Patterns of Cortical Activity and Memory Performance in Alzheimer's Disease

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Background: *Declarative memory changes are the hallmark of Alzheimer's disease, although their functional neuroanatomy is not restricted to a single structure. Factor analysis provides statistical methods for evaluating patterns of cerebral changes in regional glucose uptake.*

Methods: *Thirty-three Alzheimer's patients and 33 age- and gender-matched control subjects were studied with magnetic resonance imaging and positron emission tomography with [^{18}F] deoxyglucose. During the tracer-uptake period, subjects performed a serial verbal learning task. Cortical activity was measured in 32 regions of interest, four in each lobe on both hemispheres.*

Results: *Factor analysis with varimax rotation identified seven factors explaining 80% of the variance ("parietal cortex," "occipital cortex," "right temporo-prefrontal areas," "frontal cortex," "motor strip," "left temporal cortex," and "posterior temporal cortex"). Relative to control subjects, Alzheimer's patients showed significantly reduced values on the factors occipital cortex, right temporo-prefrontal areas, frontal cortex, and left temporal cortex. The factor temporo-prefrontal areas showed large differences between patients with good and poor performance, but little difference when control subjects were similarly divided.*

Conclusions: *Findings suggest that Alzheimer's disease is characterized by altered patterns of cortical activity, rather than deficits in a single location, and emphasize the importance of right temporo-prefrontal circuitry for understanding memory deficits.* Biol Psychiatry 2001;49: 426–436

Key Words: Dementia, Alzheimer's disease, positron emission tomography, magnetic resonance imaging, verbal memory, factor analysis

Introduction

Memory deficits are one of the core symptoms of Alzheimer's disease (AD). Although memory problems are often subtle in the earliest stages of AD, their steady progression may leave the patient in an almost entirely amnestic condition. Recent neuroimaging studies have demonstrated structural (Jobst et al 1992; Pantel et al 1997), spectroscopic (Lazeyras et al 1998), and functional (Mann et al 1992; Pearlson et al 1992; Siegel et al 1995; for reviews, see Santens and Petit 1997; Small and Leiter 1998) cerebral changes in AD. These changes strike primarily the temporal and parietal association cortices but generally extend to the frontal cortex with progression of the disease (Buchsbaum et al 1991; Haxby et al 1988; Mann et al 1992; Mielke et al 1994; Smith et al 1992; Stein et al 1998), especially with secondary depression (Hirono et al 1998a).

The relationships between the cerebral changes observed in neuroimaging studies and the clinical and neuropsychologic characteristics of the disease are not fully understood. Pearlson et al (1992) and Pantel et al (1997) linked amnestic deficits to reduced left temporo-parietal regional cerebral blood flow (rCBF), or left superior temporal gyrus and left temporal lobe atrophy, respectively. Using positron emission tomography (PET) with ^{18}F-2-deoxyglucose (FDG) as a tracer, Haxby et al (1988) found parietal hypometabolism to correlate with prominent impairment in verbal comprehension, calculation, and visuospatial tasks, whereas frontal hypometabolism was correlated with more impaired verbal fluency and attention. An association between frontal cortical changes and impaired performance in verbal fluency tasks was also reported by Mann et al (1992) and Siegel et al (1995). Although these studies underline the importance of frontal, parietal, and temporal changes in AD, the question of how these heterogeneous cerebral changes contribute to memory impairment remains unresolved.

According to a number of recent studies, memory performance should not be conceptualized as reflecting a unitary or highly localized process but, rather, as involving

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different stages and brain regions (for reviews, see Grafton 1995; Markowitsch 1995; Squire 1986; Ungerleider 1995). Although declarative memory involves medial temporal substructures, procedural and working memory are linked to basal ganglia and dorsolateral prefrontal cortex functions, respectively. Within declarative memory two critical processes (encoding vs. retrieval) and two major branches (episodic vs. semantic) are differentiated. The cerebral circuitries underlying these aspects of declarative memory functioning are only partly understood. According to the model of "hemispheric encoding/retrieval asymmetry" (Tulving et al 1994), left and right frontal cortical areas are differentially involved in encoding into episodic memory and retrieval of information from episodic memory, respectively. This hemispheric asymmetry model is generally consistent with recent PET studies (Andreasen et al 1995; Squire et al 1992; Tulving et al 1994) in healthy subjects that revealed an activation of right prefrontal and temporal areas in episodic memory retrieval. In AD, recently reported correlations between regional callosal atrophy and severity of dementia (Pantel et al 1999) indicate that interhemispheric cortico-cortical disconnection may contribute to the dementia syndrome.

