

# Cognitive Reserve–Mediated Modulation of Positron Emission Tomographic Activations During Memory Tasks in Alzheimer Disease

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**Background:** Cognitive reserve (CR) is the ability of an individual to cope with advancing brain pathological abnormalities so that he or she remains free of symptoms. Epidemiological data and evidence from positron emission tomography suggest that it may be mediated through education or IQ.

**Objective:** To investigate CR-mediated differential brain activation in Alzheimer disease (AD) subjects compared with healthy elderly persons.

**Participants:** Using radioactive water positron emission tomography, we scanned 12 AD patients and 17 healthy elderly persons while performing a serial recognition memory task for nonverbalizable shapes under 2 conditions: low demand, in which one shape was presented in each study trial, and titrated demand, in which the study list length was adjusted so that each subject recognized shapes at approximately 75% accuracy. Positron emission tomographic scan acquisition included the encoding and recognition phases. A CR factor score that summarized years of education, National Adult Read-

ing Test estimated IQ, and Wechsler Adult Intelligence Scale–Revised vocabulary subtest score (explaining 71% of the total variance) was used as an index of CR. Voxel-wise, multiple regression analyses were performed with the “activation” difference (titrated demand–low demand) as the dependent variables and the CR factor score as the independent one. Brain regions where regression slopes differed between the 2 groups were identified.

**Results:** The slopes were significantly more positive for the AD patients in the left precentral gyrus and in the left hippocampus and significantly more negative in the right fusiform, right middle occipital, left superior occipital, and left middle temporal gyri.

**Conclusion:** Brain regions where systematic relationships (slopes) between subjects’ education-IQ and brain activation differ as a function of disease status may mediate the differential ability to cope with (ie, delay or modify) clinical manifestations of AD.

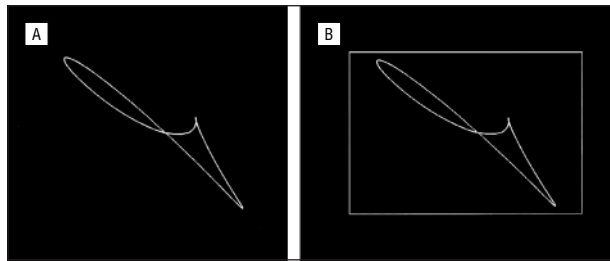
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**T**HE THEORY OF COGNITIVE reserve (CR) was initially introduced as an attempt to explain the less than perfect coupling between the degree of brain pathological changes and their clinical expression. *Cognitive reserve* can be defined as the ability of an individual to cope with advancing brain pathological conditions to minimize symptoms. Support for the concept of CR in Alzheimer disease (AD) comes not only from epidemiological<sup>1-4</sup> but also from resting imaging studies. When controlling for clinical severity, it has been shown that patients with higher educational<sup>5</sup> or occupational<sup>6</sup> attainment, higher premorbid IQ,<sup>7</sup> or a more engaged lifestyle<sup>8</sup> have more prominent resting flow or metabolism deficits (and hence more prominent pathological involvement). In other words, subjects with high CR can maintain clinical

deficits similar to those of subjects with lower CR, despite more severe brain pathological abnormalities (as assessed by resting positron emission tomography [PET]). Again, these observations support the prediction that individuals with more CR can tolerate more pathological abnormalities (lower resting flow or metabolism).

In contrast to the more straightforward interpretation of resting cerebral blood flow (CBF), the association between CR, pathological abnormalities, and changes in activation (ie, during cognitive tasks) is more complex. Direct associations between CR variables and task-related neurophysiological activity during cognitive stimulation may also exist and be amenable to testing with functional neuroimaging. Moreover, it can be hypothesized that CR might play different roles during cognitive activation for healthy and AD populations. The direct relationship



**Figure 1.** Samples of the shapes used in the nonverbal recognition task. The surrounding rectangle in B denotes a probe item.

between CR and activation has been rarely examined in healthy populations<sup>9-11</sup> and, to our knowledge, never in patients with AD. In a previous study<sup>10</sup> of healthy young and old persons, our group examined the association between CR and cerebral activation and the changes of this association as a function of aging. In this study, we sought to investigate the existence and nature of systematic relationships between CR variables and neurophysiological function in samples of AD patients and healthy elderly subjects during performance of a nonverbal (abstract shape) episodic memory task. We also examined how these relationships change as a function of AD.

