Impairment of nonverbal recognition in Alzheimer disease

A PET O-15 study

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ABSTRACT Objective: To characterize deficits in nonverbal recognition memory and functional brain changes associated with these deficits in Alzheimer disease (AD). **Methods:** Using O-15 PET, we studied 11 patients with AD and 17 cognitively intact elders during the combined encoding and retrieval periods of a nonverbal recognition task. Both task conditions involved recognition of line drawings of abstract shapes. In both conditions, subjects were first presented a list of shapes as study items, and then a list as test items, containing items from the study list and foils. In the titrated demand condition, the shape study list size (SLS) was adjusted prior to imaging so that each subject performed at approximately 75% recognition accuracy; difficulty during PET scanning in this condition was approximately matched across subjects. A control task was used in which SLS = 1 shape. **Results:** During performance of the titrated demand condition, SLS averaged $4.55 (\pm 1.86)$ shapes for patients with AD and $7.53 (\pm 4.81)$ for healthy elderly subjects ($p = 0.031$). However, both groups of subjects were closely matched on performance in the titrated demand condition during PET scanning with $72.17\% (\pm 7.98\%)$ correct for patients with AD and $72.25\% (\pm 7.03\%)$ for elders ($p = 0.979$). PET results demonstrated that patients with AD showed greater mean differences between the titrated demand condition and control in areas including the left fusiform and inferior frontal regions (Brodmann areas 19 and 45). **Conclusions:** Relative fusiform and inferior frontal differences may reflect the Alzheimer disease (AD) patients' compensatory engagement of alternate brain regions. The strategy used by patients with AD is likely to be a general mechanism of compensation, rather than task-specific. **NEUROLOGY 2007;69:32-41**

Loss of verbal memory function in Alzheimer disease (AD) has been particularly well characterized. Patients with AD also have nonverbal memory deficits.^{1,2} The relationship of these nonverbal memory performance deficits to changes in brain function has received little study with functional brain imaging.

There are differences in cerebral blood flow between patients with AD and normal controls.^{3,4} PET studies have shown more extensive recruitment of brain regions by patients with AD during task performance than is seen in elderly controls, suggesting compensation.⁵⁻¹³ Recent PET work¹⁰ found activation in a wider prefrontal network in patients with AD than in control subjects during performance of both semantic and episodic memory tasks. Activity in the proposed compensatory network was correlated with better performance by patients with AD.

We examined cerebral blood flow differences during continuous, nonverbal, recognition task performance in patients with AD vs cognitively intact elders. The cognitive activation paradigm used in this study differs from those used in many other imaging studies in that it attempts to control for level of performance, and thus task difficulty, between groups. We predicted that patients with AD would engage different regions during task performance, compared with elders, and that specific impairment might be seen in regions generally associated with declarative memory function but less affected by AD pathology. We predicted that

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Table 1 Demographics and neuropsychological test results for patients with Alzheimer disease (AD) and elders			
Measure	AD, mean $\pm$ SD (n = 11)	Elders, mean $\pm$ SD (n = 17)	p Value
Age, y	68.27 $\pm$ 9.94	71.00 $\pm$ 7.00	0.401
Education, y	14.91 $\pm$ 3.24	15.00 $\pm$ 4.05	0.951
mMMSE	48.00 $\pm$ 3.90	54.24 $\pm$ 2.46	<0.001
SRT total	31.00 $\pm$ 8.88	46.88 $\pm$ 7.74	<0.001
NART estimated IQ	112.29 $\pm$ 13.49	121.09 $\pm$ 6.94	0.079
WAIS-R Vocabulary (age scaled)	11.20 $\pm$ 3.79	13.82 $\pm$ 2.46	0.038
Digit Symbol (age scaled)	41.40 $\pm$ 9.22	46.24 $\pm$ 9.54	0.210

mMMSE = modified Mini-Mental Status Examination; SRT = Selective Reminding Test; NART = National Adult Reading Test; WAIS = Wechsler Adult Intelligence Scale.

patients with AD would show fewer hippocampal changes during titration task performance due to the neuropathologic changes associated with AD. Instead, we hypothesized that patients with AD would recruit alternate areas, such as frontal cortex, to help compensate for impairment. This study is novel in that it examines the brain activation changes related to compensation in the face of AD pathology.