The brain regions identified as crucial for the retrieval and encoding of information are known to be important sites in AD. Yet, methodological difficulties have impeded attempts to test the respective cerebral site–amnestic deficit associations proposed by the studies cited above in AD. In neuroimaging studies of mnestic functioning, subjects must perform a specific task during the amnestic investigation. Since the ability of AD patients to execute memory tasks is limited, any design that requires patients to perform a task under particular environmental stress (e.g., in a PET scanner) may create a serious methodological bias. This methodological problem may be of particular importance if several tasks are applied to address brain activation in different neuropsychologic functions. One possibility to overcome these difficulties is the use of FDG as a tracer. In contrast to tracers of cerebral blood flow, such as oxygen 15, which assesses 40 sec of activity, FDG has a relatively long uptake period that permits the subject enough time to execute the task across sufficient trials for statistical reliability, as well as to receive the tracer and perform the task while sitting in a comfortable chair in a quiet testing room before being transferred to the scanner. At the same time, the long half-life of FDG limits the temporal resolution capacity of FDG PET to approximately 30 min. Hence, one may argue that FDG PET is suitable to investigate trait metabolic patterns rather than fluctuating state-specific—that is, short time—cerebral processes. However, high correlations between regional blood flow assessed by functional magnetic resonance imaging (fMRI) and FDG PET in AD (Gonzalez et al 1995) and single photon emission computed tomography and FDG especially for the temporal lobe (Conca et al 2000) have been reported.

As demonstrated by ourselves and others (e.g., Schröder et al 1994), the patterns of cerebral activity during the performance of a particular task may be revealed with a factor-analytic approach. A similar approach with principal components analysis has been applied to FDG uptake in resting AD patients (Ichimiya et al 1994) and revealed a five-factor structure, with dementia scores correlated with a right temporo-parietal factor. This approach with the sample restricted to resting patients might enhance correlations between factor scores and severity scores because only patients entered the factor analysis, but might be weaker in differentiating normal control subjects and less severe patients or detecting patterns associated with memory task performance because these patterns might be partially obscured in patients. Several recent factor-analytic studies on FDG PET in schizophrenia (Al-Mousawi et al 1996), Parkinson's (Eidelberg et al 1994) and human immunodeficiency virus 1–seropositive (Rottenberg et al 1996) subjects have included both control subjects and patients in the factor analysis, and we adopted this approach. We used FDG PET to study patterns of cortical activity in AD patients and age-matched control subjects during the performance of a serial verbal learning task (SVLT). The SVLT involves both stages of declarative memory processing—encoding and retrieval—and may be executed during FDG uptake. The aims of our study were to 1) confirm the cortical changes in AD described in the studies cited above and 2) investigate the respective changes with respect to memory deficits in AD.

Methods and Materials

Subjects

Thirty-three patients (16 male and 17 female, mean age 70.6 years) clinically diagnosed with AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations criteria; McKhann et al 1984) were included. The degree of impairment was assessed with the Mini-Mental State Examination (MMSE; Folstein et al 1975) and the Clinical Dementia Rating (CDR; Hughes et al 1982). At the time of the scan, 10 patients met criteria for questionable AD (MMSE 25.6, SD 2.2) and 23 patients were diagnosed with probable AD (MMSE 20.9, SD 4.4). Nineteen patients had CDR scores of 0.5 (10 questionable and nine probable), 10 patients had CDR scores of 1.0, and four had CDR scores of 2.0. A comprehensive psychiatric exam was performed on all patients, and none had major depression or psychotic disorder. All subjects reviewed the institutional review board-approved consent document, and we individually discussed with each the details of the experimental procedure including insertion of intravenous lines, bruising at the venipunc-

ture site, immobilization during the scan, duration of the procedure, and radiation-associated risks. Patients' questions were answered after review of consent procedures. All patients participated in the memory task during FDG uptake and all remembered some words, indicating functioning memory capacity, albeit limited. No patient left the scanner during the image acquisition process, consistent with the voluntary cooperativeness of the sample.

Thirty-three age- and gender-matched control subjects were screened for health just as the patients were, by history, physical examination, and laboratory testing. All control subjects had CDR scores of 0, and to avoid potential ceiling effects, the MMSE was not applied. The study was approved by the local institutional review board or ethical committee.