## METHODS

### SUBJECTS

Twelve subjects with early AD (9 men and 3 women) who met *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, criteria for dementia and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD<sup>12</sup> and 17 normal elders (8 men and 9 women) who were carefully screened with medical, neurological, psychiatric, neuropsychological evaluations and brain magnetic resonance imaging scans to exclude those with dementia or questionable dementia, or cognitive impairment or other neurological, psychiatric disorders, and severe medical illnesses met criteria for entry into the study. The subjects underwent extensive neuropsychological evaluation, including the Wechsler Adult Intelligence Scale–Revised,<sup>13</sup> the American version of the National Adult Reading Test estimated IQ (NARTIQ),<sup>14,15</sup> the modified Mini-Mental State Examination,<sup>16</sup> and the Selective Reminding Test.<sup>17</sup>

All subjects were right-handed and able to see stimuli clearly without optometric correction. Informed consent was obtained after the nature and risks of the study were explained.

### CR VARIABLES AND COGNITIVE TASKS

An operational measure of CR (*CR variable* [CRV]) was defined as the principal component of the z-scored NARTIQ, Wechsler Adult Intelligence Scale–Revised vocabulary subtest score (VOC), and years of education (EDUC) with the largest eigenvalue (performed on the combined AD and control group). The rationale for the choice of these 3 variables as being representative of CR is provided by the literature on CR, which suggests that both education and IQ mediate the relationship between pathological abnormalities and clinical manifestations in AD.<sup>1,5,7,18</sup> We therefore wanted to combine education and IQ into a single factor that would best capture CR: this mixture of inherent and acquired abilities that results in differential clinical vulnerability to AD pathological insult. The NARTIQ,

VOC, and EDUC were pairwise positively correlated in the combined sample of AD and elderly subjects: NARTIQ–VOC  $r=0.74$ ,  $P<.01$ ; NARTIQ–EDUC  $r=0.49$ ,  $P<.01$ ; and VOC–EDUC  $r=0.44$ ,  $P<.05$ . The CRV explained 71% of the total variance of these z-scored measures.

We chose a nonverbal episodic memory task for the neuroimaging component of this study. Looped shapes were used because their level of complexity made verbal encoding difficult (**Figure 1**). The task comprised 2 conditions:

1. A low demand (LD) condition, in which a single shape presented during the encoding phase (different for each trial) was followed by one shape during the recognition phase (which was the same as the encoding phase shape or an unfamiliar foil).
2. A titrated demand (TD) condition that involved serial presentation of a sequence of shapes during the encoding phase, the length of which was determined in a training session on the day preceding the PET scan. During this training session, a titration procedure involved 2 titration sessions of 15 minutes each, during which the shape list size was adjusted in a staircase manner such that recognition accuracy of about 75% for each subject was attained. This shape list size value was then used in the TD condition on the day of the scan. The recognition phase of the TD condition involved presentation of shapes, some of which were studied during the preceding encoding phase, intermixed with unfamiliar foils.

During study phases in the scanner, subjects were exposed to each stimulus for 5 seconds. A 500-millisecond delay occurred at the transition to test trials, after which the recognition probes were displayed. During the recognition phase in the scanner, subjects were instructed to make a “new” or “old” response for each probe item by pressing 1 of 2 microswitches (left thumb for “new” and right thumb for “old”). Recognition probes were distinguished from encoding items by a rectangular frame (Figure 1B). A 6-second response time limit was imposed, with a premature response cutoff of 200 milliseconds. Accuracy was emphasized over speed. A new test probe was displayed immediately following the button press. New and old test probes each occurred with a frequency of 50%. Test probes were pseudorandomized so that no more than 4 consecutive trials required the same response. Each shape was used only once for each subject.

### PET SCAN ACQUISITION

Each condition was initiated 50 seconds before the start of the scan and continued throughout it. Positron emission tomographic scanning data acquisition included both the encoding and the recognition phases of the task. Scans were separated by 10 minutes and were obtained in the following order: scan at rest, LD, and TD.

