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Compensatory Recruitment of Neural Resources During Overt Rehearsal of Word Lists in Alzheimer's Disease

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Functional neuroanatomical correlates subserving maintenance rehearsal relative to a reading control task were investigated with positron emission tomography imaging of cerebral blood flow in 6 healthy older participants and 6 patients with mild Alzheimer's disease (AD). Rehearsal and reading rates and number of unique words rehearsed did not differ significantly for the 2 groups. The right dorsolateral prefrontal cortex was activated in both groups during rehearsal, highlighting this region's role in short-term maintenance of verbal information. A shift in cortical processing resources to more anterior brain regions with increased rehearsal list length was seen, likely reflecting greater demands on frontal cortex as cognitive load grows. Whereas controls showed unilateral right frontal activation during rehearsal, AD patients demonstrated bilateral frontal activation, possibly reflecting compensatory recruitment of neural resources.

Experimental and clinical studies of cognition in patients with Alzheimer's disease (AD) have identified progressive deficits in virtually all aspects of memory functioning. Although a number of these studies have attempted to relate cognitive deficits in AD to the underlying pathology, the neural basis of the memory impairment produced by the disease is not entirely clear. In addition, whether or to what extent the brain is able to compensate functionally for neuronal loss early in the course of AD is not well understood. Clinical–pathological correlations have provided the majority of data regarding the neuroanatomical basis of cognitive impairment in AD. However, activation studies using positron emission tomography (PET) permit the in vivo investigation of regional changes in cerebral blood flow (CBF) that correspond to changes in neuronal (primarily presynaptic) activity (Jueptner & Weiller, 1995).

Recent activation studies of unimpaired human participants using PET have reported prominent activation in the dorsolateral prefrontal cortex during both episodic and working memory tasks (Andreasen et al., 1995; Fiez et al., 1996; Grasby et al., 1993; Kapur et al., 1994; Shallice et al., 1994; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994a; Tulving et al., 1994b), with concomitant increases often seen in the parietal cortex (Andreasen et al., 1995; Grasby et al., 1993; Shallice et al., 1994), the superior temporal gyrus, the thalamus (Grasby et al., 1993), the anterior (Grasby et al., 1993) and retrosplenial (Grasby et al., 1993; Shallice et al., 1994) cingulate cortex, the hippocampus and parahippocampal gyrus (Grasby et al., 1993), and the cerebellum (Fiez et al., 1996; Shallice et al., 1994).

Resting PET studies of patients with AD typically reveal symmetric bilateral temporoparietal hypometabolism, but the frontal cortex may also be hypometabolic (Azari et al., 1993; Foster, 1994; Frackowiak et al., 1981; Minoshima, Frey, Koeppe, Foster, & Kuhl, 1995; Minoshima et al., 1997). This characteristic hypometabolic pattern may also be seen in nondemented relatives of AD patients who are at risk for developing AD due to their inheritance of the apolipoprotein E Type 4 allele (Reiman et al., 1996; Small et al., 1995). However, PET activation studies of memory may provide a more sensitive measure of dysfunctional brain regions earlier in the course of the disease by placing increased cognitive stress on the memory system (Baron, 1995; Duara et al., 1992). Initial memory activation studies of AD patients using PET attempted to measure memory-

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induced changes in regional cerebral metabolic rate of glucose (rCMRglc) utilization relative to a resting state using fluorodeoxyglucose (FDG) as the radiotracer (Duara et al., 1992; Kessler, Herholz, Grond, & Heiss, 1991; Miller et al., 1987). In general, most of these studies reported that AD patients demonstrated somewhat less global activation than control participants, although group differences in regional metabolic activation were not typically observed during memory tasks. In addition, Duara and colleagues (Duara et al., 1992) reported that brain regions in the AD group that were classified as hypometabolic at rest also showed significant activation during a reading memory task, suggesting their apparent viability in response to cognitive effort. Thus, regional hypometabolism at rest may not be a good index of the potential of that region to activate in response to a cognitive task.

Only one PET activation study to date has used an ^{15}O-labeled tracer to study memory in AD. Becker and colleagues (Becker et al., 1996a, 1996b; Herbster et al., 1996) reported that AD patients showed a greater spatial extent of activation than controls, both when contrasting a subspan word repetition task with rest and when contrasting a supraspan episodic memory task with subspan word repetition. These interesting results provide evidence for alterations in functional connectivity in early AD, supporting the hypothesis that the brain retains the ability to reallocate cognitive and cortical resources in response to neuronal loss. However, there were some methodological limitations that may restrict the generalizability of these findings. For example, AD and control participants differed significantly with respect to supraspan task performance, raising the possibility that differences in regional activation may have reflected task difficulty effects or increased effort on the part of the AD patients rather than specific alterations in memory circuitry per se. In addition, variations in task demands, stimulus input, and verbal output also existed across PET scans, ranging from rest, to repetition, to a series of alternating study–recall test trials. These differences in number of stimulus items presented and presentation rate across experimental tasks make the interpretation of regional blood flow differences obtained by image subtraction somewhat more difficult.

Despite these methodological limitations, the notion of functional reallocation of neural resources during cognitive tasks proposed by Becker and colleagues is consistent with the results of an ^{15}O activation study investigating visuoperceptual face-matching skills (not a memory task) in patients with AD (Grady et al., 1993). This study suggested that AD patients were capable of activating the same regions as normal controls in addition to supplementary frontal regions, possibly due to increased effort on the part of the patients. In another PET study of AD patients using a face-matching task, Horwitz and co-workers (Horwitz et al., 1995) reported that AD patients performed the task with the same accuracy as controls, although they did not use the same functional network. These PET findings are consistent with neuropathological evidence to support the notion that reorganization of neural circuits takes place in the brains of patients with AD (Geddes et al., 1985; Masliah et al., 1991). These collective results suggest that the brain may attempt to reorganize in ways that provide alternative functional pathways for essential cognitive abilities in the face of neuronal loss.

The purpose of this study was to utilize a modification of an overt, directly observed rehearsal technique (Rundus, 1971; Rundus & Atkinson, 1970) to study regional memory-induced activation patterns in mildly affected AD patients and age-, education-, and gender-matched control participants, placing a specific emphasis on controlling for stimulus number, presentation rate, and verbal output. Rehearsal processes have assumed a central role in cognitive models of memory in that they have been viewed as subject-dependent control processes (Atkinson & Shiffrin, 1968, 1971) that regulate the flow of information available to the memory system (cf. the search of associative memory model; Raaijmakers & Shiffrin, 1980, 1981). A number of cognitive studies have demonstrated that primary or working memory is particularly compromised in AD (Baddeley, Logie, Bressi, Della Salla, & Spinnler, 1986; Becker, 1988; Gathercole, 1994; Kopelman, 1994; Morris, 1984, 1986, 1994; Morris & Baddeley, 1988; Morris & Kopelman, 1986). It has been argued that impairment of the control processes associated with working memory may play a greater role than a general deficit in encoding relevant stimulus attributes in producing the primary memory deficit in AD (Morris & Baddeley, 1988). The working memory model (Baddeley, 1986, 1992) posits that these limited-capacity control processes, termed the *central executive system,* are responsible for initiating and regulating component mental processes involved with memory. Two separate storage and rehearsal mechanisms, known as the articulatory loop system and the visuospatial sketchpad, are repositories for verbal and visuospatial information, respectively, and are controlled by the central executive system. Because the components of working memory have a limited capacity, the working memory model would predict that performance would break down as task demands begin to exceed its processing capacity, particularly if the neural resources underlying the central executive system are compromised. As such, working memory may be highly vulnerable to disruption by dementia.

By varying the memory load (list length), we attempted to construct conditions that would produce increasing demand on the working memory system. The overt rehearsal technique has been shown to affect both the maintenance of information in the short-term store as well as the recall of information from the long-term store. Because the rehearsal technique places considerable demands on working memory (which is known to be impaired in AD), and on the basis of previous ^{15}O PET activation studies comparing AD patients with controls (Becker et al., 1996a; Grady et al., 1993; Horwitz et al., 1995), we hypothesized that the rehearsal tasks would produce differences in pattern and extent of regional activation between controls and AD patients that may reflect the operation of different neural circuits or resources supporting memory functioning. Specifically, we expected that there would be increased activation in dorsolateral prefrontal cortex associated with the rehearsal task in both groups, with somewhat more diffuse activation ex-

pected in regions surrounding the dorsolateral prefrontal cortex for the AD patients.

Method

Participants

Six community-dwelling patients with mild AD were recruited from the Emory Alzheimer's Disease Center (ADC) Registry of carefully characterized patients with probable AD by the National Institute of Neurological and Communications Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS—ADRDA) research criteria (McKhann et al., 1984). Despite their mild impairment, the AD patients could cooperate fully with requests to perform all experimental tasks. Six control participants were also recruited from the Emory ADC registry. Control participants performed within normal limits on the Mattis Dementia Rating Scale (DRS; Mattis, 1988) and on the Consortium to Establish at Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Welsh, Butters, Hughes, Mohs, & Heyman, 1992) and had been followed with serial neuropsychological testing for at least 2 years without evidence of decline. All participants were right-handed and community dwelling. The age range of the participants was between 60 and 81 years old, and the groups were not significantly different ($p > .05$) with respect to age (control: $M = 69.2$ years, $SD = 7.8$; AD: $M = 68.5$ years, $SD = 7.1$). We recruited an equal number of males and females in each group, and the groups were not significantly different with respect to years of education (control: $M = 14.3$ years, $SD = 4.4$; AD: $M = 16.7$ years, $SD = 3.1$). Patients and controls denied a history of prior head trauma or stroke, and controls denied a history of other neurological disease. Patients and controls also received a neurological examination, which did not reveal evidence of abnormality beyond the cognitive deficits seen in the patient group. All patients and 4 of the 6 controls also received brain magnetic resonance imaging (MRI), and none of these participants showed evidence of vascular or neoplastic lesions. MRIs were rated for degree of atrophy (none, mild, moderate, severe) by a board-certified neurologist (Scott T. Grafton) blind to diagnostic group. Two patients showed no evidence of atrophy, 3 patients showed mild atrophy, and 1 patient demonstrated moderate atrophy. Two controls showed no significant atrophy, 1 showed mild atrophy, and 1 was rated as having moderate atrophy. Participants denied taking psychoactive medications, and they denied a current or past history of psychiatric disorder. Geriatric Depression Scale (Yesavage et al., 1983) scores were within normal limits (<11) for all participants. Although controls and patients differed significantly on this measure, no participant obtained a score in the depressed range. Neuropsychological testing on the DRS and CERAD battery revealed that the AD group demonstrated memory impairment and impaired category fluency, together with a mild degree of overall dementia severity (see Table 1). Informed consent was obtained from all participants, and this research was reviewed and approved by the Emory University Human Investigations and Radiation Safety Committees.