METHODS Subjects. Potential subjects were screened with medical, neurologic, neuropsychological, and psychiatric evaluations in order to exclude those from the normal elderly group who might have dementia or cognitive impairment, and to exclude those with severe medical illnesses from both groups. Healthy elderly volunteers were recruited from the community with posted flyers and advertisements in newspapers seeking healthy elderly adults interested in participation in brain imaging. The AD subjects were outpatients with minor cognitive and functional complaints, who sought clinical evaluation at the Columbia University AD Research Center and received a clinical diagnosis of probable AD based on deficits in memory interfering with daily function and neuropsychological test profile. Diagnostic procedures included a full neurologic, medical, and neuropsychological evaluation, followed by a consensus conference attended by at least two attending neurologists and one attending neuropsychologist. Eight patients were receiving treatment with acetylcholinesterase inhibitors (seven with donepezil and one with rivastigmine) at the time of the study. All subjects received brain MRI that was clinically evaluated by a neuroradiologist. Specifically, subjects in the current study did not have any cortical infarcts or lacunes. Deep white matter or periventricular white matter signal changes were evaluated by a neuroradiologist and none of the scans acquired were considered clinically significant or outside the range typically seen in healthy adults in this age group. Subjects were also screened for medications with potential effects on brain function. All subjects were right handed and able to see stimuli clearly without optometric correction. Eleven patients with AD (mean age 68.27 $\pm$ 9.94, 8 men and 3 women, all meeting Diagnostic and Statistical Manual of Mental Disorders-III-R criteria for dementia¹⁴ and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD¹⁵) and 17 cog-

nitively intact elders (mean age 71.00 $\pm$ 7 years, 8 men and 9 women) met criteria for entry into the study. Subject demographics are shown in table 1. After an explanation of the risks involved in the study, all subjects signed informed consent in accordance with the policies of the Institutional Review Boards at Columbia University and the New York State Psychiatric Institute. Data from a portion of subjects in the current study have been included in previous reports.^{16–18}

Neuropsychological evaluation. Subjects were given extensive neuropsychological testing including the National Adult Reading Test,¹⁹ Wechsler Adult Intelligence Scale–R Vocabulary and Digit Symbol,²⁰ Selective Reminding Test,²¹ and modified Mini-Mental State Examination.²² Neuropsychological test results are shown in table 1.

Tasks and paradigm. Subjects were familiarized with the testing apparatus and trained in the tasks prior to their entering the PET scanner. An example of the nonverbal shape stimuli used in this study is shown in figure 1. Looped shapes, termed Lissajou figures, were generated to have similar characteristics that varied randomly within a given set of parameters; their complexity and looped shape was a deterrent to verbal encoding. Each stimulus was prescreened by elderly and younger subjects in a separate study to ensure that it could not be given a name. The nonverbal episodic memory task used in the neuroimaging component of this study was made up of two conditions. In both conditions, subjects were first presented a list of study items, and then a list of test items (containing some items from the study list and foils). For each condition, a trial included an encoding phase followed by a recognition phase, during which subjects made decisions as to whether the current stimulus had been presented in the encoding phase.

In the first (low demand) condition, a single shape was presented during encoding followed by one shape during the recognition phase; a different stimulus was presented during each recognition phase. Thus, study list size (SLS) was always 1; one study shape was followed by one recognition probe that was either the target (a previously seen shape) or a foil.

The second condition (titrate) used a SLS that was determined separately for each subject in a training session on the day before the scan. During this training session (after familiarizing subjects with the tasks) there were two 15-minute titration sessions during which SLS was adjusted in a staircase manner such that recognition accuracy of 75% for each individual subject was attained. This SLS was then used in the titrated demand condition on the day of the scan such that the number of stimuli used in each encode phase and each recognition phase

Figure 1 Examples of the low demand condition and titrated demand condition

Examples of the low demand condition (top line) and titrated demand condition (bottom). Each frame represents a separate stimulus that was shown to the subject. The words "new" and "old" in parentheses indicate the correct response the subject should make when prompted to respond by the presence of a box around the stimulus.

was equal to the SLS. For example, if the titrated SLS was 4, then four stimuli were presented, immediately followed by four probes. For each probe, the subject was required to identify whether the item appeared on any of the initial four trials (each probe had a 50% likelihood of appearing on the initial trials).

