Brain mechanisms of successful compensation during learning in Alzheimer disease

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Abstract—*Objective:* To determine whether patients with Alzheimer disease (AD) compensate for neuropathologic changes when performing a mnemonic task by recruiting 1) the same brain regions as age-matched, healthy controls, but to a greater extent; 2) additional brain regions not activated by controls; or 3) both. *Methods:* Twelve patients with mild probable AD and 12 healthy age- and education-matched controls participated in an fMRI study of successful encoding and retrieval of visuospatial paired associates. To ensure successful performance in both groups, participants were given multiple attempts to learn associations between two and three object locations. *Results:* The pattern of brain activity in patients with AD performing an easy version of the task was indistinguishable from that of controls performing a harder version of the task. Increased activation in left medial and right lateral prefrontal cortices was found in patients with AD compared to controls during encoding of two object locations, but not when this level of encoding in patients was compared with encoding of three object locations in controls. *Conclusions:* There was no evidence of neural plasticity in the form of recruitment of novel brain regions in patients with Alzheimer disease. Data supported greater recruitment of the same brain regions as age-matched controls as a means of compensating for neuropathology and associated cognitive impairment in Alzheimer disease.

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When patients with Alzheimer disease (AD) complete an episodic memory task, it is possible that compensatory neural activity has occurred to preserve function.[1] Data from functional imaging studies of AD suggest that such compensation may be supported by increased prefrontal activity[2-4] and increased functional connectivity within prefrontal[5] and between prefrontal and posterior cortical areas.[6] Two important questions, however, remain unanswered.

First, and most fundamental, to what extent can differences in brain activation between patients with AD and comparison subjects be attributed to differences in task performance and success rather than reflecting compensation?

Second, does functional compensation in AD involve the recruitment of brain regions not associated with task performance in healthy individuals (qualitative changes in brain activation), increased activity within networks that are normally associated with task performance (quantitative changes in brain activation), or both?

To answer these questions, we examined successful performance of easier and harder versions of a visuospatial paired associates learning task (VPAL) in mildly affected patients with AD and healthy, age-matched controls using fMRI. If functional compensation is served by qualitative changes in brain activation or neural plasticity, then we expected to see patients with AD activating brain regions not activated by controls during performance of the cognitive task. However, if functional compensation is served by quantitative changes in brain activation, then we expected to see the same pattern of brain activation that controls display during performance of a harder task in patients with AD performing an easier version of the same task.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the September 26 issue to find the title link for this article.

Methods. *Participants.* Twelve patients (five men, seven women) who fulfilled National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[7] criteria for mild probable AD and 12 healthy, age- and education-matched controls (five men, seven women) were recruited. A diagnosis of probable AD was made by an experienced consultant geriatric psychiatrist. All participants were screened for concomitant neurologic diagnoses and psychiatric history and were assessed on a set of neuropsychological tests. Seven patients were receiving acetylcholinesterase inhibitor

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(ACHeI) treatment. All participants provided written informed consent before participating in the study that had been approved by the joint Research Ethics Committee of the Institute of Psychiatry and South London and Maudsley Trust.

Materials and procedure. The VPAL task involved participants remembering the locations of color pictures of everyday objects that were presented on a computer screen (figure E-1 on the *Neurology* Web site at www.neurology.org) and was chosen because it has been shown to be sensitive to memory deficits in the early stages of AD.[8-12] In this task, a randomly chosen depicted object appeared in one of the white boxes for 5 seconds, and then 0.5 second later, another object appeared in a different white box. As each object was presented for encoding, participants heard the instruction "remember."

Six seconds after the end of the encoding phase, one of the objects that had been presented reappeared in one of the white boxes for as long as 5 seconds. At the same time, participants heard the question "was this here." They were then required to make a two-choice forced recognition decision by pressing one of two response keys (yes/no). After 0.5 second, another object was presented in one of the white boxes, to which participants had to respond. This process was repeated until memory for all objects seen in the encoding phase had been tested.