Experimental Procedure

Nine word lists (corresponding to three lists for each of the three experimental conditions) of bisyllabic nouns matched on imagery and recallability (Christian, Bickley, Tarka, & Clayton, 1978) were constructed. These lists consisted of three 5-word lists, three 10-word lists, and three 30-word lists. The 5- and 10-word lists were used in the low-load and high-load overt rehearsal conditions, respectively, and the 30-word lists were used in the reading control condition. We hypothesized that both patients and controls would be able to maintain five words in working memory relatively automatically through maintenance rehearsal, because the number of words (list length) is approximately equal to the size of the short-term memory store, and all items can theoretically be simultaneously rehearsed without much involvement of additional cognitive processes (e.g., the central executive system; Baddeley, 1986, 1992). In contrast, the 10-word list would likely require additional processing resources from the central executive system, potentially magnifying the working memory deficit in AD. The reading task was designed to control for basic cognitive processes common to the two rehearsal tasks (visual input, verbal output, and linguistic processing of words), without making any demands upon memory. In each condition, individual list words were presented visually on a color computer CRT screen positioned 1 m above the patient in the PET scanner at a fixed presentation rate (4 s/word) for a total of 120 s. Words were presented individually in 2.5-in. (6.35-cm) tall capital letters using a *sans serif* font in white letters against a black background. Each task was started 10 s before intravenous injection of a 45 mCi bolus of $H_2{}^{15}O$, and the scanner began acquisition 10 s after injection. The scan duration was 90 s, and the task continued for 10 s after scanner acquisition ended. To span the entire 120 s, each 10-word list was presented three times, and each 5-word list was presented six times. Participants' verbal output was tape-recorded to facilitate an in-depth analysis of rehearsal rate, number of rehearsals per word, and number of

Table 1
Means and Standard Deviations for Neuropsychological Variables

Variable	Controls		AD patients			
	M	*SD*	*M*	*SD*	*t*(10)	*p*
DRS total (max = 144)	139.7	2.0	125.8	5.8	5.5	<.001
List learning total (max = 30)	20.3	3.0	11.7	3.0	5.0	<.001
Delayed verbal list recall (max = 10)	7.8	1.5	2.2	1.7	6.1	<.001
List learning savings (max = 1.0)	0.92	0.2	0.44	0.3	3.2	<.009
Delayed recognition hits (max = 10)	9.7	0.8	8.0	1.4	2.5	<.04
Delayed recall intrusions (no max)	0	0	2.0	2.1	2.3	<.05
Constructional praxis recall (max = 11)	10.0	2.0	4.2	2.9	4.1	<.003
Animal fluency	19.2	4.7	10.3	3.4	3.8	<.005
Abbreviated Boston Naming (max = 15)	14.5	0.8	13.3	1.5	1.7	<.13
Constructional praxis copy (max = 11)	10.8	0.4	9.5	1.6	1.9	<.08
Geriatric depression scale (max = 30)	1.7	1.0	3.8	1.9	−2.4	<.04

Note. AD = Alzheimer's disease; DRS = Dementia Rating Scale; max = maximum.

unique words rehearsed per 4-s interval (rehearsal set). A brief 1000 Hz tone was superimposed upon the tape coincidentally with presentation of each word to delineate the rehearsal sets for each participant.

In the rehearsal conditions, participants were instructed to begin rehearsing each word aloud as it was presented on the CRT screen, in addition to other words that had previously been presented, thereby requiring continuous recall of previously presented words. In the reading condition, participants repeatedly read only the word presented on the screen at a fixed, participant-determined pace, thereby minimizing any memory demands during the reading control task. Immediately following the conclusion of PET-scanning acquisition, participants were verbally presented with four mental arithmetic distractor problems that took most participants 20–30 s to complete. This intervention was designed to clear the short-term store and to prevent further rehearsal. Participants were then asked to freely recall as many words as possible from the previously presented list. Following the rehearsal trials only, when participants could recall no more words or when they freely recalled all list words, participants were presented with a recognition task in which the words on the list were randomly interspersed with an equal number of foils, and the participants indicated whether each word was or was not on the previous list. However, no delayed recognition testing was presented in the reading condition due to our difficulty in identifying three 30-word lists of bisyllabic distractors that were matched to all other list words in terms of word frequency and recallability. Each of the three conditions (5-word rehearsal, 10-word rehearsal, and reading) was carried out three times, for a total of nine PET scans.

Imaging Procedure

Participants lay supine in the PET scanner with their heads immobilized with a custom face mask (Tru Scan, Annapolis, MD). Images of regional cerebral blood flow (rCBF) were acquired using a modified autoradiographic method (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, Herscovitch, Mintun, & Markham, 1983). For each scan, a bolus of 45 mCi $H_2{}^{15}O$ was injected intravenously commensurate with the start of the behavioral task, and scanning was initiated 10 s after tracer injection. A 90-s scan was acquired and was reconstructed using calculated attenuation correction, with boundaries derived from each emission scan sinogram. A separate transmission scan was acquired of the head holder to correct for its attenuation. The brain and head-holder maps were multiplied together to get the final attenuation correction for each image. Calculated attenuation correction was used to enhance participant comfort by not requiring participants to undergo an extra transmission scan and to minimize artifact due to head movement. If a single transmission scan is performed to correct for attenuation in all images, head movement during acquisition of any of the subsequent images will result in a greater potential for error in attenuation correction (Huang, Hoffman, Phelps, & Kuhl, 1979). Arterial blood samples were not obtained. Images of radioactive counts were used to estimate rCBF as described previously (Fox, Mintun, Raichle, & Herscovitch, 1984; Mazziotta et al., 1985).

PET images of rCBF were acquired with the Siemens 951 (5 patients and 5 controls) or 921 (1 patient and 1 control) tomograph in two-dimensional mode. These devices collect 31 (Siemens 951) or 47 (Siemens 921) contiguous 3.375-mm planes. The image-smoothing procedure consisted of the following steps. Images were initially reconstructed with a ramp filter cutoff at the Nyquist frequency. Next, the images were filtered in three dimensions with a Hanning filter with cutoff at 1 cycle/cm. The resolution of the final images was isotropic and 11.8 mm at full width half maximum (FWHM).

Image Analysis

Image processing was performed on a Sun Ultra 1 Creator 3-D (Sun Microsystems) workstation. This processing was accomplished in three steps: (a) spatial normalization, (b) global blood flow normalization, and (c) statistical analysis. For spatial normalization, a within-subject alignment of PET scans was performed using an automated registration algorithm (Woods, Cherry, & Mazziotta, 1992). A mean image of the registered and resliced images was calculated for each participant. The mean PET image from each individual was coregistered to a population-based PET CBF reference atlas centered in Talairach coordinates (Talairach & Tournoux, 1988) using an affine transformation with 12 *df* (Grafton, Woods, & Tyszka, 1994; Woods, Mazziotta, & Cherry, 1993). The parameters to be fit were three translations, three rotations, and three scalars oriented in a direction specified by the last three parameters. This method provides a direct fit of MRI or PET scans from different participants to each other. The method uses the intrinsic intensity values of the PET CBF images to perform the fitting instead of a surface contour or a limited set of internal or external landmarks. Once the PET scans were coregistered, all images were smoothed as described earlier. Previous investigations demonstrate that this smoothing enhances signal detection (Friston, Frith, Liddle, & Frackowiak, 1991; Grafton, Huang, Mahoney, Mazziotta, & Phelps, 1990; Worsley, Evans, Marrett, & Neelin, 1992). After stereotactic coregistration, a mask consisting of all pixels for which data was available from all 108 PET scans (12 participants × 9 scans per participant) was generated. For the given degree of image smoothing, the volume of this mask yielded approximately 140 gray matter resolving elements (Worsley et al., 1992).

All smoothed images were normalized to each other using proportionate scaling calculated from the global activity of each scan. Normalization was performed using the common volume mask defined previously, to avoid global normalization errors associated with missing data.