For each PET scan, a bolus of 30 mCi of radioactive water was injected intravenously. Using a Siemens EXACT 47 PET camera (Siemens, Knoxville, Tenn), 2 scan frames of 30 seconds each were acquired in the 2-dimensional mode, which were subsequently averaged. After measured attenuation correction (a 15-minute transmission scan) and reconstruction by filtered back-projection, the image resolution was 4.6 mm full width at half maximum. Arterial blood sampling was not conducted; therefore, only nonquantitative count images (referred to as “CBF,” with the understanding that it does not represent absolute measurements) could be obtained.

### PET DATA PROCESSING

The SPM99 program (Wellcome Department of Cognitive Neurology, London, England) was used to implement the following standard steps for the PET images of each subject: realign-

## DEMOGRAPHICS AND BEHAVIORAL DATA

ment to the mean image, spatial transformation to the Montreal Neurological Institute coordinates, smoothing with an isotropic gaussian kernel (12 mm full width at half maximum), proportional scaling by the global mean, and computation of voxel-wise *t* statistics for contrasts of interest (see the "General Linear Model Design for PET Data" subsection that follows). Montreal Neurological Institute coordinates of local maxima (exceeding the statistical threshold of  $\alpha = .05$ , Bonferroni corrected for the number of resets) statistical parametric maps were converted to standard Talairach brain atlas coordinates.

## GENERAL LINEAR MODEL DESIGN FOR PET DATA

Voxel-wise, multiple regression analyses<sup>19</sup> were performed with dependent variable for the regression of the PET CBF difference between the TD and LD test conditions. This difference was meant to represent functional activation related to titrated memory performance, while subtracting out activity related to basic sensory and motor processing.

The regressions modeled:

1. The effects of condition  $\times$  CRV interaction within each group. This can be conceptualized as the regression of the CRV on the TD-LD CBF difference within each group. It represents the relationship between the CRV and task-related activation within each group and assessing it is critical to testing the hypothesis that CR plays a role in the neurophysiology of memory in AD and healthy elderly populations.

2. The effects of condition  $\times$  group  $\times$  CRV interaction. This can be conceptualized as the differences between AD patients and elderly controls in the slopes of the relationship between the CRV and the TD-LD CBF. This tests the hypothesis that the role of CR in the neurophysiology of memory differs between these populations.

Because of residual deviations from the target value of 75% accuracy and a modest positive correlation between the CRV and subject accuracy in the TD condition ( $r = 0.25$ ,  $P = .19$ ), each subject's accuracy in the TD condition (expressed as the percentage correct) was included as a nuisance predictor variable in the regression analyses to obviate confounding of CRV and TD accuracy. Other nuisance variables that were included were (1) the 2 other variables yielded by the principal components analysis of NARTIQ, VOC, and EDUC (see the "CR Variables and Cognitive Tasks" subsection of the "Methods" section) and (2) the TD list size. These predictor variables were orthogonalized with respect to all the others,<sup>20,21</sup> as the purpose of their inclusion was not to avoid confounding but to explain other possible variance components in the data to increase sensitivity.<sup>19</sup>

All patients had early AD: the mean modified Mini-Mental State Examination score was 47.8 (corresponding to a Folstein Mini-Mental score of about 25) (**Table 1**). As expected, AD subjects' memory performance (Selective Reminding Test total recall and delayed recall) was inferior. Neither EDUC, NARTIQ, VOC, nor CRV (which is a summary of the former 3 measures) differed significantly between the 2 groups. The controls achieved a larger TD list length compared with the AD patients, and there was some degree of variability in accuracy during the TD condition within the groups.

## PET DATA

In the AD patients, a positive correlation was noted in the left precentral gyrus and a negative correlation in the left middle frontal and fusiform gyri (**Table 2** and **Figure 2**). In the healthy older persons, positive correlations were noted