A baseline rest period of 7.5 seconds (when there was unsuccessful completion of the problem) or 10.5 seconds (when there was successful completion of the problem or when there were five failed successive attempts) followed the retrieval phase. After this, if an incorrect response was made, then the same object locations were presented in a different order, and participants were given a second attempt at completing the problem. This process continued until there was successful completion of the problem or until participants had failed on five successive attempts, after which participants were presented with a new set of object locations.

During scanning, participants were presented with four types of problems comprising different numbers of object-location pairings. For the purposes of this article, we were only interested in the trials when two objects were paired with three locations or three objects were paired with four locations (see Gould et al.[13] for further information regarding trial types). All participants received offline practice on the task to ensure that they could perform it successfully while being scanned.

Image acquisition. Functional and structural data were acquired on the 1.5-T General Electric Signa system at the Maudsley Hospital, London. Each functional time series lasted 308 seconds in which 154 T2-weighted images depicting BOLD contrast were acquired using an interleaved echo planar (EPI) sequence at 16 whole-brain axial slices (TR = 2000 msec, TE = 40 msec, slice thickness = 7 mm). Participants received eight to 10 functional time series in two 1-hour scanning sessions (separated by approximately 1 week), apart from two patients with AD who received five functional time series in one scanning session. Three-dimensional, high-resolution whole-brain axial images were also acquired for each participant (TE = 5.8 msec, TR = 17.1 msec, thickness = 1.5 mm).

Behavioral data analyses. The Mann-Whitney *U* test was used to assess neuropsychological test performance. Behavioral measures of successful performance of the VPAL task were analyzed using a mixed-factor analysis of variance (ANOVA).

Functional imaging data analyses. Data in each functional time series were slice-timing corrected, realigned, and unwarped to correct for motion-related variance, coregistered to the high-resolution T1-weighted image, normalized into Talairach and Tournoux[14] standard space, and spatially smoothed using SPM2.[15]

Using statistical parametric mapping,[16] for each participant, the BOLD response to the stimulus onset of each trial type was modeled with an epoch design that was convolved with a canonical hemodynamic response function within the general linear model. Encoding and retrieval epochs corresponding to problems comprising two object locations lasted 11 seconds and three object-location problems lasted 16.5 seconds. Successful encoding and retrieval phases for different trial types were modeled as separate regressors. Encoding and retrieval epochs associated with unsuccessful attempts and the interval between encoding and retrieval epochs were modeled as a covariate of no interest.

Contrast-weighted images of beta parameter estimates that corresponded to successful encoding or retrieval of two or three object locations > baseline were entered into one sample *t* tests and analyses of covariance (ANCOVAs) to form statistical parametric maps (SPMs) of the *Z* statistic. Participants were treated as a random variable. The nuisance covariate entered into ANCOVAs was the mean number of attempts taken to successfully complete a two- or three-object location problem during scanning. Within-group and between-group SPMs that assessed activations across the whole-brain were thresholded at $p < 0.05$ corrected.

In addition to whole-brain analyses that assessed the recruitment of additional task-related brain regions in patients with AD compared to controls, region-of-interest (ROI) analyses examined quantitative changes in brain activation. An anatomic ROI comprised bilateral inferior, middle, and superior frontal gyri and medial prefrontal cortex (figure E-2). Functionally defined ROIs comprised all voxels activated by controls in the current study during successful three-object encoding > resting baseline (figure E-3) and three-object retrieval > resting baseline (figure E-4). In all ROI analyses, small volume corrections (SVCs) for multiple comparisons were calculated, with only those voxels surviving a corrected height threshold of $p < 0.05$ being reported.

A more detailed Methods section can be found on the *Neurology* Web site.