Uptake Task

Subjects performed an SVLT during the 35-min FDG uptake period while comfortably seated in a darkened and sound-attenuated room. The SVLT, modified from the California Verbal Learning Test (Delis et al 1987) according to the demands of PET scanning, contains five sets of 16 words, with each set consisting of four words belonging to a single conceptual category. Categories were selected for concreteness and ability to generate brief words for stimuli. Words were chosen based on their scores on "level of associability" norms (Battig and Montague 1981).

Each list was presented five times in a fixed, random order on a computer monitor at a 1.5-sec rate. Words from the same conceptual category were not presented contiguously. Free recall was required of the subjects after each presentation. Responses were recorded by a research assistant. After the first 16-item list had been presented five times, the second list was presented, with each successive 16-item list being presented after the previous list had been given five times. For analysis, mean number of words correctly recalled, number of perseverative errors and intrusions, and number of semantic categories recognized were calculated. The task began 30 sec before FDG administration and continued throughout the 35-min uptake period, at which time FDG uptake and metabolic trapping was largely complete; subjects were then moved to the scanner for imaging.

Imaging

Changes in regional brain activity were imaged as glucose metabolic rate using sterile, pyrogen-free FDG, prepared as described elsewhere (Buchsbaum et al 1989). To minimize head movement and facilitate MRI/PET coregistration, an individually molded, thermosetting plastic headholder was made for each subject. During FDG uptake, subjects were seated in a darkened room to execute the SVLT. An intravenous line of 0.9% saline drip was inserted into the subject's left arm for blood sampling and another into the right arm for injection of the labeled glucose. The left arm was wrapped in a hot pack for arterialization of venous blood.

After FDG uptake, subjects were transferred to the adjacent scanning room where PET scans were obtained with a head-dedicated scanner (model 2048, GE Medical Systems, Milwaukee). Fifteen slices at 6.5-mm intervals were acquired in two sets to cover the entire brain. Slice counts of 1.5 to 3 million were typical. Scans were reconstructed with a blank and a transmission scan using the Hann filter, width 3.15. Magnetic resonance imaging scans were obtained using the GE Sigma 5× system with the SPGR sequence (repetition time = 24 msec, echo time = 5 msec, flip angle = 40°, slice thickness = 1.2 mm), for contiguous slices with a 256 × 256 pixel matrix in a 23-cm field of view. Magnetic field inhomogeneities were monitored with a cylindrical water-filled phantom; after application of a one-pass gaussian filter, the histogram is <10 units wide and no differences in values are observable at the four cardinal points. Image geometric linearity is monitored with a 100-mm square-cross phantom; current data show a 1.6% vertical/horizontal difference, well within measurement error.

Positron emission tomography scans were reconstructed with a blank and transmission image attenuation correction. For accurate anatomic analysis, every PET was coregistered with MRI using a modification of the surface-fitting method of Pelizzari et al (1989), as described elsewhere (Shihabuddin et al 1998). Brain edges were visually traced on an MRI axial slice at a midstriatal level and at an approximately matching PET slice. Intertracer reliability on 27 individuals was .99 for area. Positron emission tomography volume was translated and rotated on the center of mass to minimize differences between the MRI and PET edges expressed as the square root of the difference for each edge pixel, squared. In a further step, the PET image was resectioned and a sagittal PET and MRI edge similarly generated. Positron emission tomography volume is translated and rotated in the sagittal plane using the atlas bone as the rotation point to avoid mismatch in some other coregistration systems due to nonanatomic rotation. The coronal plane is treated similarly, and the axial plane redone as the fourth step. The reliability of the coregistration procedure is described elsewhere (Shihabuddin et al 1998).

MRI Overlay and PET Assessment of the Cortical Peel

Magnetic resonance images were first segmented into gray matter, white matter, and cerebrospinal fluid (CSF) through the application of cutoff values individually derived in each subject from an examination of the frequency histogram of within-edge MRI pixel values. We used two midventricular slices and chose the points of rarity between gray and white and gray and CSF as the dividing values. In a few subjects there was no clear point of rarity for the gray/CSF distinction and we substituted a criterion of the mean percentage from the other subjects (26% of the gray value). Four complementary approaches to validating gray/white segmentation have been carried out. First, we validated MRI intensity value histogram peak and trough selection with two raters. The intraclass correlations (ICCs) for gray, white, and CSF components for two tracers were .98, .99, and .92, respectively, in 28 subjects used in pilot data analysis. Second, we used the stereology approach to visually identify gray and white matter (Keshavan et al 1995). We counted points on frontal coronal sections on 20 individuals and obtained a .87 correlation between gray volume by visual inspection point-counting and gray volume using automated segmentation. Third, we compared