For the within-groups analyses, two-way repeated-measures analyses of variance (ANOVAs) with planned comparisons of means across task conditions were used to identify significant task effects (Neter, Wasserman, & Kutner, 1990; Woods, Iacoboni, Grafton, & Mazziotta, 1996). The effects (and sources of variance) in this approach based on the general linear model of multivariate analysis were *task, repetition,* and *subject.* Two planned comparisons of task means were calculated. The first identified a low-load rehearsal effect (5-word rehearsal minus reading control), and the second identified a high-load rehearsal effect (10-word rehearsal minus reading control). Because of the potential effects of atrophy in the AD population, the comparisons were performed separately for each group, and intergroup differences were not calculated on a pixel-by-pixel basis (Woods, 1996). An image of the resultant t test values (i.e., a t map image) for each of these contrasts was calculated on a pixel-by-pixel basis and a threshold was set for $t(24) = 3.091$, $p < .005$. Peak sites on the t map above this threshold were localized, and maximal t and p values were tabulated. The resultant t maps were superimposed on a reference MRI atlas from 1 normal participant centered in Talairach coordinates using the fitting algorithm described previously. To improve the description of response localization with respect to surface brain anatomy, we rendered the images of rCBF significance in three-dimensional perspective on the surface of the MRI reference atlas using the display software AVS (Advanced Visualization Systems, Waltham, MA).

The within-groups analysis described earlier serves more as an exploratory data analytic technique, facilitating the identification of candidate regions of activation in each group. A between-groups analysis of regional blood flow values, testing the hypothesis of whether the specific regions significantly activated by one group are activated to a similar extent in the other group, functions as a confirmatory analytic technique. Relative blood flow values were extracted for those regions significantly activated by controls, and blood flow values in those same regions were obtained for the AD patients. We also obtained the blood flow values associated with only those regions significantly activated by AD patients and extracted blood flow values in those same regions for controls. Using these regional blood flow values, for those specific regions significantly activated by controls, we investigated group-related (control vs. AD) and task-related (5- or 10-word rehearsal vs. reading) differences in CBF. Conversely, for those specific regions activated by AD patients, we examined group- and task-related differences in CBF. A two-way mixed-design ANOVA using task (rehearsal vs. reading) as the within-subjects variable was used to test for significant ($p < .05$) Group × Task interaction effects in each region significantly activated by one group relative to the other. This set of analyses allowed us to determine whether each group was able to demonstrate a similar degree of rehearsal-induced regional blood flow change as the other group.

Results

Performance Data

Possible interlist differences in recall and recognition were examined for each group and list length separately using a one-way repeated-measures ANOVA with list replication (three levels) as the within-subjects variable. No significant differences across list replication were observed for either group for rehearsal rate, number of unique words rehearsed, or number of words recalled or recognized. Therefore, data for each of the three replications of the 5- and 10-word lists and for the reading control task were averaged across like conditions for subsequent analyses.

Rehearsal performance. This set of analyses focused on participants' task performance during each PET study and provided an analysis of the working memory component of the tasks. The two main rehearsal measures of interest were rehearsal rate and number of unique words rehearsed in a rehearsal set. Group performance on these measures is presented in Table 2. Neither the mean rehearsal rate (the number of total words articulated during each scan) nor the mean number of unique words rehearsed during each rehearsal set was significantly ($p < .05$) different between groups, suggesting statistically equivalent task performance for each group during image acquisition. These results suggest that AD patients' articulatory rehearsal mechanisms are intact (as manifested by the statistically equivalent rehearsal rates, particularly for the low memory load condition), which is consistent with previous findings suggesting that the working memory deficit in AD is not attributable to deficient articulatory rehearsal mechanisms (Morris, 1987, 1994). Although patients were not significantly different from controls with respect to the number of unique words rehearsed in each rehearsal set, the pattern of means suggests that the very early AD patients' ability to simultaneously track multiple items in working memory has likely started to decline. Nevertheless, power estimates (Cohen, 1988) based on the observed means and standard deviations are somewhat low given a sample size of 6 per group, $\alpha = .05$, and a one-tailed test, making it somewhat more difficult to detect a significant difference in these measures. Thus, some degree of caution is warranted in interpreting the absence of significant differences on these dependent measures.

Recall and recognition performance. A second group of analyses focused on the extent to which participants' recall and recognition after each PET study and distractor task differed as a function of group membership. This group of analyses evaluated participants' ability to recall the previously presented information after each 2-min rehearsal or reading trial.

Recall performance (number of list words correctly recalled) was analyzed using independent group t tests, and the results of this analysis are presented in Table 3. For the 5-word list, similar performance was observed between groups. However, control participants outperformed AD patients during delayed recall following both the 10-word list and reading conditions. Recognition performance was similar between groups for the 5-word list, but controls outperformed the AD patients on the 10-word list recognition. Recall and recognition performance deficits were observed for the AD group across the 10-word lists, relative to controls, whereas such differences were absent between patients and controls with the 5-word lists. The significant difference between groups on recall of the reading list suggests that the minimal interitem associations that were allowed to develop during this task (because the size of the rehearsal set was constrained to be only one word) had a

Table 2
Rehearsal Performance Data for Study Participants

Variable	Controls		AD patients		Power	$t(10)$	p
	M	*SD*	*M*	*SD*			
Rehearsal rate							
5 words	139.2	21.1	116.9	44.8	.27	1.1	<.30
10 words	131.3	19.8	105.1	35.4	.43	1.6	<.15
Reading	118.1	24.8	110.6	27.7	.12	0.5	<.90
Unique words rehearsed							
5 words	3.6	0.7	2.7	1.0	.52	1.8	<.12
10 words	3.1	0.5	2.3	0.9	.55	1.7	<.12

Note. AD = Alzheimer's disease.

Table 3
Recall and Recognition Performance Data for Study Participants

Performance variable	Controls		AD patients			
	M	*SD*	*M*	*SD*	*t*(10)	*p*
Recall						
5 words	4.8	0.4	3.6	1.5	1.9	>.05
10 words	6.3	0.9	3.1	1.9	3.7	<.004
Reading	4.5	1.5	1.1	0.7	5.0	<.001
Recognition						
5 words	4.9	0.1	4.6	0.5	1.6	>.05
10 words	9.5	0.7	7.2	1.7	3.0	<.02

Note. AD = Alzheimer's disease.

substantial effect on AD patients' later incidental recall of the words on the reading list.

Imaging Data

Within-groups analyses. In the two rehearsal tasks, participants were required to maintain within working memory and articulate words that were presented on the screen, as well as words that were presented previously, whereas in the reading task, participants were required only to repeatedly articulate the individual word presented on each trial. Subtractions of activation between the rehearsal conditions and the reading control condition were expected to highlight those areas that participate in working memory to maintain multiple units of information over a brief period of time. The significant ($p < .005$) foci resulting from these subtractions were performed for each group separately to highlight potentially different patterns of activation and are presented in Tables 4 and 5.

Figure 1 illustrates the cortical activation pattern for both groups (controls in yellow and AD patients in blue) in each hemisphere for the five-word rehearsal versus reading comparison. Control participants demonstrated prominent activation of right-hemisphere cortical regions, with the largest area of regional activation seen in the right middle frontal gyrus in Brodmann area (BA) 46/9, also commonly described as dorsolateral prefrontal cortex. Other right-hemisphere cortical regions activated during the low-load rehearsal condition included two other foci in middle frontal gyrus (BA 6 and 10), precuneus (BA 19), and precentral gyrus (BA 4/6). In addition, bilateral cerebellar activation was noted.

In addition to showing a similar pattern of activation in the right middle frontal gyrus (dorsolateral prefrontal cortex), right precentral gyrus, and right precuneus (although in a slightly different cytoarchitectonic region), AD patients showed additional regional activation in the left hemisphere, including two foci in left dorsolateral prefrontal cortex (BA 9 and 46), left inferior parietal lobule (BA 39), and left medial frontal gyrus (BA 32). Bilateral cerebellar activation was again present. Table 4 also suggests that the AD patients showed more significant areas of activation relative to controls. This finding would be consistent with the theory

Table 4
Significant Foci of Regional Cerebral Blood Flow Increases Resulting From Five-Word Rehearsal Minus Reading Subtraction

Region	Talairach coordinates				Blood flow (ml/min/50 g)								
					Five-word rehearsal				Reading				
					Controls		AD patients		Controls		AD patients		
	x	y	z	t_{max}	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	p^a
Regions of activation for controls													
Right middle frontal gyrus (Areas 46/9)	37	37	23	4.56	72.8	7.6	68.2	8.5	70.9	7.1	65.7	9.5	.712
Right middle frontal gyrus (Area 10)	37	45	−1	4.01	64.0	4.0	59.7	2.8	60.6	2.9	57.4	4.5	.501
Right precuneus (Area 19)	31	−76	33	4.37	65.0	4.3	62.4	8.5	62.4	3.3	61.3	7.9	.357
Right middle frontal gyrus (Area 6)	22	19	53	4.20	63.5	1.7	58.0	4.0	61.3	2.1	58.2	3.6	.004
Right precentral gyrus (Areas 4/6)	45	1	51	4.25	65.3	5.1	58.4	3.2	61.8	4.1	58.2	4.2	.046
Right lateral cerebellum	33	−57	−20	6.11	82.7	7.9	83.7	4.9	79.1	6.9	82.6	5.0	.143
Left posterior middle cerebellum	−5	−76	−23	5.05	71.0	6.4	65.0	7.2	67.8	8.4	65.5	7.0	.018
Right middle cerebellum	2	−50	−15	4.49	73.5	7.2	78.5	5.2	69.7	4.9	77.9	3.8	.101
Regions of activation for AD participants													
Right middle frontal gyrus (Area 10/46)	32	42	13	6.16	71.5	7.1	66.1	6.9	69.3	7.5	64.3	6.9	.709
Left middle frontal gyrus (Area 9)	−46	2	41	6.16	72.0	6.2	76.2	7.3	72.4	4.8	73.1	6.7	.008
Left middle frontal gyrus (Area 46)	−32	−51	5	5.84	65.7	6.7	66.2	4.6	65.0	4.7	62.6	3.9	.153
Left inferior parietal lobule (Area 39)	−36	−65	39	5.46	67.3	5.0	67.5	6.1	67.1	5.0	64.3	5.5	.013
Left medial frontal gyrus (Area 32)	−15	14	44	4.83	58.7	4.4	61.2	4.9	57.9	3.9	57.8	2.8	.060
Right precuneus (Area 7)	2	−68	39	5.58	83.0	7.1	72.3	9.1	82.0	8.0	69.1	7.8	.221
Right precentral gyrus (Area 6)	33	−3	51	4.06	67.4	3.6	65.7	5.3	66.8	5.2	63.5	4.9	.059
Right lateral cerebellum	38	−62	−25	5.55	81.8	5.9	85.4	6.4	79.8	6.9	82.3	4.6	.484
Right medial cerebellum	5	−62	−28	5.19	81.0	6.9	87.4	4.0	80.2	7.5	85.0	6.4	.319
Left lateral cerebellum	−34	−49	−23	3.96	78.5	4.1	80.4	3.5	76.7	5.5	77.9	3.3	.691

Note. AD = Alzheimer's disease.
[a]Denotes *p* value associated with the Group × Task interaction from the two-way mixed-design analysis of variance.