Results. *Behavioral data.* Table 1 presents the results of the neuropsychological tests for patient and control groups. Patients with AD were found to perform worse than controls on the Mini-Mental State Examination ($p < 0.001$), WMS Immediate ($p < 0.005$), and Delayed Logical Memory ($p < 0.0001$), DRS-2 Initiation/Perseveration subscale ($p < 0.01$), DRS-2 Memory subscale ($p < 0.0001$), DRS-2 Total Score ($p < 0.001$), and Clock Drawing Test ($p < 0.05$).

Behavioral measures of successful performance of the VPAL task for patients with AD and controls are presented in table 2. In line with mnemonic and visuospatial impairments described above, patients with AD took more attempts to learn two and three object locations in the VPAL task than controls.

For the mean number of attempts per problem, there was a main effect of number of object-location ($F[1,22] = 10.82$, $p < 0.005$, 1.16 attempts for two-object problems vs 1.54 attempts for three-object problems) and group ($F[1,22] = 8.10$, $p < 0.01$, 1.57 attempts for patients with AD vs 1.13 attempts for controls) and an interaction ($F[1,22] = 6.32$, $p < 0.05$). Patients with AD took more attempts to successfully complete object-location problems than controls, especially for three-object problems. For the percentage of problems correct on the first attempt, there was a main effect of number of object locations ($F[1,22] = 26.54$, $p < 0.0001$, 86.32% of two-object problems correct on the first attempt vs 71.54% of three-object problems correct on first attempt) and group ($F[1,22] = 14.50$, mean SE = 5,021.70, $p < 0.001$, 68.70% of problems correct on the first attempt for patients with AD vs 89.16% of problems correct on the first attempt for controls), and an interaction ($F[1,22] = 10.99$, $p < 0.005$). Fewer trials were correct on the first attempt for patients with AD than controls, especially for three-object problems. For the mean number of successfully completed problems, the main effects of number of object locations and group and the interaction were not significant. Patients with AD and controls successfully completed the same number of two- and three-object problems.

fMRI data: Within-group analyses. Compared to a resting baseline, encoding of two-object-location problems was accompanied by increased activation in inferior and middle frontal gyri, medial prefrontal cortex, inferior and

Table 1 *Demographics and neuropsychological test scores for patients with Alzheimer disease and healthy controls, matched on age and years of education*

	Patients with AD	Controls
Age, y	77.3 (4.9)	77.3 (4.8)
Years of education	11.3 (3.2)	11.4 (3.4)
MMSE‡	26.33 (2.06)	29.08 (0.90)
GDS (15-item)	2.64 (1.91)	1.73 (1.35)
NART Errors	12.22 (10.67)	14.36 (14.49)
DRS-2 AMSS Attention	11.73 (1.56)	12.09 (1.58)
Raw score out of 37	35.91 (0.83)	36.18 (0.87)
DRS-2 AMSS Initiation/Perseveration†	6.36 (3.26)	10.27 (2.65)
Raw score out of 37	30.55 (5.13)	35.18 (3.16)
DRS-2 AMSS Construction	10.00 (0.00)	10.00 (0.00)
Raw score out of 6	6.00 (0.00)	6.00 (0.00)
DRS-2 AMSS Conceptualization	9.64 (2.38)	11.45 (2.81)
Raw score out of 39	35.27 (3.58)	36.73 (2.83)
DRS-2 AMSS Memory§	4.09 (3.33)	12.82 (1.25)
Raw score out of 25	16.82 (3.54)	24.73 (0.65)
DRS-2 AMSS Total Score‡	6.18 (2.40)	12.73 (3.44)
Raw score out of 144	124.55 (8.51)	138.82 (6.06)
WMS Immediate Logical Memory (max. 25)†	8.27 (3.98)	17.64 (5.90)
WMS Delayed Logical Memory (max. 25)§	1.00 (2.72)	16.64 (6.77)
Verbal Fluency (letter S)	17.50 (5.64)	16.27 (5.73)
Clock Drawing (0–3 range)*	0.50 (0.53)	0.09 (0.30)