the left and right hemisphere gray, white, and CSF segmentation values as a rough validator of how our segmentation method identified a reliable whole-brain subject trait from an independent brain area; these ICCs were .85, .74, and .86. This demonstrates that the final result from segmentation yields statistically significant tissue type separation. Fourth, to assess test–retest reliability over time, we examined a set of MRI pairs obtained 4–6 weeks apart on 16 schizophrenic patients. The second MRI of each pair was coregistered to the first using the algorithm of Woods et al (1992). Images were resectioned and brain edges traced on the first member of each pair. These edges were then overlaid on the second MRI and the segmentation program run using the gray–white–CSF thresholds from the first MRI. Thus, this approach provides the worst case reliability because it examines segmentation on the second MRI with the edges traced independently on the first and uses threshold values from the first MRI. We obtained frontal gray, CSF, and white matter reliability for the middle frontal gyral region with ICC values of .88, .77, and .75, respectively. Note that measurement of the second scan was entirely automated with coregistration by algorithm and edges and thresholds obtained from the first scan.

Because many sulci are difficult to identify on MRI slices in AD patients and the cortical folding pattern may be multiple or variable from individual to individual, the lateral cortical regions were divided into 16 regions of interest in each hemisphere using a previously described "cortical peel" technique (Buchsbaum et al 1982; Siegel et al 1992). This technique and analogous "cortical circumferential profile" approaches have been found to be reliable and accurate (Harris et al 1991). To address potential interindividual differences, regional glucose use was expressed as relative glucose metabolic rate (GMR), defined as the ratio of regional GMR to whole brain GMR as in many recent AD metabolic studies (e.g., Hirono et al 1998a, 1998b; Vander Borght et al 1997). Although some studies have used the cerebellum rather than the whole brain as a reference (e.g., Desgranges et al 1998; Pickut et al 1999), other studies indicating decreases in the metabolic rate in the cerebellum itself in AD (Ishii et al 1997) suggest the utility of retaining whole brain metabolic rate for normalization across subjects.

Data Analysis

The Statistical Analysis System (SAS Institute 1990) package was used for all computations. First, relative cortical metabolic activity was investigated for underlying dimensions by calculating a principal component factor analysis with varimax rotation. The number of factors retained was determined by the eigenvalue criterion. The ratio of number of subjects to number of variables entered into the analysis was 66 to 32, sufficiently high to achive reliable results (Geider et al 1982). The identified cortical factors, representing patterns of cortical activity, allowed the construction of factor scales as recommended by Bernstein (1988) and Geider et al (1982). Scores for each cortical factor were calculated for each patient and control subject by averaging the metabolic rates in brain regions that have factor weights of 0.550 or above on each factor. For example, for factor 3 we averaged the metabolic rates for right inferior frontal, right superior temporal, right middle temporal, right inferior temporal, and right Brodmann area 19 (Table 1). This was done using the factor structure identified in the combined group of AD and control subjects because we expected that the greater variability of cortical activity values in both groups would lead to a better definition of the structure of the factors.

Two sources of variation correspond to the correlations between the cortical regions and the factor structure identified. Cortical activity is altered by AD itself, creating patient–control subject differences; in addition, variation may be induced by the task, as reflected by differences between good and poor performers (Horwitz et al 1991; Schröder et al 1994). To analyze these sources of variation, patients and control subjects were divided into two subgroups according to their performance (number of correct answers) by calculating a median split. A two-way analysis of variance was calculated to compare factor scale values between diagnostic groups (AD patients vs. control subjects) and performance groups (patients with poor and good performance, control subjects with poor and good performance).

To address the relationship between severity of dementia and cortical activity changes, AD patients were categorized as mildly (MMSE $>$ 21) and moderately (MMSE $<$ 22) impaired based on the median MMSE. Subsequently, factor scale values were compared between these groups and the control subjects with a Duncan test.