In training the subjects, accuracy was emphasized over speed. All parameters and equipment related to task presentation during the training session were identical to that used in the actual test session in the scanner. Three verbal memory conditions and one visual non-memory condition were also presented, but are not discussed in the present report.

Stimuli (during both encode and recognition, and in both conditions) were presented at a rate of one every 5 seconds. Presentation of the items to be encoded was followed by a 500-msec delay, after which the recognition phase began. Recognition probes were distinguished from encoding items by a rectangular frame around the shape (see figure 1). During the recognition phase, subjects were instructed to make a "new" or "old" response to each stimulus by pressing a micro switch with their right or left hand; a left press indicated "new" and a right press indicated "old." Subjects had 6 seconds in which to respond when they were in the recognition phase of the study, with a 200 msec premature response cutoff. After 6 seconds, the stimuli disappeared from the screen. Stimuli automatically advanced if the subject responded prior to the predetermined time limit. Fifty percent of the test probes were "new." Test probes were pseudorandomized so that no more than four consecutive trials required the same response. Each shape was used only once for each subject. To ensure that the average level of complexity was balanced across lists (and between groups), lists were created that were matched in complexity. Lists were randomly sampled, without repetition, for each condition. It should be noted that the number of items processed did not vary systematically as a function of SLS. Those with shorter SLS were exposed to more trials than those with higher SLS, but the total amount of information presented was defined by the radiotracer uptake period.

Conditions were presented in a fixed order in the scanner, with presentation in order of task difficulty. This was done to minimize confusion in the AD subjects due to switching between low and high demand conditions, since three verbal memory conditions were also presented in separate scans. The order of verbal and nonverbal scans was counterbalanced across subjects. In total, six activation scans and one rest scan were collected for each subject.

Image acquisition. Each activation task was initiated 50 seconds prior to the start of the PET scan and continued throughout the scan period. Subjects viewed the stimuli on an overhead monochrome monitor while lying in a supine position. Scans for each condition were separated by 10 minutes.

For each scan, a bolus of 30 mCi $H_2^{15}O$ was injected IV. Scan acquisition was triggered by the detection of a threshold level of true counts from the camera. Employing a Siemens HR+ PET camera, two 30-second scan frames were acquired in 2-D mode and averaged. After measured attenuation correction (15-minute transmission scan) and reconstruction by filtered back-projection, image resolution was 4.6 mm FWHM. Arterial blood sampling was not conducted. Thus, the non-quantitative count images obtained in this study do not represent absolute measurements.

Image processing and statistical analysis. The SPM99 program (Wellcome Department of Neurology) was used to implement the following steps: 1) a mean image was generated for each subject; 2) all images for a given subject were realigned to the mean image; 3) the mean image was used to determine a spatial transformation to the PET MNI space template included with SPM99; 4) this spatial transformation was applied to the individual images; 5) normalized images were smoothed with an isotropic, Gaussian kernel (full-width-at-half-maximum = 12 mm); 6) images were proportionally scaled by the global image mean; 7) group data were modeled with a separate GLM (see below for model details) for the pair of conditions to avoid reliance on sphericity assumptions; 8) voxel-wise t-statistics corresponding to contrasts of interest were computed; 9) MNI coordinates of local maxima of thresholded ($\alpha_{corrected} = 0.05$) SPM {t} maps were converted to standard Talairach coordinates (using mni2tal.m, written by Matthew Brett; <http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>). False-positive rates were controlled with Bonferroni correction for the number of statistically independent resolution elements (resels) across which regressions were calculated.²³

An automated procedure was used to assign anatomic labels, based on the Talairach Atlas,²⁴ to these coordinates by searching for the label associated with the nearest gray matter coordinate²⁵ (Talairach Daemon information is located at <http://ric.uthscsa.edu/projects/talairachdaemon.html>).