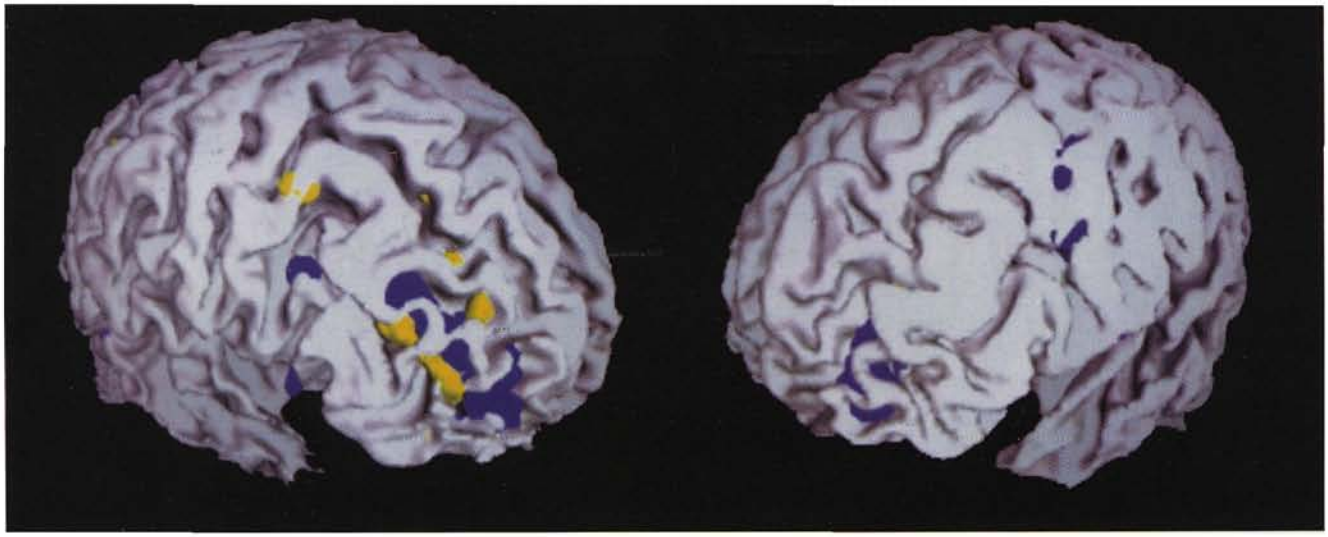

Figure 1. Areas of significant ($p < .005$) activation for the 5-word rehearsal versus reading comparison for controls (in yellow) and for Alzheimer's disease (AD) patients (in blue). Note that activation sites for the controls are confined to the right hemisphere, whereas the activation sites for the AD patients are evident in both hemispheres. For both groups, more posterior areas of activation (premotor and parietal cortex) are evident during this low-load rehearsal versus reading comparison.

that compensatory functional recruitment of additional neural resources occurs in AD.

Figure 2 illustrates the activation patterns for the controls (yellow) and AD patients (blue) for the 10-word rehearsal versus reading comparison. In contrast to the low-load rehearsal condition, controls demonstrated a single focus of activation in the right dorsolateral prefrontal cortex in largely the same region as that seen in the low-load rehearsal versus reading condition.

The AD patients demonstrated a similar pattern of activation in more anterior cortical regions associated with the increased cognitive load, activating only bilateral frontal cortical regions, right ventroanterior thalamus, and bilateral cerebellum (see Table 5). As was seen with the controls, right dorsolateral prefrontal cortex (BA 9) was activated in both low- and high-load rehearsal conditions relative to the reading task, although the magnitude of this activation was somewhat diminished. The AD patients again demonstrated

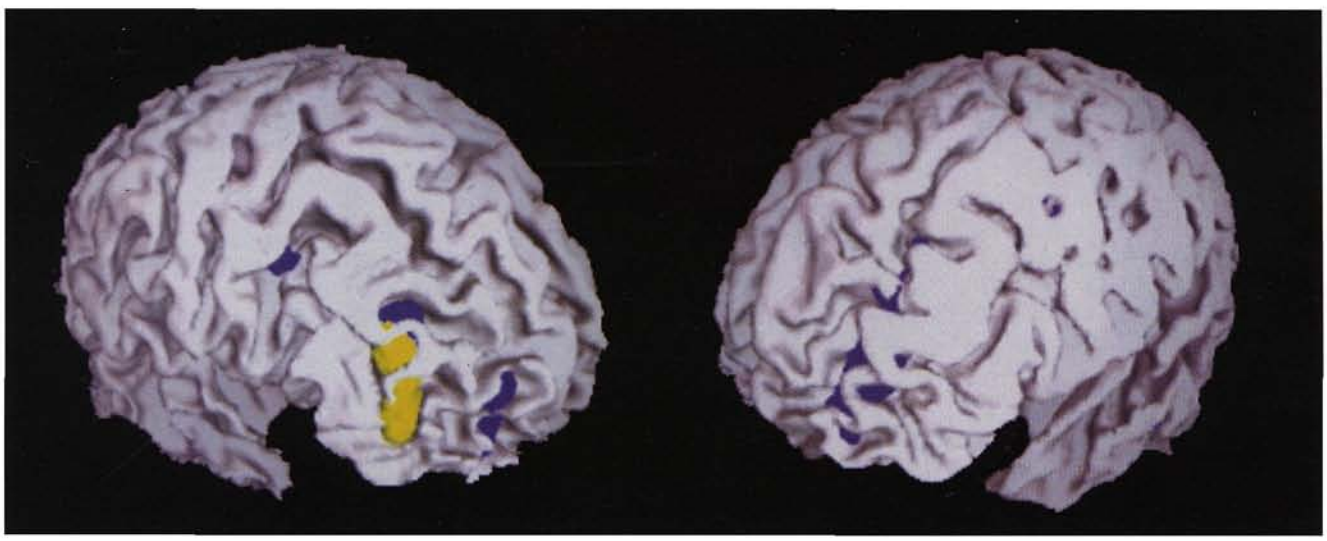

Figure 2. Areas of significant ($p < .005$) activation for the 10-word rehearsal versus reading comparison for controls (in yellow) and for Alzheimer's disease (AD) patients (in blue). Note that activation sites for the controls are again confined to the right hemisphere, whereas the activation sites for the AD patients are again evident in both hemispheres. For both groups, areas of activation are evident only in anterior cortical regions during this high-load rehearsal versus reading comparison.

Table 5
Significant Foci of Regional Cerebral Blood Flow Increases Resulting From 10-Word Rehearsal Minus Reading Subtraction

Region	Talairach coordinates				Blood flow (ml/min/50 g)								
					10-word rehearsal				Reading				
					Controls		AD patients		Controls		AD patients		
	x	y	z	t_{max}	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	p^a
Regions of activation for controls													
Right middle frontal gyrus (Area 46)	43	35	21	5.24	69.2	5.4	64.6	6.6	66.2	3.4	64.3	6.7	.211
Regions of activation for AD participants													
Left middle frontal gyrus (Area 46/10)	−32	50	9	5.24	67.7	7.3	67.7	6.0	65.8	5.9	65.4	5.0	.807
Left middle frontal gyrus (Area 10)	−40	0	44	6.16	68.7	7.9	73.0	4.5	67.8	7.3	70.4	3.3	.356
Right middle frontal gyrus (Area 10)	30	46	−1	4.25	67.6	6.6	65.7	8.8	66.1	4.5	62.8	7.1	.330
Left superior frontal gyrus (Area 8)	−16	13	48	4.56	59.0	3.5	64.6	4.2	59.6	3.4	61.7	3.6	.010
Right middle frontal gyrus (Area 9)	39	31	31	4.78	70.4	5.3	66.7	8.7	67.8	4.7	63.4	8.6	.562
Right middle frontal gyrus (Area 6)	31	−1	48	5.05	59.4	5.7	60.0	2.8	59.6	6.5	57.2	3.7	.014
Right ventroanterior thalamus	12	−7	12	4.32	57.5	3.5	62.8	2.7	58.2	2.6	59.9	2.1	.034
Right medial frontal gyrus (Area 6)	1	2	54	4.95	69.7	4.8	68.7	6.1	70.1	4.9	65.6	5.3	.008
Right middle frontal gyrus (Area 46/9)	25	52	16	3.81	58.1	5.0	58.7	3.7	58.3	4.8	56.5	3.2	.003
Right lateral cerebellum	40	−59	−25	5.04	76.0	5.1	78.6	5.9	75.0	5.9	75.3	4.4	.042
Left lateral cerebellum	−30	−61	9	4.44	84.8	4.8	87.2	5.1	83.9	4.9	82.9	6.3	.005

Note. AD = Alzheimer's disease.
[a]Denotes *p* value associated with the Group × Task interaction from the two-way mixed-design analysis of variance.

two activation foci in left middle frontal gyrus (dorsolateral prefrontal cortex), together with a focus of activation in the left medial frontal and precentral gyri, which were both consistent with the activation pattern they demonstrated in the low-load rehearsal condition. Relative to the low-load condition, AD patients also showed areas of activation in right middle frontal gyrus (BA 46/9), right ventroanterior thalamus, and right medial frontal gyrus. Figure 2 presents the activation patterns of the control participants and AD patients for the 10-word rehearsal versus reading comparison superimposed upon a cortical rendering.