**Table 1. Demographic Characteristics, Neuropsychological Profile, and Behavioral-Cognitive Performance During the Experimental Paradigm in the 2 Groups\***

| Variable                               | Alzheimer Disease Subjects (n = 12) | Control Subjects (n = 17) | P Value† |
|--|-------------------------------------|---------------------------|----------|
| Age, y                                 | 69 (9.9)                            | 71 (7)                    | .58      |
| Modified Mini-Mental State Examination | 47.8 (4.4)                          | 54.2 (2.5)                | .001     |
| SRT Total Recall                       | 30.4 (8.8)                          | 46.9 (7.7)                | .001     |
| SRT Delayed Recall                     | 2.2 (2.2)                           | 6.9 (2.9)                 | .001     |
| WAIS-R Digit symbol                    | 10.5 (3.8)                          | 12.7 (2.4)                | .07      |
| Education                              | 16 (2.9)                            | 15 (4.1)                  | .47      |
| NARTIQ                                 | 115.5 (10.4)                        | 121.1 (6.9)               | .09      |
| WAIS-R vocabulary                      | 11.9 (2.8)                          | 13.8 (2.5)                | .06      |
| Accuracy, % correct                    | 0.72 (0.09)                         | 0.72 (0.07)               | .95      |
| Titrated demand list length            | 4.4 (1.8)                           | 7.5 (4.8)                 | .04      |

Abbreviations: NARTIQ, National Adult Reading Test estimated IQ; SRT, Selective Reminding Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

\*Data are given as mean (SD).

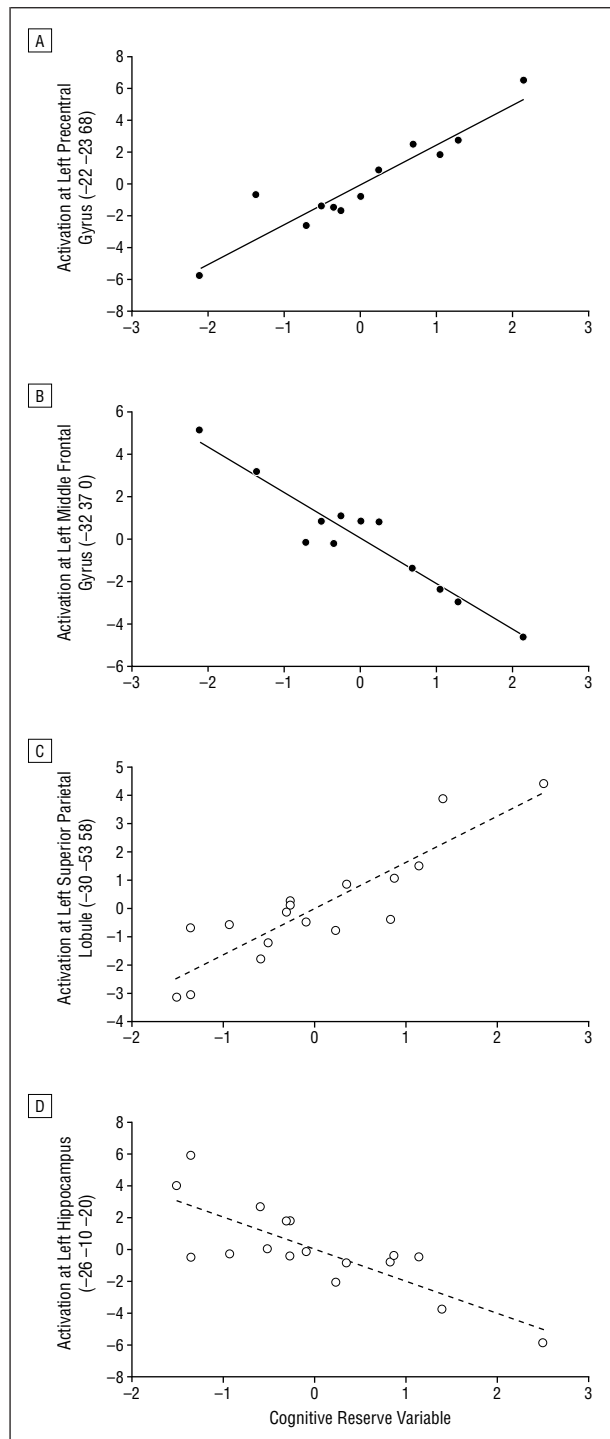
†*t* Test.