Two main sets of analyses were conducted. In the first, the mean activation difference between titrate and low demand was calculated, which we refer to as Condition. The first contrast examined mean differences between the two groups in the effect of Condition (i.e., Group by Condition interaction). This analysis was intended to isolate activation differences between the groups when performance accuracy was matched. The second set of analyses examined the differential slopes (between groups) on the regression between SLS and Condition (i.e., Group by Condition by SLS interaction); this analysis was intended to examine regional differences between patients with AD and normal elders in the relationship between SLS and Condition and was designed to illustrate the degree of individual differences in brain activity as a function of task performance.

A conjunction analysis was conducted to identify regions of activation that were common to the patients with AD and elder subjects in the titrate vs low demand condition. For each group, the contrast image representing the differential activation of titrate vs low demand was thresholded at the square root of the Bonferroni corrected threshold. A conjunction of these images

Table 2 PET titrated task performance data, patients with Alzheimer disease (AD) and normal elders

Measure	AD, mean $\pm$ SD (n = 11)	Elders, mean $\pm$ SD (n = 17)	p Value
Study list size	4.55 $\pm$ 1.86	7.53 $\pm$ 4.81	0.031
Percent correct	72.17 $\pm$ 7.98	72.25 $\pm$ 7.03	0.979
Percent hits	73.30 $\pm$ 13.58	69.96 $\pm$ 17.72	0.579
Percent correct rejections	71.80 $\pm$ 20.70	74.78 $\pm$ 18.88	0.613

was generated such that only voxels that survived the threshold in both images, representing areas of similar activation between the groups, were included.

An additional model was created to identify group differences in brain regions that were associated with total SRT scores, to examine how activation during the titration task was related to performance on a prototypical task of declarative memory. This model was similar to the Group by Condition by SLS interaction described above, but examined the between-group differences in the relationship between SRT and Condition. As above, group differences were determined by identifying regions in which the slopes of the relationship between Condition and SRT performance differed between the AD and elderly group.

RESULTS Task performance. Subject demographics are summarized in table 1. Patients with AD and elders were well matched on age and years of education. The patients' scores on the modified Mini-

Mental State Examination (mMMSE), a 57-point scale, indicated that their degree of dementia was in the mild range. To estimate the patients' level of impairment with the more classic version of the MMSE,²⁶ we used the following regression equation: $MMSE = 1.495 + (0.495) (mMMSE)$, which yielded estimated values of 25.25 and 28.34 for the patients with AD and normal elders. As would be expected, total recall on the Selective Reminding Test was also significantly lower in the patients with AD vs elders.

Ten of the 11 patients with AD and 9 of the elderly controls were given a more comprehensive battery as part of their involvement in a related study. No significant differences emerged ($p > 0.05$) when the two groups were compared on measures of category and letter fluency, verbal abstraction, and visual construction.

Elderly subjects attained a significantly larger SLS than did patients with AD in the titrate condition (table 2). However, as intended, percent correct in the titrate condition did not differ significantly between the two groups. Percent hits and percent correct rejections during performance of the titrate condition were also comparable in the two groups (table 2). As the elderly control group had more female participants, the contrasts were rerun with subject gender as a covariate. The pattern of the results obtained was not altered.

Table 3 PET results for comparisons of patients with Alzheimer disease (AD) (n = 11) and normal elders (n = 17), with contrast values

Comparison	Effect	Talairach coordinates			Brain region	Brodmann area	Contrast value, AD	Contrast value, elder
		x	y	z				
Condition by Group interaction (titrate—low demand)	Higher in AD (figure 2)	−36	−72	−8	L fusiform gyrus	19	3.00	−0.83
		−48	28	8	L inferior frontal gyrus	45	3.04	−0.20
	Lower in AD (figure 3)	34	34	−20	R middle frontal gyrus	11	−2.66	1.26
		−28	46	−14	L middle frontal gyrus	11	−0.62	2.19
Condition by Group by SLS interaction (titrate—low demand by SLS)	Higher slope in AD (figure 4)	−28	44	−12	L middle frontal gyrus	11	1.30	0.11
		22	−24	62	R precentral gyrus	4	1.34	0.05
	Lower slope in AD (figure 5)	−8	17	60	L superior frontal gyrus	6	−1.14	0.05
		−40	−68	−2	L inferior occipital gyrus	19	−1.69	0.42
		36	−39	−1	R parahippocampal gyrus	19	−1.79	−0.04

Figure 2 Glass brain

Glass brain displaying areas in which patients with AD had greater slopes than normal elders in the Condition by Group interaction (see table 3). Regions included left fusiform gyrus and left inferior frontal gyrus. Global maximum value superimposed on a template brain is displayed in the lower right. Histograms displaying PET signal differences between the two groups in the left fusiform gyrus and left inferior frontal gyrus.