Imaging results: Between-groups analyses. Table 4 presents the blood flow data associated with each of the regions of activation for the five-word rehearsal condition and the reading control task. There were no significant Group × Task interactions in the right middle frontal gyrus (BA 46/9 and BA 10) or precuneus (BA 19), suggesting that the AD patients demonstrated similar blood flow in these regions as controls. However, significant Group × Task interactions were observed in premotor cortex (BA 6) and right precentral gyrus (BA 4/6), with controls showing greater activation than patients in these sites. A significant Group × Task interaction was also seen in the left posterior middle cerebellum.

In like manner, for those regions significantly activated in the AD patients, we examined whether there were significant ($p < .05$) group differences in blood flow in those regions across the two tasks (five-word rehearsal vs. reading). This set of analyses was expected to determine whether the AD patients tended to activate additional brain regions during the rehearsal task over and above those activated by controls. Significant Group × Task interactions were observed in left middle frontal gyrus (BA 9) and left inferior parietal lobule (BA 39). Nonsignificant trends ($p < .06$) associated with Group × Task interactions were seen in left medial frontal gyrus (BA 32) and right precentral gyrus (BA 6). No significant differences were seen in left middle frontal gyrus (BA 46), right middle frontal gyrus (BA 46/10), or for right precuneus (BA 7). Thus, it appears that AD patients are not only capable of activating most of the regions that are activated by controls to a similar degree, but they also activate additional brain regions not activated by controls.

We also repeated these two sets of analyses for the 10-word rehearsal versus reading comparison (see Table 5). For the single activation site seen for controls, there was no significant Group × Task interaction in right middle frontal gyrus (BA 46). For those sites activated significantly in AD patients, significant Group × Task interactions were seen in left superior frontal gyrus (BA 8), right ventroanterior thalamus, right medial frontal gyrus (BA 6), and two sites in right middle frontal gyrus (BA 46/9 and 6). The activation site in BA 46/9 was somewhat more superior and medial to the region activated by the control group. A significant Group × Task interaction was observed in the right and left lateral regions of the cerebellum. No significant Group × Task interactions were observed in two regions in left middle frontal gyrus (BA 46/10 and 10) or two areas in right middle frontal gyrus (BA 9 and 10).

Discussion

The findings from this study indicate that the right dorsolateral prefrontal cortex was activated in both controls and AD patients during both rehearsal conditions (relative to the reading control condition), suggesting that this region is important in the short-term maintenance of verbal information irrespective of load. In both groups, the five-word rehearsal condition activated not only frontal regions but also more posterior regions, including parietal and precentral cortex. In both groups, the 10-word rehearsal condition

activated exclusively frontal cortical regions (along with right ventroanterior thalamus and bilateral cerebellum in the AD patients). The working memory model predicts this shift in cortical processing resources to more anterior brain regions during conditions of increased cognitive load. That is, this shift in neural resources associated with greater cognitive load may be due to increased participation of frontal cortical areas to coordinate, manipulate, and maintain more items in working memory. In addition, more posterior structures thought to be associated with the articulatory loop component of the working memory model, such as Broca's area (articulatory rehearsal mechanism) and supramarginal gyrus (phonological store), might be expected to show greater activation during low-load conditions, due to the fact that a small number of items can be maintained in the articulatory loop without requiring extensive frontal cortical resources. However, with an increased number of items, frontal cortical regions appear to play a greater role in coordinating the rehearsal of the longer list.

Differential patterns and magnitudes of activation for AD patients and controls were also observed for the two maintenance rehearsal tasks with different cognitive loads. In the AD patients, the activation pattern reflected a greater number of regions activated in both rehearsal conditions, activation of bilateral cortical regions (as opposed to the exclusively right-hemisphere activation seen for the controls in both conditions), and greater number of pixels activated (volume of activation), particularly during the five-word rehearsal condition. This differential activation pattern was seen despite the fact that the measured performance of the patients was not statistically different from controls in terms of both rehearsal rate as well as number of unique words rehearsed in a rehearsal set. Given that the mild AD patients' task performance was not significantly different from that of controls, their greater number of activation sites may reflect compensatory recruitment of neural resources to perform the two working memory tasks. Because the rehearsal performance data reflect participants' performance during image acquisition, it is noteworthy that there are no statistical differences between the two groups, particularly for the low-load condition. If significant performance differences existed between the groups, it would be more difficult to directly address the issue of compensatory reallocation of neural resources by comparison of images between groups, because performance differences might imply use of different strategies between groups or simply differential task difficulty between cognitively impaired and intact participants.

The significance of the cerebellar activation pattern is somewhat uncertain. Figure 3 shows significant activation of the cerebellum bilaterally for the AD patients in both rehearsal conditions, whereas a similar pattern of cerebellar activation was seen in the controls only for the five-word rehearsal versus reading condition. Several other studies of working memory in general (Shallice et al., 1994) and silent maintenance rehearsal in particular (Fiez et al., 1996) have reported a similar pattern of cerebellar activation, which has been posited to reflect a possible neuroanatomical component of the articulatory loop system within the working memory model (Baddeley, 1986, 1992). These PET studies have also suggested the involvement of premotor cortex (BA 6), supplementary motor area, and left frontal operculum (Broca's area) in the articulatory loop system. The activation of both cerebellum and frontal cortex is consistent with converging evidence supporting the role of the cerebellum in cognition (Schmahmann, 1991), together with studies demonstrating the existence of corticopontocerebellar pathways between association areas of the premotor and prefrontal regions and cerebellum (Beck, 1950; Wiesendanger, Wiesendanger, & Ruegg, 1979).

Prefrontal cortex is known to be important in the mediation of memory tasks, particularly for primary or working memory (memory for material or events lasting 30 s or less). Lesions in the region of the prefrontal cortex, particularly in the regions of BA 9 and 46, have long been known to produce impairment on spatial delayed response tasks in animal studies of memory (Jacobsen, 1936). The delayed response task requires the use of short-term representational (internalized) memory or working memory, in the absence of external cues, holding the relevant information in mind or on line for a temporal interval (Goldman-Rakic, 1987). Electrophysiological evidence has shown that neurons in prefrontal cortex become activated during a delay period of a delayed response task, suggesting that this temporarily enduring neuronal activity is a cellular correlate of representational or short-term memory (Goldman-Rakic, 1995). Delayed response performance is intact after lesions in other areas of the cortex, including posterior parietal cortex, superior and inferior temporal cortices, or periarcuate or premotor regions (Goldman & Nauta, 1977; Goldman & Rosvold, 1970; Harlow, Davis, Settlage, & Meyer, 1952). A meta-analytic study reviewing experiments involving patients with documented frontal lobe lesions reported strong evidence that such damage is associated with impaired performance on episodic memory testing (Wheeler, Stuss, & Tulving, 1995). The importance of prefrontal cortex in mediating memory is further underscored by neuroanatomical studies that have revealed prefrontal-parietal, prefrontal-hippocampal, and thalamic-prefrontal-parietal-cingulate-medial temporal connections (Goldman-Rakic, 1987; Selemon & Goldman-Rakic, 1988). These neuroanatomical connections between prefrontal cortex and parietal and inferotemporal cortex may play a role in the transfer of information between working memory and long-term memory. Thus, the results of our study concur with these electrophysiological, neuroanatomical, lesion, and animal studies, adding further evidence for the importance of prefrontal cortex in maintenance rehearsal–working memory in both AD patients and demographically matched controls.

The results of this study also suggest that frontal cortical dysfunction may potentially play a role in the working memory dysfunction in early AD. The medial temporal lobe system, consisting of the amygdala, hippocampus, and adjacent anatomically related cortices, including entorhinal, perirhinal, and parahippocampal cortices, is known to play a critical role in normal episodic memory (memory for facts and events; Squire, 1987; Squire & Zola-Morgan, 1991). In addition, in AD, neuropathological studies have revealed

substantial changes in brain regions associated with the medial temporal lobe system, such as neuronal loss, gliosis, reduction of dendritic arborization, and reduction of synaptic density in the hippocampus (Davies, Horwood, Isaacs, & Mann, 1992; Flood, 1991; Hamos, DeGennaro, & Drachman, 1989; Hanks & Flood, 1991; Vijayan et al., 1991) and amygdala (Coleman & Flood, 1987; Herzog & Kemper, 1980; Scott, DeKosky, & Scheff, 1991; Scott, DeKosky, Sparks, Knox, & Scheff, 1992; Unger, Lapham, McNeill, Eskin, & Hamill, 1991; Zweig et al., 1988). However, there is recent evidence to suggest that hippocampal pathology may be a necessary but not sufficient condition for the clinical expression of dementia, and that cortico-cortical disconnection is more salient to the functional decline in patients with AD (Bouras, Hof, Giannakopoulos, Michel, & Morrison, 1994). For example, loss of cortical neurons (Ball et al., 1988) and widespread loss of cortical synaptic density (Scheff, DeKosky, & Price, 1990; Scheff & Price, 1993) have been demonstrated in AD. In attempting to correlate specific anatomic findings with the severity of cognitive impairment in patients who have come to autopsy, researchers have found that neocortical counts of plaques and tangles offer variable degrees of correlations with cognitive measures, whereas there are much stronger correlations with cortical synapse loss (Bennett et al., 1993; Blessed, Tomlinson, & Roth, 1968; DeKosky et al., 1992; DeKosky & Scheff, 1990; Mölsä, Säkö, Paljärvi, Rinne, & Rinne, 1987; Terry et al., 1991). Recently, there is evidence to support the notion that synaptic density in the midfrontal–prefrontal cortex is an excellent correlate of dementia severity in patients with AD (Samuel, Terry, DeTeresa, Butters, & Masliah, 1994). Thus, the diffuse activation bilaterally in frontal and prefrontal cortex seen in the AD patients may reflect the effects of cortical synapse loss in these regions, which may, in turn, be associated with the need for compensatory recruitment of additional neural input.

