associative memory performance and brain activation revealed a significant quadratic model between the associative memory score and left superior parietal activation (see Table 3), whereas the linear model was not significant. Both the linear and quadratic models were found significant when examining the relationship between associative memory performance and activation in the left middle temporal lobe. The difference in AIC was <2 between the two models, indicating that both models were statistically indiscernible. Thus, the linear model was retained, where superior memory performance was associated with higher activation.

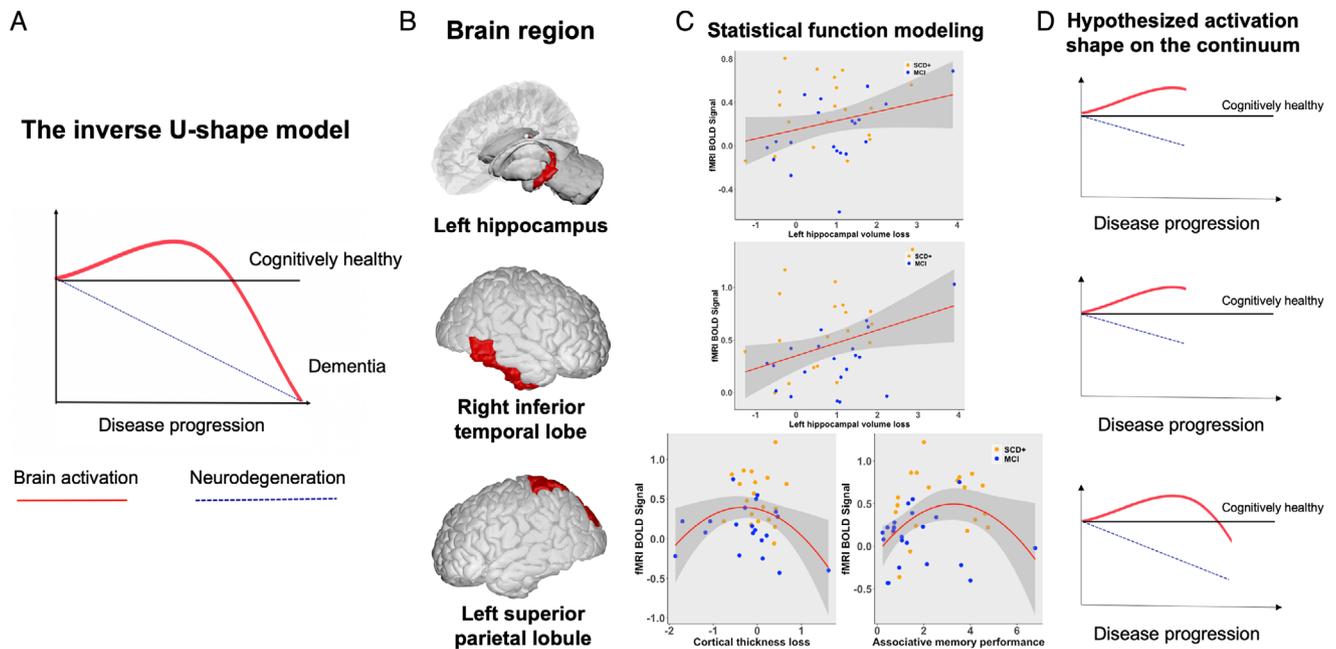


FIGURE 2 Graphical representation and statistical fitting of the inverse U-shape model of brain activation trajectory with AD progression. A, Graphical depiction of the inverse U-shape model of brain activation trajectory with AD progression. Increased activation (ie, hyperactivation) is found in the early phase of the disease when neurodegeneration is mild, while decreased activation (ie, hypoactivation) is observed in the later stages when structural damage becomes more prominent. B,) Brain regions that showed a significant linear or quadratic relationship with measures of neurodegeneration or memory performance. BrainPainter was used to display brain images.³² C, Polynomial regressions (ie, linear or quadratic) between functional magnetic resonance imaging activation from brain regions depicted in (B), and measures of neurodegeneration (hippocampal volume, cortical thickness) or associative memory performance controlling for scanning site, age, sex, and white matter lesions. D, The hypothesized shape of activation along the disease continuum for brain regions shown in (B) according to the mathematical model that best fitted the relationship between brain activation and proxies of disease severity shown in (C)