Neuroimaging. Results of the SPM contrasts are summarized in table 3 and displayed visually in figures 2 through 5 together with histograms that display individual differences in PET signal. Compared to elders, patients with AD showed greater mean differences between low and titrated demand conditions than elders in the left fusiform and left inferior frontal cortex (Brodmann areas 19 and 45, respectively). The elders showed greater mean differences than patients with AD in bilateral middle frontal gyri (Brodmann area 11). It should be noted that these comparisons do not include SLS in the model. Results from the conjunction analysis indicated that areas of similar activation in the two groups included the right superior frontal gyrus and the left precentral gyrus.

There was a significant condition by group by SLS interaction. This interaction is equivalent to a difference between groups in the slope of the relationship of titrate–low demand PET activation with SLS. The slope was greater in patients with AD compared with elders in the left middle frontal gyrus (Brodmann area 11) and right precentral gyrus (Brodmann area 4). The slope was greater in elders in the left superior frontal gyrus (Brodmann area 6), left inferior occipital gyrus (Brodmann area 19), and

an area encompassing the right parahippocampal gyrus (Brodmann area 19).

When group differences in the slopes of the relationship between activation during titrated task performance (titrated – low demand) and SRT were examined, AD slopes were significantly greater than controls in the right hippocampus (BA 22), left superior temporal gyrus (BA 21), and right parahippocampal gyrus (BA 27). Areas where controls' slopes were greater than AD patients' slopes included the right precentral gyrus (BA 9) and the subthalamic nucleus. Examination of the interaction at the level of the right hippocampus revealed a positive slope in patients with AD and a negative slope in the elderly controls.

DISCUSSION Taken together, the findings described above support our hypotheses of nonverbal memory performance deficits and recruitment of differing brain regions in the patients with AD compared to controls. Differences in the patients with AD could reflect use of alternative brain regions, relative to controls, perhaps as a general compensatory response to the putative AD-related pathology. This focus differs from much of the prior work in AD, which has emphasized deficits in patients with AD but has not examined how brain activity changes with attempts to compensate.

Findings of performance differences between the patients with AD and normal elders are not surprising. Although nonverbal memory functioning in AD has received relatively less attention than verbal memory, several authors have reported AD-associated nonverbal memory decline.^{1,2,27,28} The patients with AD included in the current study were mildly impaired and behavioral differences with controls were of relatively small effect size. Nonetheless, the findings support the idea that there are nonverbal memory changes that begin early in the course of the disease. Demonstration of small, but reliable, performance differences on the behavioral task was important for two reasons. First, it allowed for the comparison of the two groups when performance was matched to a set accuracy level (i.e., 75%). Second, it allowed for analysis of regional brain activity as a function of individual differences in memory task performance.

The primary finding from the current study suggests that patients with AD engage compensatory brain regions when performing at a similar accuracy level to that seen in elderly controls. Patients with AD showed greater activation in the fusiform gyrus and inferior frontal gyrus, whereas controls engaged the middle frontal gyrus, suggesting that patients with AD utilized additional posterior neural

Figure 3 Glass brain

Glass brain displaying areas in which normal elders had greater slopes than patients with AD in the Condition by Group interaction (see table 3). Regions included right middle frontal gyrus and left middle frontal gyrus. Global maximum value superimposed on a template brain is displayed in the lower right. Histograms displaying PET signal differences between the two groups in the right middle frontal gyrus and left middle frontal gyrus.