Values represent mean (SD). For patients with Alzheimer disease, n = 12 for MMSE; n = 11 for GDS, WMS, and DRS-2; n = 10 for Clock Drawing and Verbal Fluency; and n = 9 for NART. For controls, n = 11 for all tests except the MMSE, where n = 12. As suggested in the DRS-2 manual, an age-corrected DRS-2 total score of 6 falls within the sixth to 10th percentile range (which equates to a clinical interpretation of mild impairment), whereas a score of 13 falls within the 82nd to 89th percentile range (equating to a clinical interpretation of average intact performance).[17] Further, it is suggested that an age-corrected scaled Total Score of 5 to 7 on the DRS-2 is equivalent to a Total Score of 123 on the original DRS.

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; § $p < 0.0001$ (denoting neuropsychological tests in which control participants performed better than patients with Alzheimer disease).

MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; NART = National Adult Reading Test; DRS-2 AMSS = Dementia Rating Scale-2 age-corrected scaled scores, WMS = Wechsler Memory Scale.

Table 2 *Behavioral measures of performance of a visuospatial paired associate learning task in patients with AD and age-matched controls*

Behavioral measures	Patients with AD	Controls
Two object-location pairs		
Mean no. attempts per problem	1.24 (0.20)*	1.08 (0.07)
% problems correct on 1st attempt	80.84 (14.62)*	91.79 (6.98)
Mean no. problems	9.17 (3.04)	9.58 (2.27)
Three object-location pairs		
Mean no. attempts per problem	1.90 (0.90)*	1.17 (0.19)
% problems correct on 1st attempt	56.56 (20.43)*	86.52 (14.50)
Mean no. problems	8.92 (2.91)	9.50 (1.83)

Values represent mean (SD).

* Comparisons in which patients with Alzheimer disease performed worse than controls on the task measure ($p < 0.05$).

superior parietal lobule, precuneus, middle temporal, middle occipital and fusiform gyri, and cerebellar regions in patients with AD (figure 1, table E-1). Controls activated a similar network of regions to patients with AD, although the spatial extent of frontal activations appeared to be smaller (figure 1, table E-1). During successful encoding of three-object-location problems, significant signal intensity changes were located in precentral, inferior frontal, middle frontal, and anterior cingulate gyri; medial prefrontal cortex; inferior parietal lobule/precuneus; inferior temporal/middle occipital and fusiform gyri; and cerebellar regions in patients with AD and similarly in controls (figure E-5, table E-2).

Successful retrieval of two object locations in comparison to a resting baseline was accompanied by significant activation changes in the medial prefrontal cortex, inferior and middle frontal gyri, precuneus, cuneus, and cerebellum in patients with AD (figure 2, table E-3). Controls activated similar frontoparietal cortices and also occipitotemporal and thalamic regions (figure 2, table E-3). When retrieving three object-location pairs, patients with AD displayed increased activation in inferior and middle frontal gyri, medial prefrontal cortex, precuneus, middle temporal/middle occipital gyrus, and thalamus (figure E-6, table E-4). A similar pattern was found in controls, with peak activations also being located in the lateral parietal cortex and cerebellum (figure E-6, table E-4).

Overall, lateral and medial prefrontal, parietal, occipitotemporal, and cerebellar regions were associated with successful encoding and retrieval of object-location pairs in patients with AD and controls.

fMRI data: Between-group analyses. No significant differences in activation were found between patients with AD and controls during encoding and retrieval of two and three object locations in comparison to a resting baseline after correcting for multiple comparisons across the whole brain. This suggests that patients with AD did not recruit extra brain regions to successfully encode and retrieve object locations. However, some significant differences in activation were observed between patients with AD and controls when SVCs were performed in our functional and anatomic ROIs. Within the functional ROI that corresponded to all activated voxels during three-object encoding in controls, patients with AD were found to activate the left medial prefrontal cortex (Brodmann's area [BA] 6, −8 5 55, $Z = 3.83$) greater than controls during successful encoding of two object locations. No brain regions were activated greater in controls than patients with AD. Within the functional ROI defined by the contrast three-object retrieval > baseline in controls, there were no significant differences in activation between patients and controls during retrieval of two object locations. Turning to the anatomic ROI that included medial and lateral prefrontal regions, successful encoding of two object locations was accompanied by increased activation in the right middle frontal gyrus (BA6, 28 12 53, $Z = 4.40$ and BA9, 30 39 33, $Z = 3.73$) and left medial prefrontal cortex (BA6, −10 5 55, $Z = 4.12$) in patients with AD compared to controls (figure E-7). There were no brain regions that controls activated to a greater extent than patients with AD. Additionally, there were no significant differences in activation between patients with AD and controls during successful