TABLE 2 Results from significant linear and quadratic models between proxies of disease severity and fMRI activation in the prodromal Alzheimer's disease group

fMRI ROI	Independent variable	Model	F	P	Standardized β	CI lower boundary	CI upper boundary	Adjusted R^2	AIC
Left hippocampus	Left hippocampal volume	Linear	6.201	.017	-0.101	-1.33	-0.027	.122	-97.43
		Quadratic	1.634	.119	0.048	-0.007	0.061	—	-95.15
Right inferior temporal lobe	Left hippocampal volume	Linear	5.272	.028	-0.100	-0.174	-0.027	.112	-76.98
		Quadratic	7.319	0.01	-0.091	-0.177	-0.006	—	-77.78
Left superior parietal lobe	Mean global cortical thickness	Linear	<1	.867	0.025	-0.181	0.232	—	-71.55
		Quadratic	5.303	.028	-0.164	-0.311	-0.017	.128	-77.12
Left middle temporal gyrus	Associative memory score	Linear	9.898	.000	0.069	0.019	0.119	.331	-95.38
		Quadratic	7.063	.001	0.010	0.001	0.017	—	-94.85
Left superior parietal lobe	Associative memory score	Linear	1.762	.192	0.052	-0.028	0.013	—	-74.05
		Quadratic	3.773	.009	-0.053	-0.096	-0.009	.110	-72.45

Abbreviations: AIC, Akaike information criterion; CI, confidence interval (set at 95%); fMRI, functional magnetic resonance imaging; ROI, region of interest. Notes: Adjusted R^2 are only reported for retained models. Smaller AIC indicates a better fit of the model. All analyses were performed controlling for scanning site, age, sex, and white matter lesions.

3.4 | Task-related activations

Within-group task-related activation maps for the associative memory contrast are presented in Figure 3A, where the three groups are shown separately. Table 3 and Figure 3B present group comparisons

of activation related to associative memory encoding. Higher levels of activation were found in participants with SCD⁺ compared to HC and participants with MCI. Higher activation levels in SCD⁺ occurred in the left and right hippocampi, left and right middle temporal lobes, left superior parietal lobe, right inferior temporal lobe, and right