resources. Regions that were common to both groups, demonstrated with a conjunction analysis, included the right superior frontal gyrus and left precentral gyrus. The results are consistent with previous efforts to examine compensatory brain regions in AD. For example, areas in the prefrontal and posterior cortex related to semantic memory task performance in patients with AD have been found.¹⁰ Specific regional differences between the two groups may be interpreted in the context of functional imaging studies of declarative memory tasks, although it is difficult to dissociate specific aspects of memory (e.g., encoding vs retrieval) in the current study because data acquisition occurred during both phases in a single scan. The fusiform gyrus has been implicated in both encoding and retrieval aspects of visual memory task performance. Normal elders have shown reduced activation, relative to young volunteers, in the fusiform during picture encoding.^{10,29} The fusiform is also involved in face encoding, recognition, processing of nonsense shapes, and successful retrieval.³⁰⁻³⁴ In the current study, patients with AD may have used the fusiform and related areas to compensate for compromised neural resources in other regions affected by disease pathology. The lower SLS attained by the patients

with AD indicates that this was not an entirely successful strategy.

Prefrontal cortex activation has been implicated in a number of short-term and long-term memory paradigms, during both memory encoding and retrieval, with both verbal and nonverbal stimuli.^{35,36} Activation differences between the patients with AD and elders suggest reliance on different neural systems to perform at similar accuracy levels. The middle frontal gyrus is typically reported to be involved with encoding of visual and nonvisual stimuli.³⁷⁻⁴⁰ Similar areas have been reported to interact with the limbic system to promote acquisition of new information in monkeys.^{41,42} It is possible that the increased activation in the middle frontal gyrus, combined with the parahippocampal engagement seen in elders with superior performance on the slope comparison, is indicative of frontal-limbic network involvement.⁴³ The inferior frontal gyrus and other regions of the ventral frontal lobe have been shown to be active during retrieval of nonverbal stimuli.^{40,44}

The Condition by Group by SLS interactions demonstrated that, in comparison to elders, the slope of the relationship between PET activation and SLS was more positive in the AD group in the left middle frontal gyrus. In a recent study,¹⁰ patients with AD were found to engage bilateral dorsolateral prefrontal and posterior cortices during both semantic and episodic memory performance, a pattern not seen elderly controls. In those patients with AD, bilateral middle frontal gyri blood flow increases, as part of a proposed compensatory network, correlated with better task performance for both types of tasks. An fMRI study⁴⁵ also found differential frontal changes in patients with AD compared with controls during performance on a semantic memory task. Recruitment of additional prefrontal resources with increasing task demand has been shown in an array of differing paradigms in studies of nonimpaired subjects, suggesting a generalized compensatory response.⁴⁶⁻⁴⁸

Conversely, elders showed more positive slopes in several regions, including right parahippocampal gyrus. The lack of medial temporal lobe differences in patients with AD relative to elders has been reported in other nonverbal memory imaging studies.^{7,8} Diminished hippocampal activity in all subregions was found in patients with AD compared to controls during face encoding.⁴⁹ This result would be expected given that pathologic changes in AD generally occur first in the hippocampus and surrounding regions⁵⁰ and its role in consolidation of new information has been well-described in lesion, animal, and imaging work.⁵¹⁻⁵⁵

Figure 4 Glass brain

Glass brain displaying areas in which patients with AD had greater slopes than the normal elderly subjects in the Condition by Group by SLS interaction (see table 3). Regions included left middle frontal gyrus and right precentral gyrus. Global maximum value superimposed on a template brain is displayed in the lower right. Slope differences plotted for the left middle frontal gyrus and right precentral gyrus.

In an earlier study by our group,⁶ patients with AD and normal controls performed an analogous word list-learning task, with the same titrated accuracy. Using a covariance analysis of region-of-interest activation patterns during titrated-low demand conditions, greater SLS was associated with greater activation in the left anterior cingulate and left insula, and with diminished activation in the basal ganglia among normal elderly adults. In patients with AD, greater SLS was associated with increased activation in the left posterior temporal lobe, calcarine cortex, posterior cingulate, and the vermis of the cerebellum. In the current study, increased SLS was associated with increased titrate-low demand activation in the right globus pallidus, and with decreased activation in right parahippocampal gyrus and cingulate among the elderly group. In the AD group, increased SLS was associated with increased activation in the left middle frontal gyrus and with decreased activation in the left superior frontal gyrus. While the study designs between the two studies were similar, results are difficult to compare for a number of reasons. First, in our previous study,⁶ a multivariate covariance data analysis approach was used; in the current study,

univariate analyses were conducted. Second, regions of interest were defined a priori in the earlier study, whereas a voxel-by-voxel approach was used in the current study. Finally, the two studies utilized different modalities for task presentation (i.e., verbal vs visuospatial).