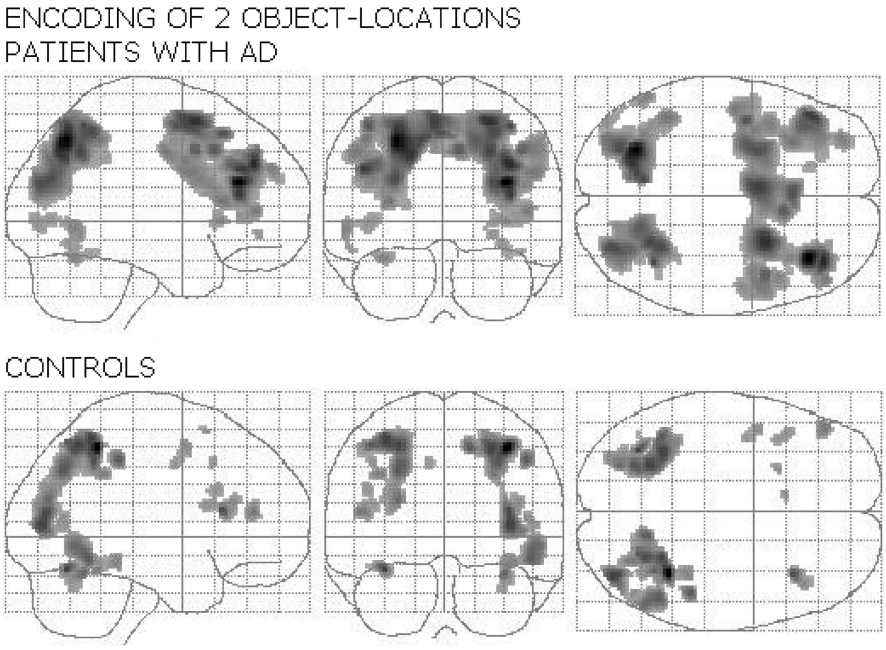

Figure 1. Brain regions showing increased activation during successful encoding of two object locations compared to a resting baseline in patients with Alzheimer disease (AD) and age-matched controls.

encoding of three object locations or retrieval of two or three object-location pairs.

Figure 3 presents mean contrast values for two- and three-object location encoding > rest in brain regions that patients with AD activated to a greater extent than controls during two-object encoding. In the left medial prefrontal cortex, the main effect of number of object locations and the objects-by-group interaction were not significant. However, there was a main effect of group ($F[1,22] = 13.94$, $p < 0.001$). Mean contrast values were greater for patients with AD than controls, irrespective of the number of objects to be encoded. In the right middle frontal gyrus (BA6), there was a trend for a main effect of number of objects ($F[1,22] = 3.76$, $p < 0.07$), while there was a main effect of group ($F[1,22] = 9.09$, $p < 0.01$) and an interaction ($F[1,22] = 9.80$, $p < 0.01$). Mean contrast values were greater for patients with AD than controls when two but not three object locations were encoded. In the right middle frontal gyrus (BA 9), the main effect of number of objects was not significant. However, there was a trend for a main effect of group ($F[1,22] = 3.99$, $p < 0.06$) and there was an interaction ($F[1,22] = 4.21$, $p < 0.05$). Again, differences in mean contrast values between patients with AD and controls were observed during two- but not three-object location encoding.