**Table 2. Areas Where Significant\* Correlations Between Brain Activation and the Cognitive Reserve Variable Were Detected Within Each Group Separately**

| Group                      | Direction of Correlation | Talairach Coordinates |     |     | <i>t</i> <sub>17</sub> Value | Cluster Size, No. of Voxels† | Location (Brodmann Area)          |
|----------------------------|--------------------------|-----------------------|-----|-----|------------------------------|------------------------------|-----------------------------------|
|                            |                          | x                     | y   | z   |                              |                              |                                   |
| Alzheimer disease subjects | Positive                 | -22                   | -23 | 68  | 6.8                          | 65                           | Left precentral gyrus (4)         |
|                            | Negative                 | -32                   | 37  | 0   | 5.0                          | 6                            | Left middle frontal gyrus (10)    |
|                            |                          | -36                   | -44 | -23 | 4.8                          | 9                            | Left fusiform gyrus (20)          |
| Control subjects           | Positive                 | -30                   | -53 | 58  | 5.9                          | 17                           | Left superior parietal lobule (7) |
|                            | Negative                 | -26                   | -10 | -20 | 5.0                          | 5                            | Left hippocampus                  |
|                            |                          | 13                    | 60  | 0   | 5.0                          | 14                           | Right medial frontal gyrus (10)   |
|                            |                          | 18                    | 38  | 31  | 4.9                          | 1                            | Right superior frontal gyrus (9)  |
|                            |                          |                       |     |     |                              |                              |                                   |

\* $P < .05$ , Bonferroni corrected.

†Each voxel is 8 mm<sup>3</sup>.



**Figure 2.** Voxel-wise multiple regression of the cognitive reserve variable against brain activation within each of the 2 groups. This is a graphic representation of some of the results presented in Table 2, showing voxels with highest *t* values for positive and negative slopes for Alzheimer disease patients (A and B) and for control subjects (C and D). Diagonal lines indicate regression lines.

in the left superior parietal lobule, while negative correlations were observed in the left hippocampus and the right medial and superior frontal gyri (Table 2 and Figure 2). These results suggest that CR modulates neurophysiological activity during cognitive tasks in AD patients and in healthy elderly persons.

Compared with elderly controls, AD patients manifested significantly more positive slopes of activation in the left precentral gyrus and the left hippocampus and significantly more negative slopes of activation in the right fusiform and middle occipital, left superior occipital, and middle temporal gyri (Table 3, Figure 3, and Figure 4). Therefore, these results suggest that the effect of CR in the neurophysiological activity of cognitive tasks differs between the 2 groups.

#### COMMENT

This study was designed to explore the neural implementation of CR in normal aging and AD. The main focus of the analyses conducted in the present study was to provide a first approximation of how CR might be related to disease-associated changes: ie, what is the neurophysiological correlate of the noted epidemiological associations between CR and clinical manifestations of AD? It is plausible to hypothesize that areas where slope differences were noted may be part of this neural implementation of CR.

We identified areas where systematic relationships between CR and brain activation differed as a function of AD. Given the experimental design that equated for task difficulty, the observed associations cannot be attributed to differential effort. We observed 2 patterns of slope differences: (1) regions with positive slopes for the AD patients and negative slopes for the controls (Figures 3A and 4A) and (2) regions with negative slopes for the AD patients and positive slopes for the controls (Figures 3B and 4B). To formulate hypotheses to explain the different observed patterns of slope differences, we assumed the following premises: (1) Healthy subjects' activation represents optimal normal brain function, while AD can cause deviations from this standard due to disease-related physiological changes. (2) Higher CR is associated with more efficient or optimal patterns of brain activation.

In pattern 1 (Figure 4A), the optimal response for high-CR AD subjects differs from that for high-CR healthy subjects: rather than less activation, increasing activation for increasing CR is noted. In other words, in the left precentral gyrus and the left hippocampus, deactivation is the optimal response for the controls, while higher activation is the optimal response for the AD subjects. The opposite happens in pattern 2 (Figure 4B): while higher activation for elderly persons with higher CR seems to be the optimal function, AD subjects with higher CR show more prominent deactivation. Therefore, in areas such as the right fusiform, right middle occipital, left superior occipital, and left middle temporal gyri, increased activation is the optimal function for the controls, while deactivation is the optimal function for the AD subjects.