Results

Following the eigenvalue criterion, factor analysis of cortical regions of interest identified seven factors explaining 80% of the common variance (Table 1). Factor 1 was labeled "parietal cortex," as it encompassed the right supramarginal gyrus region, right and left angular gyrus, and right and left superior parietal gyrus. The occipital areas—Brodmann areas 19 (left), 17 (right and left), 21 (right and left), and 18 (right and left)—constituted factor 2, labeled "occipital cortex." Factor 3, which had weights for the right inferior frontal gyrus area, right superior and middle temporal gyrus areas, and right occipital area 19, was labeled "right temporo-prefrontal areas." Factor 4, labeled "frontal cortex," consisted of the activity measured in the superior frontal and middle frontal regions (right and left) and in the left inferior frontal region. Measures of relative GMR in the precentral motor cortex and parietal regions (left precentral gyrus region, left and right postcentral gyrus region, and left supramarginal gyrus region) showed high loadings on factor 5, which was labeled "motor strip." Factor 6 encompassed the left superior, middle, and inferior temporal regions, and factor 7, the right and left posterior temporal regions. Factors 6 and 7 were labeled "left temporal cortex" and "posterior temporal cortex," respectively. The measure of the right posterior frontal gyrus did not show any preferential loadings.

Table 2 compares control subjects and the whole AD group with respect to the factor scales. Significantly decreased activity values were found in the AD group on

Table 1. Results of the Factor Analysis (Varimax rotated) of the Cortical Peel Data

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Superior frontal gyrus, R	.222	−.257	.170	.816	.042	−.174	−.103
Superior frontal gyrus, L	.019	.008	−.319	.834	.142	.166	−.204
Middle frontal gyrus, R	.310	−.126	.406	.791	.156	−.015	−.010
Middle frontal gyrus, L	.102	.088	−.150	.813	.280	.282	−.227
Inferior frontal gyrus, R	−.014	.073	.570	.382	−.008	−.273	−.353
Inferior frontal gyrus, L	−.361	−.019	−.232	.586	.097	.301	−.317
Precentral gyrus, R	.320	−.009	.521	.297	.447	−.286	.143
Precentral gyrus, L	−.127	.041	−.024	.414	.749	.205	−.236
Postcentral gyrus, R	.308	−.137	.361	−.024	.550	−.412	.315
Postcentral gyrus, L	.043	.034	−.092	.190	.886	−.015	−.145
Supramarginal gyrus, R	.687	−.078	.274	−.098	.427	−.026	.274
Supramarginal gyrus, L	.402	.049	−.213	.045	.754	.238	.106
Angular gyrus, R	.807	.152	.382	.197	.040	.090	−.007
Angular gyrus, L	.686	.293	−.065	.177	.266	.421	−.019
Superior parietal gyrus, R	.823	.219	.040	.069	−.040	−.126	.015
Superior parietal gyrus, L	.701	.286	−.326	.001	.202	.099	−.082
Superior temporal gyrus, R	−.145	−.177	.783	−.253	.069	−.098	−.182
Superior temporal gyrus, L	−.192	−.285	−.035	−.059	.272	.679	.037
Middle temporal gyrus, R	.139	.086	.875	−.015	−.173	.159	.007
Middle temporal gyrus, L	.161	.282	.091	.271	−.014	.838	.093
Inferior temporal gyrus, R	.106	.213	.632	−.127	−.180	.173	.593
Inferior temporal gyrus, L	.155	.376	.006	.061	−.075	.673	.422
Posterior temporal gyrus, R	−.045	.093	−.048	−.217	−.050	.185	.822
Posterior temporal gyrus, L	.038	.251	−.082	−.207	.019	.012	.795
Brodmann area 19, R	.388	.453	.657	.042	−.086	.038	.245
Brodmann area 19, L	.349	.667	.036	.145	−.027	.526	.179
Brodmann area 17, R	.563	.476	.349	.112	−.060	−.100	.019
Brodmann area 17, L	.507	.684	−.024	.203	−.027	.090	−.004
Brodmann area 21, R	.113	.715	.373	−.168	.186	−.051	.101
Brodmann area 21, L	.173	.812	−.031	−.049	.109	.226	.125
Brodmann area 18, R	.057	.591	.224	−.166	−.195	−.370	.391
Brodmann area 18, L	.087	.822	−.128	−.154	−.067	.033	.093
Eigenvalue	**7.8**	**5.8**	**4.3**	**2.7**	**2.3**	**1.6**	**1.3**
Percent of variance after Varimax rotation	**13.9**	**13.6**	**12.6**	**12.3**	**9.7**	**9.6**	**8.7**

R, right; L, left.

the factors occipital cortex [$F(1,64) = 6.3$, $p < .025$], right temporo-frontal cortex [$F(1,64) = 12.6$, $p < .005$], frontal cortex [$F(1,64) = 7.8$, $p < .01$], and left temporal cortex [$F(1,64) = 12.6$, $p < .005$]. For further analysis, AD patients were subdivided into mildly and moderately/severely impaired groups, and a Duncan test was calculated (Table 2). Apart from motor strip and posterior temporal cortex, all factors in the control group were higher than in either the mildly or the moderately impaired AD subgroup. The effect sizes were in the range