Significant differences in brain activation between patients and controls were only found during successful encoding of two object locations. The left medial prefrontal cortex was identified from both anatomic and functional ROI analyses, indicating a quantitative rather than qualitative change in regional brain activation in patients with AD compared to controls. Right lateral prefrontal regions were only identified in analyses using the anatomic ROI, implying that these regions were additionally activated in

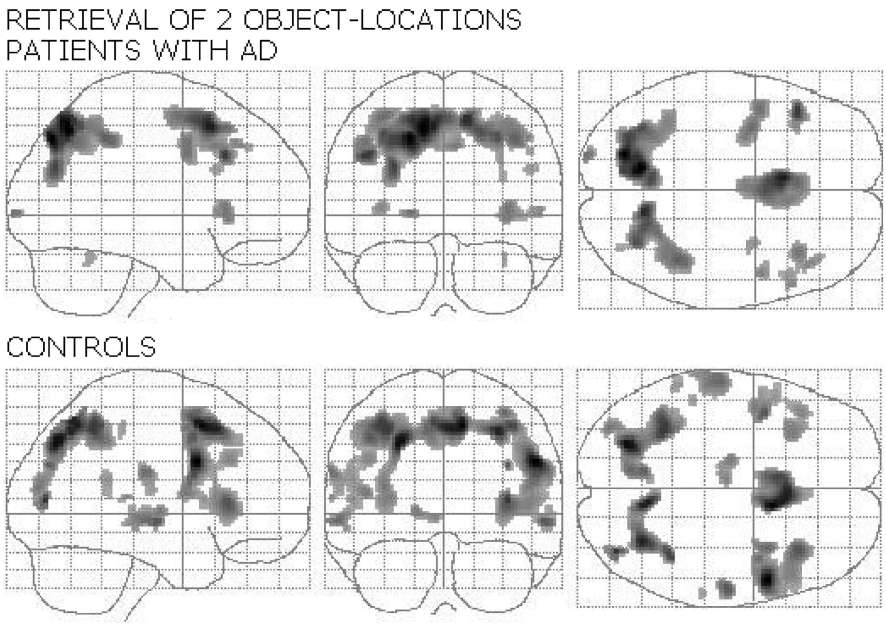

Figure 2. Brain regions showing increased activation during successful retrieval of two object locations compared to a resting baseline in patients with Alzheimer disease (AD) and age-matched controls.