Pathological abnormalities in AD start in the temporal regions and spread to the temporal-parietal-occipital association areas.<sup>22,23</sup> Therefore, changes in CR-related slopes in regions such as the hippocampus, for example, may be the result of the direct pathological insult itself. However, it is also well documented that perirolandic cortex is typically spared of pathological changes,<sup>22,23</sup> and CR-related changes in the precentral gyrus were noted in our study. For such areas, presumably representing still healthy neural substrate, CR-related changes of activation direc-

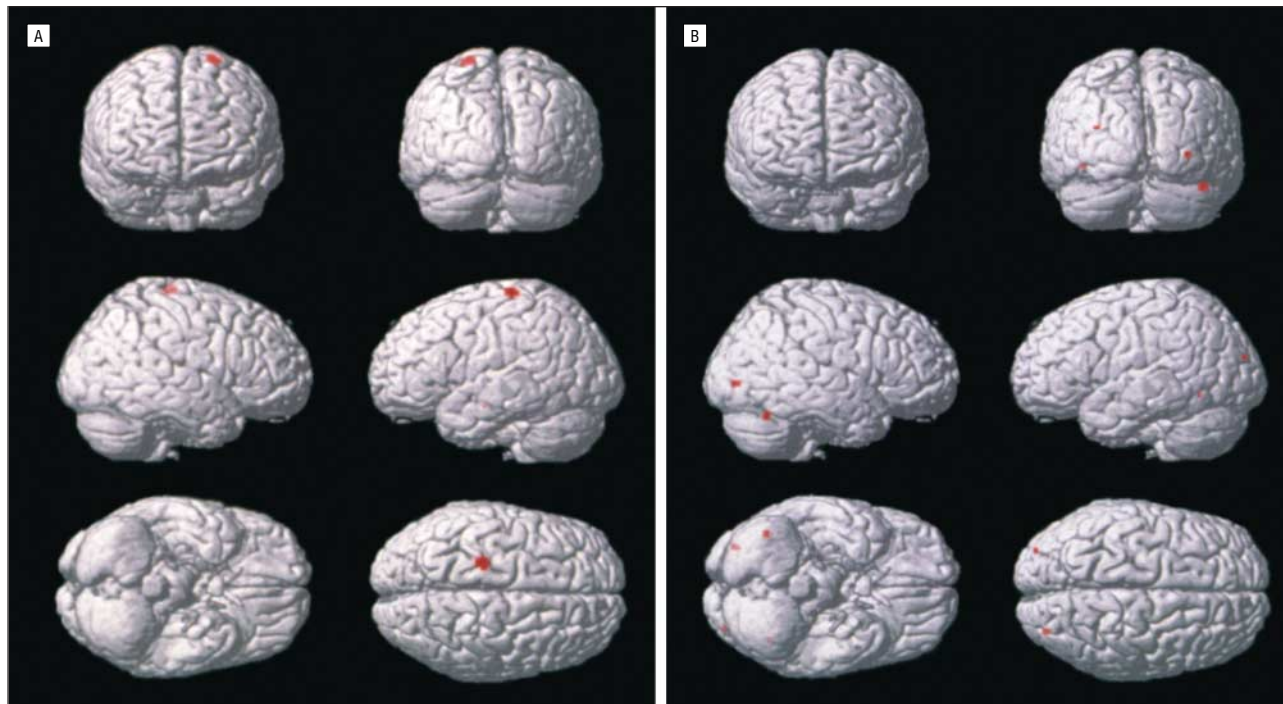
**Table 3. Brain Areas Where Regression Slopes of the Cognitive Reserve Variable Against Brain Activation Were Significantly\* Different Between the 2 Groups**

| Slope Interaction                         | Talairach Coordinates |     |     | $t_{17}$ Value | Cluster Size<br>No. of Voxels† | Location (Brodmann Area)           |
|---|-----------------------|-----|-----|----------------|--------------------------------|------------------------------------|
|   | x                     | y   | z   |                |                                |                                    |
| AD slope more positive than control slope | -22                   | -24 | 68  | 6.2            | 45                             | Left precentral gyrus (4)          |
|   | -28                   | -10 | -15 | 4.6            | 1                              | Left hippocampus                   |
| AD slope less positive than control slope | 44                    | -63 | -20 | 4.9            | 10                             | Right fusiform gyrus (37)          |
|   | 32                    | -81 | 2   | 4.7            | 8                              | Right middle occipital gyrus (18)  |
|   | -32                   | -88 | 23  | 4.7            | 2                              | Left superior occipital gyrus (19) |
|   | -42                   | -59 | -5  | 4.7            | 2                              | Left middle temporal gyrus (37)    |

Abbreviation: AD, Alzheimer disease.