The notion that that frontal cortical dysfunction likely underlies the working memory impairment in AD is consistent with other empirical work that has also suggested evidence for frontal cortical disruption in AD. For example, cognitive psychology studies have reported that AD patients exhibit a breakdown in ability to inhibit incorrect responses and increased probability of endorsing distractor items (Simone & Baylis, 1997), as well as increased susceptibility to interference and breakdown of inhibition on the Stroop task (Spieler, Balota, & Faust, 1996). Verbal fluency mea-

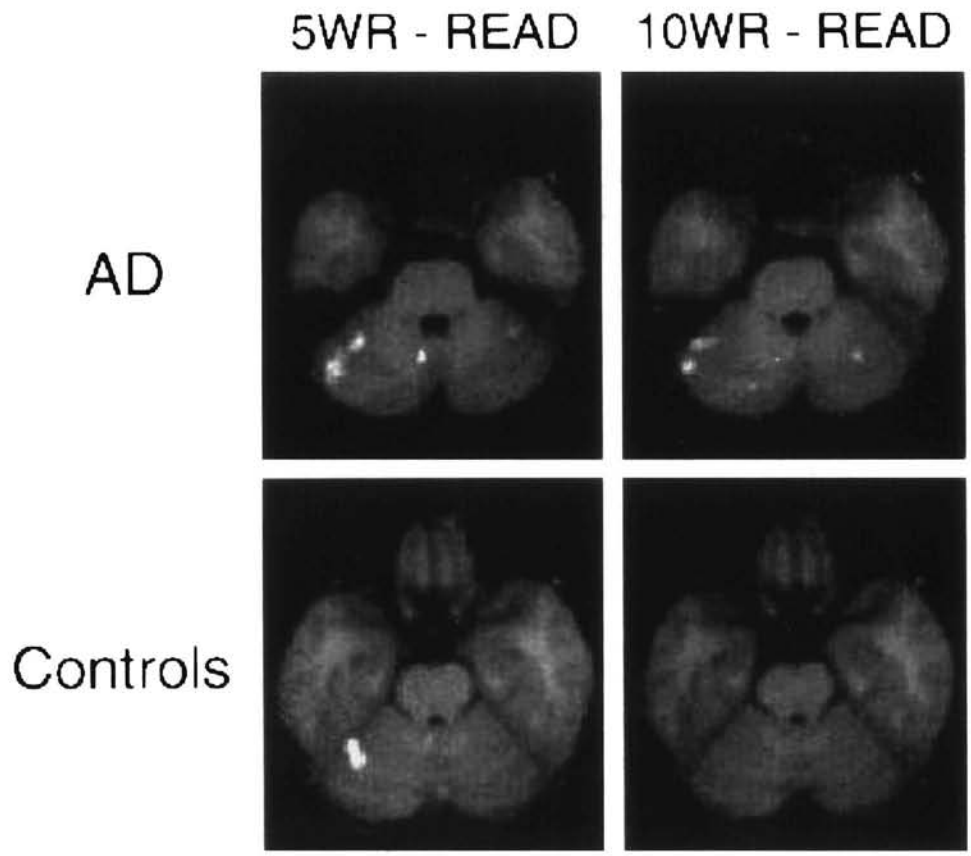

Figure 3. Areas of significant ($p < .005$) cerebellar activation for the 5-word rehearsal (5WR) versus reading comparison and the 10-word rehearsal (10WR) versus reading comparison for controls (bottom two panels) and for Alzheimer's disease (AD) patients (top two panels). Note the absence of cerebellar activation in controls for the 10-word versus reading comparison. In AD patients, the same cerebellar regions were activated in both rehearsal conditions.

sures (particularly category fluency) have also been shown to be diminished in even mild AD (Monsch et al., 1992). These abilities have been viewed frequently as signature frontal lobe tasks (Bench, Frith, & Grasby, 1993; Benton, 1968; Benton, Hamsher, Varney, & Spreen, 1983; Malloy & Richardson, 1994; Mega & Cummings, 1994; Petrides, 1985; Salloway, 1994).

One limitation of this study is the small sample size, which limits our overall power to detect significant effects. We attempted to address this issue by repeating each of the three tasks in triplicate, which has the effect of improving the signal-to-noise ratio overall. A replication of this study using a larger sample size would be helpful in confirming the validity of our results. Such a replication is currently underway in our laboratory. Although our findings that AD patients do not demonstrate the same pattern of activation relative to controls during a working memory task concur with other PET studies and suggest the possibility of compensatory recruitment of neural resources in AD (Becker et al., 1996b; Grady et al., 1993; Horwitz et al., 1995), we cannot conclusively rule out the possibility that such differences may potentially be associated with differential levels of effort or different cognitive strategies. Another consideration that should also be taken into account in the interpretation of the results from PET studies using patient populations is that heterogeneity in the neuropathology associated with AD may have affected the degree to which patients showed different patterns of activation. Finally, poorer cognitive ability may also underlie more diffuse regional activation.

In summary, these results point to several important differences between AD patients and controls in the activation of regions presumed to be part of the neural circuitry of memory. An interesting question that is yet unresolved is why the right dorsolateral prefrontal cortex is exclusively activated more than the left in control participants. A possible model for interpretation of this finding is found in studies by Tulving (Tulving et al., 1994a). Because the rehearsal tasks require continuous retrieval of previously presented words from memory, the increased right dorsolateral prefrontal cortex activity is consistent with Tulving's model of hemispheric encoding–retrieval asymmetry. This model states that right dorsolateral prefrontal cortex activation is seen during episodic retrieval and left dorsolateral prefrontal cortex activation is observed during episodic encoding. In contrast, the bilateral dorsolateral prefrontal cortex activation seen in the mildly affected AD patients suggests possible dysfunction in prefrontal circuitry associated with the executive processes of working memory in the early stages of AD. Alternatively, AD patients may have used a different cognitive strategy during the 10-word rehearsal condition, which may also have produced the apparent cortical reallocation of neural resources. These results might also be accounted for by a combination of these two notions. That is, loss of critical brain regions due to AD may result in compensatory activity in other brain regions in an attempt to support the cognitive activity being performed.

There have been few PET activation studies of memory in patients with AD relative to the number of such studies performed with healthy control participants. Activation studies using patients with AD are important to complement PET studies of normal participants by facilitating the identification of critical neural circuits that are specifically impaired by the disease process. Following characterization of these neural circuits, the efficacy of pharmacological interventions for AD could be evaluated in terms of their ability to alter the interactions between components of the neural circuitry underlying memory functioning (Heiss et al., 1993). Further, PET studies of AD patients could permit the characterization of possible functional reorganization as the brain attempts to compensate for failing cognitive abilities, providing insights into how the human brain copes with neuronal loss. Although neurophysiological and neuroanatomical studies have made considerable progress in tracing the neural circuitry involved in memory in experimental animal studies, PET methods permit the observation of the interactions between these identified brain regions in humans, assessing these neural circuits *in vivo*. If changes in functional connectivity do occur in AD, therapeutic efforts can also be directed toward capitalizing on the viability of newly recruited areas. Finally, a more thorough understanding of the changes in the networks of activation of memory induced by the dementing process or by the aging process in general is important for the advancement of theories regarding neurobiological substrates of memory and can be explored using PET activation methodology.

References

Andreasen, N. C., O'Leary, D. S., Arndt, S., Cizadlo, T., Hurtig, R., Rezai, K., Watkins, G. L., Boles Ponto, L. L., & Hichwa, R. D. (1995). Short-term and long-term verbal memory: A positron emission tomography study. *Proceedings of the National Academy of Sciences, USA, 92,* 5111–5115.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K. W. Spence & J. T. Spence (Eds.), *The psychology of learning and motivation* (pp. 89–195). New York: Academic Press.

Atkinson, R. C., & Shiffrin, R. M. (1971). The control of short-term memory. *Scientific American, 225,* 82–90.

Azari, N. P., Pettigrew, K. D., Schapiro, M. B., Haxby, J. V., Grady, C. L., Pietrini, P., Salerno, J. A., Heston, L. L., Rapoport, S. I., & Horwitz, B. (1993). Early detection of Alzheimer's disease: A statistical approach using positron emission tomographic data. *Journal of Cerebral Blood Flow and Metabolism, 13*(3), 438–447.

Baddeley, A. D. (1986). *Working memory.* Oxford: Oxford University Press.

Baddeley, A. D. (1992). Working memory. *Science, 255,* 556–559.

Baddeley, A. D., Logie, R., Bressi, S., Della Salla, S., & Spinnler, H. (1986). Dementia and working memory. *The Quarterly Journal of Experimental Psychology, 38A,* 603–618.

Ball, M. J., Griffith-Brooks, S., MacGregor, J., Nagy, B., Ojalvo-Rose, E., & Fewster, P. H. (1988). Neuropathological definition of Alzheimer's disease: Multivariate analyses in the morphometric distinction between Alzheimer dementia and normal aging. *Alzheimer's Disease and Associated Disorders, 2,* 29–37.