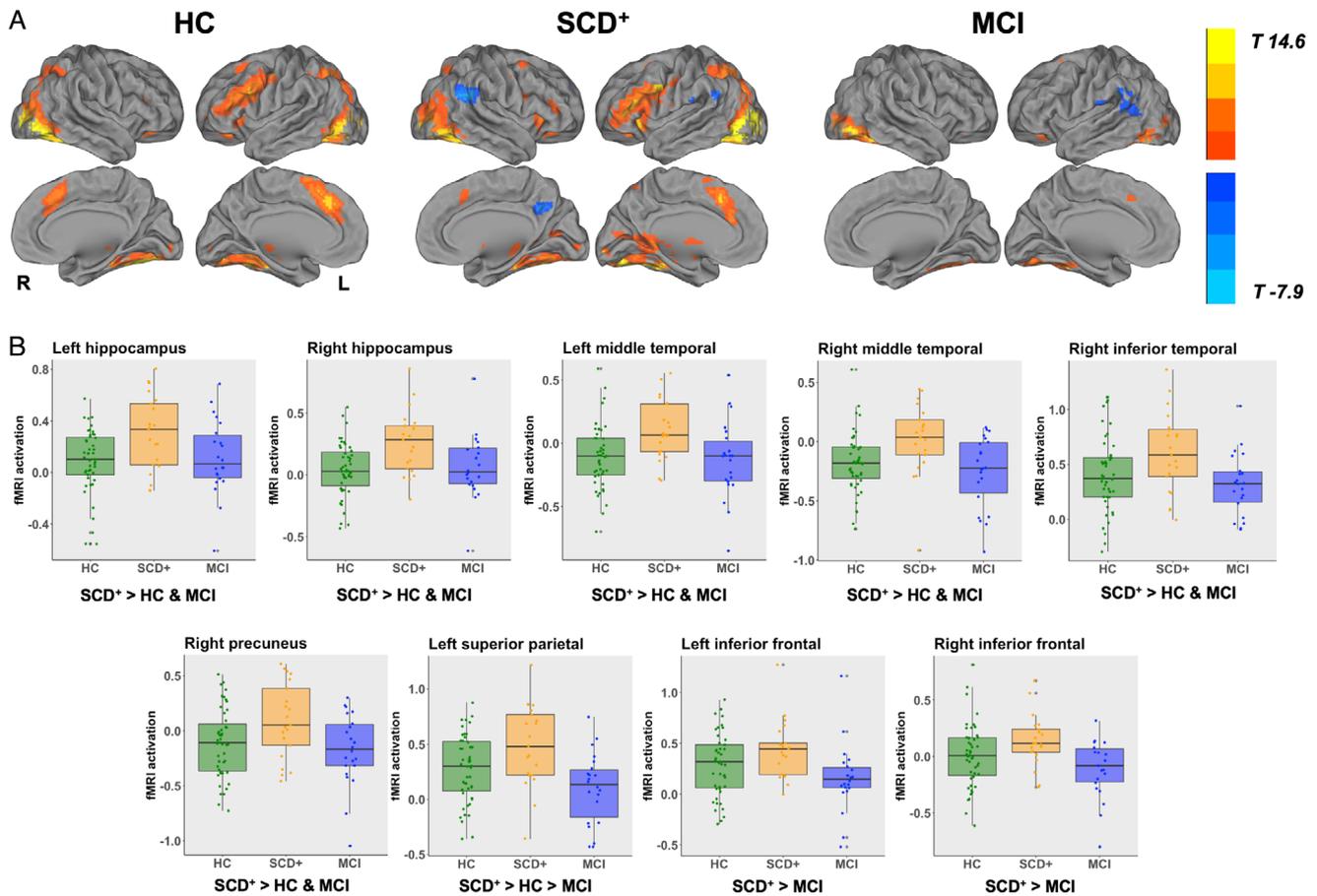


FIGURE 3 Within-group activation maps and group-wise comparisons in functional magnetic resonance imaging (fMRI) activation. A, Within-group activation maps for the associative memory contrast (activation associated with gray squares subtracted from activation associated with the successfully encoded item with their position). The family-wise error (FWE) correction was applied with a $P < 0.05$ threshold at the cluster and peak levels. B, Group-wise differences in fMRI activation in both hippocampi and regions from the cortical signature of Alzheimer's disease for the associative memory contrast

precuneus. Participants with MCI showed a lower level of activation in the left superior parietal lobule compared to those with those with SCD⁺ and HC. In addition, individuals with SCD⁺ showed greater activation in the left and right inferior frontal lobes than individuals with MCI but not HC. There were no other significant group differences.

4 | DISCUSSION

The main goal of this study was to characterize hyperactivation by identifying the function that best fits the relationship between proxies of disease severity and memory-related activation in a group of individuals at risk of AD. A quadratic inverse U-shape function modeled the relationship between activation in the left superior parietal lobule and proxies of disease severity. Linear models accounted for the relationship between activation in the left hippocampus, and the right inferior temporal and left hippocampal volume. Evidence of hyperactivation was found in individuals with SCD⁺ in the hippocampi and several cortical regions, including the middle temporal lobes bilaterally,

the left superior parietal lobule, right inferior temporal lobe, and right precuneus.

Activation in the left superior parietal region is described by a quadratic function when using cortical thickness or associative memory performance as a proxy for disease severity. Furthermore, group comparisons in this region indicate hyperactivation in individuals with SCD⁺ and hypoactivation in those with MCI. This supports the hypothesis of early hyperactivation followed by hypoactivation at later stages of AD. Activation in the left hippocampus and right inferior temporal regions was better described by a negative linear relationship when related to hippocampal volume. Figure 2C shows that this is due to increased activation as volume is reduced. Thus, the functions appear to reflect activation in the ascending portion of the inverse U-shape.

The finding of hyperactive brain regions in individuals with SCD⁺ but not those with MCI suggests that hyperactivation may characterize individuals with SCD and precede the occurrence of measurable cognitive impairment. It thus has potential as a marker to identify individuals who are cognitively intact but at risk of future progression to dementia, although this will require confirmation with longitudinal prospective studies. This finding is consistent with other studies that report

TABLE 3 Results from between-group comparisons for fMRI brain activation during the associative memory contrast correcting for scanning site, age, sex and white matter lesions

Brain region	F	P-value	η^2	Post hoc (P-value)
Left hemisphere				
Hippocampus	4.903	.009	.09	SCD ⁺ > HC (.008)
Medial temporal lobe	5.904	.004	.091	SCD ⁺ > HC (.009) and MCI (.013)
Inferior temporal lobe	<1	.480	—	—
Temporal pole	1.470	.236	—	—
Angular gyrus	1.274	.285	—	—
Superior frontal gyrus	<1	.715	—	—
Superior parietal lobule	7.524	.000	.151	SCD ⁺ > HC (.043) and MCI (.001); HC > MCI (.039)
Supramarginal	1.652	.198	—	—
Precuneus	2.491	.089	—	—
Inferior frontal gyrus	4.445	.014	.098	SCD ⁺ > MCI (.011)
Right hemisphere				
Hippocampus	6.535	.002	.110	SCD ⁺ > HC (.002)
Medial temporal lobe	5.807	.004	.086	SCD ⁺ > HC (.023) and MCI (.006)
Inferior temporal lobe	4.489	.014	.096	SCD ⁺ > HC (.026) and MCI (.006)
Temporal pole	1.873	.160	—	—
Angular gyrus	1.578	.212	—	—
Superior frontal gyrus	<1	.986	—	—
Superior parietal lobule	<1	.942	—	—
Supramarginal	<1	.937	—	—
Precuneus	3.424	.014	.081	SCD ⁺ > HC (.046) and MCI (.022)
Inferior frontal gyrus	4.676	.011	.102	SCD ⁺ > MCI (.009)