\* $P < .05$ , Bonferroni correction.

†Each voxel is 3 mm<sup>3</sup>.

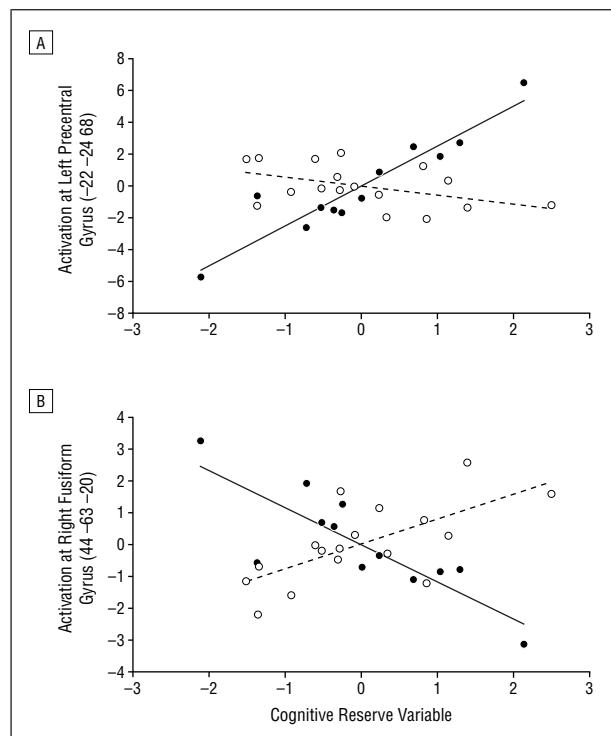


**Figure 3.** Three-dimensional brain rendering of a statistical parametric map depicting areas where regression slopes of the cognitive reserve variable against brain activation were significantly ( $P < .05$ , Bonferroni corrected) different among the groups: A, Areas where Alzheimer disease (AD) patients had significantly more positive slopes of activation. B, Areas where AD patients had significantly less positive slopes of activation. The location of these regions is presented in Table 3, and a graphic representation of some of the regressions is shown in Figure 4.

tionality may indicate compensatory reorganization of function in the face of pathological changes in different brain regions. Because a coordinated activity of many brain areas (ie, a network) is usually necessitated for performance of most cognitive tasks, it is reasonable to hypothesize that perturbations in a single site of this network (ie, in the hippocampus because of AD pathological changes) would result in changes and rearrangements of the response of other regions participating in the network (ie, in the precentral gyrus, still spared of AD pathological changes). Alternatively, it is conceivable that even in areas such as the precentral gyrus, the reason for changes in the CR-related slopes could be early AD pathological alterations. This is less likely because this is a sample of patients with early AD and we know that AD pathological changes affect such regions later on in the course. Nevertheless, it is not in-

conceivable because there are known early biochemical changes in neuronal processes and synapses (that may affect activation) long before structural pathological abnormalities (amyloid plaques and neurofibrillary tangles) are detected.<sup>24-26</sup> In either case, such regions may represent areas that partially mediate the CR-related clinical protection noted in epidemiological studies<sup>1-4</sup> and in previous resting PET studies.<sup>5-8</sup>

Overall, the present study demonstrates the existence of associations between a subject's inherent abilities (such as education and IQ) and neurophysiological activity during cognitive tasks. In addition, it identifies brain areas where there may be reorganization of brain responses as a response to AD pathological changes. As a test of the concept of CR, the results demonstrate that there are differences in this reorganization as a function



**Figure 4.** Voxel-wise multiple regression of the cognitive reserve variable against brain activation: A, In the left precentral gyrus (where the slope for the Alzheimer disease [AD] patients was significantly [ $P < .05$ , Bonferroni corrected] more positive than for control subjects). B, In the right fusiform gyrus (where the slope for the AD patients was significantly [ $P < .05$ , Bonferroni corrected] less positive than for controls). This is a graphic representation of some of the results (voxels with highest  $t$  values) presented in Table 3 and Figure 3, with AD patients' data depicted in solid circles and solid regression lines and healthy elderly controls' data in open circles and dashed regression lines.

of the CRV. This is a first step toward understanding the neural implementation of the epidemiological evidence of reserve and compensation.

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