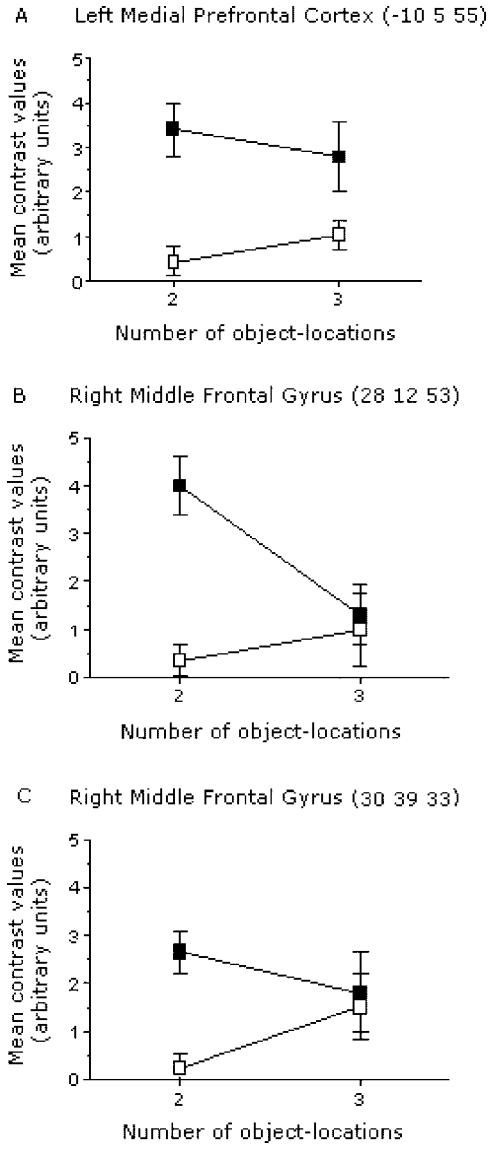

Figure 3. Mean contrast values (± SEM) for brain regions displaying greater activation during encoding of two object locations in comparison to a resting baseline in patients with Alzheimer disease (represented by solid squares) and controls (represented by open squares).

patients with AD but not in controls performing a more difficult version of the task. These regions may simply have been subthreshold to accepted levels of significance in the functional ROI. Therefore, as a further test of functional compensation we compared two-object location encoding in patients with AD with three-object location encoding in controls. If the functional response to encoding easier object location problems in AD is to recruit the same brain regions that healthy individuals employ to encode more difficult object-location problems, then we expected to find no significant differences in activation between patients and controls. If the functional response in AD is to recruit different brain regions compared to controls, then right prefrontal differences in activation should still be present. No significant differences in activation were found between patients and controls, even after applying SVCs within our frontal ROI. Thus, increases in activation associated with successful encoding appear to resemble quantitative rather than qualitative changes in brain activation in prefrontal regions in AD (figure E-8).

Discussion. Our findings suggest that patients with AD recruit the same rather than novel brain regions to successfully encode paired object locations, supporting the notion that prefrontal brain regions involved in task performance in health work harder (or are active to a greater degree) to functionally compensate for neuropathology in AD. The question that remains is what underlies these increases in activation in prefrontal regions during encoding of object locations in AD.

Because brain activations associated with successful task performance were examined in both AD patients and controls, we can be certain that increases in the right middle frontal gyrus (BA6 and 9) and left medial prefrontal cortex (BA6) are not related to differences in performance failure or success across groups. Increases in prefrontal activations could be a reflection of variations in the subjective difficulty of the cognitive task between patients and controls because activations in mid-dorsolateral and mid-ventrolateral prefrontal and dorsal anterior cingulate cortices have been found under conditions of increased objective cognitive load.[18] Although we were able to gather ratings of subjective task difficulty in controls, we were unable to do this for patients with AD as ratings proved to be unreliable, and so we have no direct means of comparing subjective task difficulty between groups. However, if we take each participant's mean number of attempts to successfully learn object-locations as a proxy measure of subjective task difficulty, then we have an indirect way of controlling for variations in subjective task difficulty across individuals. Given that the effect of this measure was covaried out of all between-group analyses, activation increases in prefrontal regions at a given level of objective task difficulty may reflect true functional compensation in AD rather than differences in subjective task difficulty. The neurophysiologic basis of such functional compensation could be a "broadening of the cortical field in response to the altered cortical connections caused by neuropathologic changes"[2] as has previously been suggested following the observation of an increased spatial extent of brain activation in patients with AD compared to controls.

Alternatively, such increases in brain activation may be related to differences in the extent to which attention- or memory-related processes are engaged in the task at a given level of objective task difficulty. Right prefrontal activations are commonly found in studies of sustained attention,[19] and greater increases in regional cerebral blood flow in the right medial prefrontal cortex (BA6) and right middle frontal gyrus (BA6 and 46/9) have been reported during rehearsal of 10-word lists in patients with AD compared to controls.[3] Thus, increased right lateral prefrontal activations in the current study may reflect a greater engagement of attentional resources

or a greater reliance on subvocalization/rehearsal processes in patients with AD compared to controls to successfully encode visuospatial information at a given level of objective task difficulty.