Abbreviations: fMRI, functional magnetic resonance imaging; HC, healthy control; MCI, mild cognitive impairment; SCD⁺, subjective cognitive decline plus.

similar results using smaller sample sizes and a behaviorally defined group of individuals with SCD.^{33–35} However, this is the first study to find hyperactivation in individuals with SCD with biomarker features (ie, APOE ϵ 4 allele and hippocampal volume) that increase the likelihood of pathophysiological processes of AD. In the presence of mild neurodegeneration, a high level of activation may be consistent with a higher risk of progression in cognitively intact older adults complaining about their memory. Furthermore, while some studies investigated fMRI dynamics in relation to amyloid and tau,³⁶ this is the first study to link a quadratic trajectory of brain activation with neurodegeneration, a recognized proxy of clinical severity^{37,38} and time to dementia.⁵

Longitudinal prospective diagnostic studies will be needed to confirm that the presence of regional hyperactivation in SCD⁺ predicts progression to dementia, and biomarkers of neuropathology will be required to assess whether it is specific to individuals with AD as the underlying cause. If hyperactivation is confirmed as an early marker of dementia or AD, it will be critical to improve its clinical feasibility and scalability. In this study, activation was elicited using a brief language-free memory task harmonized across different scanning sites, which seems to suggest that scalability could be achieved. However, validation and normalization procedures will be necessary for such an assessment to be used at a larger scale and useful in clinical practice. Elec-

troencephalogram (EEG) could be considered an alternative to fMRI to measure hyperactivation, particularly because subclinical epileptiform activity was found on EEG in early AD and MCI (for a review, see Vossel et al.³⁹). However, EEG is not easily accessible for large-scale diagnosis or clinical purposes.

Although this study was not designed to address the cause of hyperactivation, this issue should be briefly addressed here, as it is debated in the literature. The compensatory view posits that increased activation may reflect protective brain plasticity.^{1–5,40} In contrast, the excitotoxic view suggests that abnormally high levels of activation would accelerate AD-related pathophysiological processes and contribute to cognitive impairment.^{41–47} The two opposing views may not be mutually exclusive as compensatory hyperactivation and pathologically driven hyperactivation may occur at different points in time or in different regions. This study's finding of a positive relationship between memory and activation in the left superior parietal region but not in the hippocampus could indeed reflect different mechanisms in the hippocampus versus cortical regions as has been suggested.^{48,49} However, this is hypothetical and should be investigated in future studies.

Some limitations must be recognized. A major limitation of this study is that it was not possible to access tau or amyloid brain imaging for this study's participants. There is a possibility that some of the study

participants may not meet criteria for biologically defined AD according to the recent NIA-AA A/T/N research framework.⁵⁰ However, our results fit the aforementioned models and studies that assessed the relationships between AD biomarkers and changes in fMRI activation and connectivity. The sample is relatively small, although it is larger than most previous studies on this issue. It is nonetheless noteworthy that CIMA-Q is one of the rare cohorts that includes task-related activation data. Individuals in the MCI group were on average older than HC. Although our results remained significant when controlling for age, we acknowledge that age difference might partially account for the hypoactivation observed in the MCI group compared to HC. Activation and cerebral blood flow differences have been observed in studies comparing older adults to participants in their twenties.²⁹ Nevertheless, we believe that hypoactivation observed in MCI is unlikely to be related to solely an age effect, as our findings confirm those of other studies, which found hypoactivation in individuals with MCI while relying on age-matched groups.¹⁻⁵ Finally, although the BOLD signal reflects neuronal activity, it is an indirect measure and other factors may modify the relationship between true neuronal activity and the observed BOLD signal.

In conclusion, novel findings are reported to support the presence of very early and transient hyperactivation in people at risk of AD. We show that activation increases linearly in some regions and follows an inverse U-shape in others, when examined as a function of disease severity. Overall, the results suggest that hyperactivation is present in the early stages of the disease such as in individuals who have genetic and/or brain markers of AD and meet criteria for SCD, and has potential as a biomarker indicating future progression to AD. However, future studies are needed to determine the value of hyperactivation as a predictor of dementia in comparison to other markers and to better understand the pathophysiology that underlies hyperactivation in early AD.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in relation to this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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