Baron, J. C. (1995). Étude de la neuro-anatomie fonctionnelle de la perception par la tomographie à positons. [Study of the func-

tional neuroanatomy of perception using positron emission tomography]. *Revue Neurologique (Paris), 151,* 511–517.

Beck, E. (1950). The origin course and termination of the prefrontopontine tract in the human brain. *Brain, 73,* 368–391.

Becker, J. T. (1988). Working memory and secondary memory deficits in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 10,* 739–753.

Becker, J. T., Mintun, M. A., Aleva, K., Wiseman, M. B., Nichols, T., & DeKosky, S. T. (1996a). Alterations in functional neuroanatomical connectivity in Alzheimer's disease: Positron emission tomography of auditory verbal short-term memory. *Annals of the New York Academy of Sciences, 777,* 239–242.

Becker, J. T., Mintun, M. A., Aleva, K., Wiseman, M. B., Nichols, T., & DeKosky, S. T. (1996b). Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. *Neurology, 46,* 692–700.

Bench, C. J., Frith, C. D., & Grasby, P. M. (1993). Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia, 31,* 907–922.

Bennett, D. A., Cochran, E. J., Saper, C. B., Leverenz, J. B., Gilley, D. W., & Wilson, R. S. (1993). Pathological changes in frontal cortex from biopsy to autopsy in Alzheimer's disease. *Neurobiology of Aging, 14,* 589–596.

Benton, A. (1968). Differential behavioral effects in frontal lobe disease. *Neuropsychologia, 6,* 53–60.

Benton, A. L., Hamsher, K., Varney, N. R., & Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual.* New York: Oxford.

Blessed, G., Tomlinson, B. E., & Roth, M. (1968). The association between quantitative measurements of dementia and of senile changes in the cerebral gray matter of elderly subjects. *British Journal of Psychiatry, 114,* 797–811.

Bouras, C., Hof, P. R., Giannakopoulos, P., Michel, J.-P., & Morrison, J. H. (1994). Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: A quantitative evaluation of a one-year autopsy population from a geriatric hospital. *Cerebral Cortex, 4,* 138–150.

Christian, J., Bickley, W., Tarka, M., & Clayton, K. (1978). Measures of free recall of 900 English nouns: Correlations with imagery, concreteness, meaningfulness, and frequency. *Memory and Cognition, 6,* 379–390.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Coleman, P. D., & Flood, D. G. (1987). Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiology of Aging, 8,* 521–545.

Davies, D. C., Horwood, N., Isaacs, S. L., & Mann, D. M. A. (1992). The effect of age and Alzheimer's disease on pyramidal neuron density in the individual fields of the hippocampal formation. *Acta Neuropathologica, 83,* 510–517.

DeKosky, S. T., Harbaugh, R. E., Schmitt, F. A., Bakay, R. A. E., Chui, H. C., Knopman, D. S., Reeder, T. M., Shetter, A. G., Senter, H. J., & Markesbery, W. R. (1992). Cortical biopsy in Alzheimer's disease: Diagnostic accuracy and neurochemical, neuropathological and cognitive correlations. *Annals of Neurology, 32*(5), 625–632.

DeKosky, S. T., & Scheff, S. W. (1990). Synapse loss in frontal cortex biopsies in Alzheimer's disease: Correlation with cognitive severity. *Annals of Neurology, 27,* 457–464.

Duara, R., Barker, W. W., Chang, J., Yoshii, F., Loewenstein, D. A., & Pascal, S. (1992). Viability of neocortical function shown in behavioral activation state PET studies in Alzheimer disease. *Journal of Cerebral Blood Flow and Metabolism, 12*(6), 927–934.

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., & Petersen, S. E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *The Journal of Neuroscience, 16,* 808–822.

Flood, D. G. (1991). Region-specific stability of dendritic extent in normal human aging and regression in Alzheimer's disease. II. Subiculum. *Brain Research, 540,* 83–95.

Foster, N. L. (1994). PET imaging. In R. D. Terry, R. Katzman, & K. L. Bick (Eds.), *Alzheimer's disease.* New York: Raven Press.

Fox, P. T., Mintun, M. A., Raichle, M. E., & Herscovitch, P. (1984). A noninvasive approach to quantitative functional brain mapping with $H_2{}^{15}O$ and positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism, 4,* 329–333.

Frackowiak, R. S. J., Pozzili, C., Legg, N. J., Du Boulay, G. H., Marshall, J., Lenzi, G. L., & Jones, T. (1981). Regional cerebral oxygen supply and utilization in dementia. A clinical and physiological study with oxygen-15 and positron tomography. *Brain, 104,* 753–788.

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1991). Comparing functional (PET) images: The assessment of significant change. *Journal of Cerebral Blood Flow and Metabolism, 11*(4), 690–699.

Gathercole, S. E. (1994). Neuropsychology and working memory: A review. *Neuropsychology, 8,* 494–505.

Geddes, J. W., Monoghan, D. T., Cotman, C. W., Lott, I., Kim, R. C., & Chui, H. C. (1985). Plasticity of hippocampal circuitry in Alzheimer's disease. *Science, 230,* 1179–1181.

Goldman, P., & Nauta, W. (1977). An intricately patterned prefrontocaudate projection in the rhesus monkey. *Journal of Comparative Neurology, 171,* 369–386.

Goldman, P. S., & Rosvold, H. E. (1970). Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. *Experimental Neurology, 171,* 291–304.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In F. Plum & V. Mountcastle (Eds.), *Handbook of physiology* (Vol. 5, pp. 373–417). Bethesda, MD: American Physiological Society.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14,* 477–485.

Grady, C. L., Haxby, J. V., Horwitz, B., Gillette, J., Salerno, J. A., Gonzalez, A. A., Carson, R. E., Herscovitch, P., Schapiro, M. B., & Rapoport, S. I. (1993). Activation of cerebral blood flow during a visuoperceptual task in patients with Alzheimer-type dementia. *Neurobiology of Aging, 14*(1), 35–44.

Grafton, S. T., Huang, S. C., Mahoney, D. K., Mazziotta, J. C., & Phelps, M. E. (1990). Analysis of optimal reconstruction filters for maximizing signal to noise ratios in PET cerebral blood flow studies. *Journal of Nuclear Medicine, 31,* 865.

Grafton, S. T., Woods, R. P., & Tyszka, J. M. (1994). Functional imaging of procedural motor learning: Relating cerebral blood flow with individual subject performance. *Human Brain Mapping, 1,* 221–234.

Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S. J., & Dolan, R. J. (1993). Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain, 116,* 1–20.

Hamos, J. E., DeGennaro, L. J., & Drachman, D. A. (1989). Synaptic loss in Alzheimer's disease and other dementias. *Neurology, 39,* 355–361.

Hanks, S. D., & Flood, D. G. (1991). Region-specific stability of dendritic extent in normal human aging and regression in Alzheimer's disease. I. CA1 of hippocampus. *Brain Research, 540,* 63–82.

Harlow, H. F., Davis, R. T., Settlage, P. H., & Meyer, D. R. (1952). Analysis of frontal and posterior association syndromes in brain

damaged monkeys. *Journal of Comparative Physiological Psychology, 45,* 419–429.

Heiss, W. D., Kessler, J., Slansky, I., Mielke, R., Szelies, B., & Herholz, K. (1993). Activation PET as an instrument to determine therapeutic efficacy in Alzheimer's disease. *Annals of the New York Academy of Sciences, 695,* 327–331.

Herbster, A. N., Nichols, T., Wiseman, M. B., Mintun, M. A., DeKosky, S. T., & Becker, J. T. (1996). Functional connectivity in auditory-verbal short-term memory in Alzheimer's disease. *Neuroimage, 4,* 67–77.

Herscovitch, P., Markham, J., & Raichle, M. E. (1983). Brain blood flow measured with intravenous $H_2{}^{15}O$. I. Theory and error analysis. *Journal of Nuclear Medicine, 24,* 782–789.

Herzog, A. G., & Kemper, T. L. (1980). Amygdaloid changes in aging and dementia. *Archives of Neurology, 37,* 625–629.

Horwitz, B., McIntosh, A. R., Haxby, J. V., Furey, M., Salerno, J. A., Schapiro, M. B., Rapoport, S. I., & Grady, C. L. (1995). Network analysis of PET-mapped visual pathways in Alzheimer type dementia. *Neuroreport, 6,* 2287–2292.

Huang, S. C., Hoffman, E. J., Phelps, M. E., & Kuhl, D. E. (1979). Quantitation in positron emission computed tomography: 2. Effects of inaccurate attenuation correction. *Journal of Computer Assisted Tomography, 3,* 804–814.

Jacobsen, C. F. (1936). Studies of cerebral function in primates. *Comparative Psychology Monograph, 13,* 1–68.

Jueptner, M., & Weiller, C. (1995). Review: Does measurement of regional cerebral blood flow reflect synaptic activity?—Implications for PET and fMRI. *Neuroimage, 2,* 148–156.

Kapur, S., Craik, F. I. M., Tulving, E., Wilson, A. A., Houle, S., & Brown, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proceedings of the National Academy of Sciences, USA, 91,* 2008–2011.

Kessler, J., Herholz, K., Grond, M., & Heiss, W. D. (1991). Impaired metabolic activation in Alzheimer's disease: A PET study during continuous visual recognition. *Neuropsychologia, 29*(3), 229–243.

Kopelman, M. D. (1994). Working memory in the amnesic syndrome and degenerative dementia. *Neuropsychology, 8,* 555–562.

Malloy, P. F., & Richardson, E. D. (1994). Assessment of frontal lobe functions. *Journal of Neuropsychiatry and Clinical Neurosciences, 6,* 399–410.