A potential explanation for the findings of differential brain activation patterns between patients with AD and controls is that the two groups engaged different cognitive strategies to perform the same task. There are three means by which formerly viewed information can be recalled: comparison with items still available in working memory, pattern familiarity using implicit memory (priming), and conscious recognition using explicit memory. Greater activation in frontal regions seen in the patients with AD might suggest that they utilized either short term explicit memory or working memory strategies to complete the task.³⁵ Similarly the greater slopes observed in the control participants in the hippocampus might suggest their utilization of long-term explicit memory strategies. However, this conceptualization is not consistent with the design of the current study. The titration procedure ensured that each participant worked to maximum capacity given the fixed accuracy level, and pushed each subject to a list length that was above the capacity of his or her working memory. Alternatively, the patients with AD may have used implicit strategies to compensate for explicit memory deficits. Patients with AD have been shown to have intact implicit memory.⁵⁶ Recent fMRI studies with patients with AD during intentional scene encoding demonstrated that patients with AD show intact activation of areas associated with visual implicit memory,⁵⁶ including parietal, cingulate, and secondary visual cortices.^{57,58} In the current study, however, significant activation differences between the normal elderly subjects and patients with AD were not seen in areas involved in implicit memory function in studies of normal subjects, suggesting the two groups did not differ on use of implicit strategy. It is therefore possible that the two groups relied on different brain systems to perform at similar accuracy levels, but unlikely that it was a working or implicit memory task for one and an explicit memory task for the other. When we examined the relationship between SRT performance and regional activation, slopes differed between the patients with AD and controls in the right hippocampus; better SRT performance was associated with greater regional activation among patients with AD, whereas among controls, better SRT performance was associated with diminished activation. This might suggest that patients with

Figure 5 Glass brain

Glass brain displaying areas in which normal elderly subjects had greater slopes than patients with AD in the Condition by Group by SLS interaction (see table 3). Regions included left superior frontal gyrus, left inferior occipital gyrus, and right parahippocampal gyrus. Global maximum value superimposed on a template brain is displayed in the lower right. Slope differences plotted for the left superior frontal gyrus, left inferior occipital gyrus, and right parahippocampal gyrus.

AD with more intact memory utilized the hippocampus to a greater degree. In contrast, in the normal elderly participants, relatively better memory performance was associated with less activation in the hippocampus. These findings are consistent with the idea that patients with AD with more intact hippocampal function (better SRT performance) are more able to activate this area in a demanding task. For intact controls, less hippocampal activation might be needed on this task for individuals with larger memory capacity. It should be noted that patients were matched with controls for SLS on the activation task. Since this task taps multiple cognitive functions, the relationship between task activation and SLS differs from that with SRT. For the same reason, the compensatory strategies that may have been utilized by patients with AD to optimize task performance were likely part of a general response to deficits rather than a task or domain specific occurrence. In a recent PET study of patients with AD,¹⁰ it was found that the same compensatory network was used for both episodic and semantic tasks, arguing against task-specific compensation.

The current study differs from prior imaging

studies with patients with AD in that the titrated demand memory condition attempted to match each subject on task difficulty. This allows us to be more confident that the differences in activation in the AD group truly represent compensatory changes. A limitation to the current study is that the order in which task conditions were presented was fixed (as opposed to randomized or counterbalanced). This was done to minimize confusion in the patients with AD. The consequence of using a fixed task order is the possibility of a confounding effect between condition and position in the task sequence, such as fatigue effects toward the end of the study. However, the counterbalancing of the verbal and nonverbal tasks across subjects mitigates against this concern, since four other scans were also collected. Another potential limitation is the use of an older version of SPM to conduct the image analyses. Although we are unaware of empirical evidence, there is the possibility that SPM99 might have less sensitivity to detect activation than later versions of the software.

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