Although these explanations may fit the observations associated with two-object encoding, neither can explain the lack of significant differences in activation between patients and controls during three-object encoding. Instead, a physiologic explanation concerning the association between the BOLD response and increasing task difficulty in prefrontal regions may suffice. Implicit in the quantitative hypothesis was the assumption that a linear relationship exists between the BOLD response and cognitive load. Although many brain regions are known to display such linear relationships, some studies have provided evidence of a nonlinear relationship between the BOLD response and increasing cognitive load in prefrontal regions.[20-22] For example, a capacity-constrained or inverted-U response, in which signal change increased with load, peaked at maximum capacity, and then decreased, has been reported in the left dorsolateral prefrontal cortex in a verbal *n*-back working memory task.[20] A similar response function to increasing working memory load was reported within the dorsolateral prefrontal cortex in participants in the placebo arm of a ketamine infusion study.[21] Therefore, increased prefrontal activations during two- but not three-object encoding in patients with AD compared to controls may be suggestive of a capacity-constrained response that peaks at an earlier level of cognitive load in AD than in health. With only two load levels per subject, the supposition of such a nonlinear response in prefrontal regions is speculative, and further research is necessary to fully describe load-response functions in prefrontal cortices in AD.

A final factor that may have influenced prefrontal activations during two-object encoding in patients with AD is medication status. In the current study, seven of 12 patients with AD were receiving AChEI treatment for memory problems. Previous studies have demonstrated that cholinergic stimulation increases activation in prefrontal cortices during performance of explicit memory tasks in patients with AD and older adults with mild cognitive impairment (MCI),[23,24] whereas cholinergic blockade decreases activation in these regions in healthy, younger adults.[25,26] To assess the influence of medication on prefrontal increases in activation in patients with AD, mean contrast values from left medial and right middle frontal regions were submitted to mixed-factor ANOVAs. There were no significant main effects of group (medication vs no medication), or object locations (two vs three) or an interaction in the left medial prefrontal cortex (BA 6) or right middle frontal gyrus (BA 9). There was a main effect of object locations and an interaction in the right middle frontal gyrus (BA 6) ($p < 0.05$), although the interaction did not survive post hoc pairwise comparisons. Although it is difficult to draw strong conclusions from such post hoc analyses due to the small number of participants in groups not matched for age or cognitive status, it would appear that medication status of patients with AD had minimal influence on activation increases in prefrontal regions during encoding of two object locations.

Turning to the lack of significant differences in brain activation between patients with AD and controls during retrieval, evidence suggests that encoding processes may be more impaired in the earlier stages of AD than retrieval operations.[27-30] For example, older adults with MCI were more impaired on an encoding compared to retrieval task than adults without MCI.[27] Furthermore, the same category cues at encoding and retrieval have been found to significantly enhance memory performance in mild dementia compared to cueing at retrieval alone.[28] Thus, the finding of differential responses in prefrontal regions during successful encoding, but not retrieval, in mildly affected patients with AD compared to controls is in accord with previous findings.

As an aside, it is important to note that brain activations associated with the endpoint of learning (i.e., successful encoding and retrieval of paired associates), but not the learning process itself, were examined in the current study. It is possible that patients with AD achieved successful learning through different mechanisms from healthy controls, and so an examination of the learning process would provide further insight into functional compensation in AD. Unfortunately, it was not possible to examine the learning process in the current study due to the small number of attempts taken to successfully complete object-location problems in control and patient groups, especially for two-object location problems. Thus, future research should examine learning across multiple attempts to elucidate the functional mechanisms by which patients with AD are able to successfully learn new information rather than just the endpoints.

Finally, some may consider the cohort of patients with AD in the current study to be more representative of older adults with MCI. Thus, a caveat of the current study is that functional compensation exhibited in the form of quantitative rather than qualitative changes in brain activation during successful encoding of paired associates may actually be a feature of MCI rather than mild AD. It may be that qualitative changes in functional compensation would have been observed in addition to quantitative changes if a more impaired group of patients with AD had participated in the current study. Further research is necessary to determine whether functional compensation differs between patients in more advanced stages of the disease and more mildly affected patients and whether this functional compensation changes, either quantitatively or qualitatively, with disease progression.

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