Masliah, E., Mallory, M., Hansen, L., Alford, M., Albright, T., DeTeresa, R., Terry, R., Baudier, J., & Saitoh, T. (1991). Patterns of aberrant sprouting in Alzheimer's disease. *Neuron, 6,* 729–739.

Mattis, S. (1988). *Dementia rating scale.* Odessa, FL: Psychological Assessment Resources.

Mazziotta, J. C., Huang, S.-C., Phelps, M. E., Carson, R. E., MacDonald, N. S., & Mahoney, K. (1985). A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. *Journal of Cerebral Blood Flow and Metabolism, 5,* 70–78.

McKhann, G. M., Drachman, D., Folstein, M. F., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS—ADRDA work group. *Neurology, 34,* 939–944.

Mega, M. S., & Cummings, J. L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. *Journal of Neuropsychiatry and Clinical Neurosciences, 6,* 358–370.

Miller, J. D., de Leon, M. J., Ferris, S. H., Kluger, A., George, A. E., Reisberg, B., Sachs, H. J., & Wolf, A. P. (1987). Abnormal temporal lobe response in Alzheimer's disease during cognitive processing as measured by 11C-2-deoxy-D-glucose and PET. *Journal of Cerebral Blood Flow and Metabolism, 7*(2), 248–251.

Minoshima, S., Frey, K. A., Koeppe, R. A., Foster, N. L., & Kuhl, D. E. (1995). A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *Journal of Nuclear Medicine, 36,* 1238–1248.

Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Annals of Neurology, 42,* 85–94.

Mölsä, P. K., Säkö, E., Paljärvi, L., Rinne, J. O., & Rinne, U. K. (1987). Alzheimer's disease: Neuropathological correlates of cognitive and motor disorders. *Acta Neurologica Scandinavia, 75,* 376–384.

Monsch, A. U., Bondi, M. W., Butters, N., Salmon, D. P., Katzman, R., & Thal, L. J. (1992). Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer's type. *Archives of Neurology, 49,* 1253–1258.

Morris, R. G. (1984). Dementia and the functioning of the articulatory loop system. *Cognitive Neuropsychology, 1,* 143–157.

Morris, R. (1986). Short-term forgetting in senile dementia of the Alzheimer's type. *Cognitive Neuropsychology, 3,* 77–97.

Morris, R. G. (1987). Articulatory rehearsal in Alzheimer's type dementia. *Brain and Language, 30,* 351–362.

Morris, R. G. (1994). Working memory in Alzheimer-type dementia. *Neuropsychology, 8,* 544–554.

Morris, R., & Baddeley, A. (1988). Primary and working memory functioning in Alzheimer-type dementia. *Journal of Clinical and Experimental Neuropsychology, 10,* 279–296.

Morris, R. G., & Kopelman, M. D. (1986). The memory deficits in Alzheimer-type dementia: A review. *The Quarterly Journal of Experimental Psychology, 38A,* 575–602.

Neter, J., Wasserman, W., & Kutner, M. H. (1990). *Applied linear statistical models* (3rd ed.). Boston: Irwin.

Petrides, M. (1985). Deficits on conditional associative-learning tasks after frontal- and temporal lobe lesions in man. *Neuropsychologia, 23,* 601–614.

Raaijmakers, J. G. W., & Shiffrin, R. M. (1980). SAM: A theory of probabilistic search of associative memory. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (Vol. 14, pp. 207–262). New York: Academic Press.

Raaijmakers, J. G. W., & Shiffrin, R. M. (1981). Search of associative memory. *Psychological Review, 88,* 93–134.

Raichle, M. E., Martin, W. R., Herscovitch, P., Mintun, M. A., & Markham, J. (1983). Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *Journal of Nuclear Medicine, 24*(9), 790–798.

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N., & Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the ϵ-4 allele for apolipoprotein E. *New England Journal of Medicine, 334,* 752–758.

Rundus, D. (1971). Analysis of rehearsal processes in free recall. *Journal of Experimental Psychology, 89,* 63–77.

Rundus, D., & Atkinson, R. C. (1970). Rehearsal processes in free recall: A procedure for direct observation. *Journal of Verbal Learning and Verbal Behavior, 9,* 99–105.

Salloway, S. P. (1994). Diagnosis and treatment of patients with "frontal lobe" syndromes. *Journal of Neuropsychiatry and Clinical Neurosciences, 6,* 388–398.

Samuel, W., Terry, R. D., DeTeresa, R., Butters, N., & Masliah, E. (1994). Clinical correlates of cortical and nucleus basalis pathology in Alzheimer dementia. *Archives of Neurology, 51,* 772–778.

Scheff, S. W., DeKosky, S. T., & Price, D. A. (1990). Quantitative assessment of cortical synaptic density in Alzheimer's disease. *Neurobiology of Aging, 11,* 29–37.

Scheff, S. W., & Price, D. A. (1993). Synapse loss in the temporal lobe in Alzheimer's disease. *Annals of Neurology, 33,* 190–199.

Schmahmann, J. (1991). An emerging concept: The cerebellar contribution to higher function. *Archives of Neurology, 48,* 1178–1187.

Scott, S. A., DeKosky, S. T., & Scheff, S. W. (1991). Volumetric atrophy of the amygdala in Alzheimer's disease: Quantitative serial reconstruction. *Neurology, 41,* 351–356.

Scott, S. A., DeKosky, S. T., Sparks, D. L., Knox, C. A., & Scheff, S. W. (1992). Amygdala cell loss and atrophy in Alzheimer's disease. *Annals of Neurology, 32,* 555–563.

Selemon, L., & Goldman-Rakic, P. (1988). Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: Evidence for a distributed neural network subserving spatially guided behavior. *Journal of Neuroscience, 8,* 4049–4068.

Shallice, T., Fletcher, P., Frith, C. D., Grasby, P., Frackowiak, R. S. J., & Dolan, R. J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature, 368,* 633–635.

Simone, P. M., & Baylis, G. C. (1997). Selective attention in a reaching task: Effect of normal aging and Alzheimer's disease. *Journal of Experimental Psychology: Human Perception and Performance, 23,* 595–608.

Small, G. W., Mazziotta, J. C., Collins, M. T., Baxter, L. R., Phelps, M. E., Mandelkern, M. A., Kaplan, A., La Rue, A., Adamson, C. F., Chang, L., Guze, B. H., Corder, E. H., Saunders, A. M., Haines, J. L., Percak-Vance, M. A., & Roses, A. D. (1995). Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *Journal of the American Medical Association, 273,* 942–947.

Spieler, D. H., Balota, D. A., & Faust, M. E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *Journal of Experimental Psychology: Human Perception and Performance, 22,* 461–479.

Squire, L. R. (1987). *Memory and brain.* New York: Oxford University Press.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253,* 1380–1386.

Talairach, J., & Tournoux, P. (1988). *A co-planar stereotaxic atlas of a human brain.* Stuttgart: Thieme.

Terry, R. D., Masliah, E., Salmon, D. P., Butters, N., DeTeresa, R., Hill, R., Hansen, L. A., & Katzman, R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Annals of Neurology, 30,* 572–580.

Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., & Houle, S. (1994a). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Sciences, USA, 91,* 2016–2020.

Tulving, E., Kapur, S., Markowitsch, H. J., Craik, F. I. M., Habib, R., & Houle, S. (1994b). Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition. *Proceedings of the National Academy of Sciences, USA, 91,* 2012–2015.

Unger, J. W., Lapham, L. W., McNeill, T. H., Eskin, T. A., & Hamill, R. W. (1991). The amygdala in Alzheimer's disease: Neuropathology and Alz 50 immunoreactivity. *Neurobiology of Aging, 12,* 389–399.

Vijayan, V. K., Geddes, J. W., Anderson, K. J., Chui, H. C., Ellis, W. G., & Cotman, C. W. (1991). Astrocyte hypertrophy in the Alzheimer's disease hippocampal formation. *Experimental Neurology, 112,* 72–78.

Welsh, K. A., Butters, N., Hughes, J. P., Mohs, R. C., & Heyman, A. (1992). Detection and staging of dementia in Alzheimer's disease: Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. *Archives of Neurology, 49,* 429–576.

Wheeler, M. A., Stuss, D. T., & Tulving, E. (1995). Frontal lobe damage produces episodic memory impairment. *Journal of the International Neuropsychological Society, 1,* 525–536.

Wiesendanger, R., Wiesendanger, M., & Ruegg, D. G. (1979). An anatomical investigation of the corticopontine projection in the primate (*Macaca fascicularis and saimiri sciureus*). II: The projection from frontal and parietal association areas. *Neuroscience, 4,* 747–765.

Woods, R. P. (1996). Modeling for intergroup comparisons of imaging data. *Neuroimage, 4,* 584–594.

Woods, R. P., Cherry, S. R., & Mazziotta, J. C. (1992). Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography, 16,* 620–633.

Woods, R. P., Iacoboni, M., Grafton, S. T., & Mazziotta, J. C. (1996). Three-way analysis of variance. In R. Myers, V. Cunningham, & D. Bailey (Eds.), *Quantification of brain function using PET* (pp. 353–358). New York: Academic Press.

Woods, R. P., Mazziotta, J. C., & Cherry, S. R. (1993). MRI-PET registration with automated algorithm. *Journal of Computer Assisted Tomography, 17,* 536–546.

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism, 12*(6), 900–918.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17,* 37–49.

Zweig, R. M., Ross, C. A., Hedreen, J. C., Steele, C., Cardillo, J. E., Whitehouse, P. J., Folstein, M. F., & Price, D. L. (1988). The neuropathology of aminergic nuclei in Alzheimer's disease. *Annals of Neurology, 24,* 233–242.

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