Table 2. Means and SDs of Factor Scales in Mild, Moderately Impaired, and All Alzheimer's Disease (AD) Patients and Healthy Control Subjects with the Results of a Duncan Test Contrasting Subgroups with Control Subjects

Factor scale	Mild AD	Moderate AD	All AD	Control Subjects	Duncan test
Parietal cortex	0.944 ± 0.14	0.940 ± 0.14	0.943 ± 0.14	0.995 ± 0.13	ns
Occipital cortex[a]	1.104 ± 0.12	1.077 ± 0.14	1.097 ± 0.12	1.157 ± 0.07	g2 < g3
R temporo-prefrontal cortex[b]	1.119 ± 0.09	1.120 ± 0.09	1.119 ± 0.08	1.185 ± 0.06	g1, g2 < g3
Frontal cortex[a]	1.105 ± 0.09	1.064 ± 0.10	1.095 ± 0.18	1.151 ± 0.07	g2 < g3
Motor strip	1.176 ± 0.09	1.216 ± 0.13	1.186 ± 0.10	1.180 ± 0.08	ns
L temporal cortex[b]	1.113 ± 0.07	1.102 ± 0.10	1.110 ± 0.07	1.169 ± 0.06	g1, g2 < g3
Posterior temporal cortex	1.220 ± 0.22	1.288 ± 0.24	1.236 ± 0.22	1.219 ± 0.23	ns

g1, mild AD; g2, moderate AD; g3, healthy control subjects; R, right; L, left.
[a] $p < .05$, t test for all AD vs. healthy control subjects.
[b] $p < .005$, t test for all AD vs. healthy control subjects.

Table 3. Characteristics of Alzheimer's Disease (AD) Patients and Healthy Control Subjects Subdivided on the Basis of Performance on the Serial Verbal Learning Test (SVLT) with the Results of a Duncan Test at the 5% Level

	AD patients		Healthy control subjects		
	Good performance	Poor performance	Good performance	Poor performance	Duncan test
Age	67.8 ± 6.6	73.1 ± 10.6	65.8 ± 10.6	72.8 ± 8.4	g1, g2 > g3
MMSE	25.2 ± 2.4	20.0 ± 5.3	—	—	
SVLT					
Correct	5.2 ± 1.5	2.5 ± 0.8	13.8 ± 0.8	10.4 ± 1.8	g3 > g4 > g1 > g2
Perseveration	0.4 ± 0.3	0.2 ± 0.3	0.4 ± 0.5	0.8 ± 0.7	g4 > g3, g2, g1
Intrusions	1.1 ± 1.2	1.8 ± 2.0	0.1 ± 0.1	0.2 ± 0.1	g2, g1 > g4, g3
Semantic categories	1.3 ± 0.9	0.4 ± 0.2	9.2 ± 1.4	5.4 ± 2.3	g3, g4 > g1, g2

g1, good performers; g2, poor performers among AD patients; g3, good performers; g4, poor performers among healthy control subjects; MMSE, Mini-Mental State Examination.

of 0.6 to 0.8, or between large and moderate (Cohen 1969). Both AD subgroups had significantly lower scores on the factors right temporo-prefrontal areas and left temporal cortex than the control group. Values on the factors occipital cortex and frontal cortex were significantly smaller in the moderately impaired AD subgroup than in the control subjects. However, these factors showed no significant differences between mildly impaired patients and control subjects, suggesting the absence of significant changes in the occipital and frontal cortices in early stages of AD.

Table 3 presents findings of AD patients and healthy control subjects categorized by good versus poor performance as determined by the median SVLT score. Although task performance varied significantly between groups, corresponding differences for age or years of education were not found. None of the factors were significantly correlated with age, years of education, or severity of dementia.

Table 4 gives the means and SDs of the factor scales in well- versus poorly performing patients and healthy control subjects. The main effect of diagnosis was significant for the factors occipital cortex [$F(3,62) = 5.8$, $p < .05$], right temporo-prefrontal areas [$F(3,62) = 16.6$, $p < .005$], and left temporal cortex [$F(3,62) = 6.3$, $p < .05$]. The main effect of test performance was statistically significant for the factor right temporo-prefrontal areas [$F(3,62) = 6.6$, $p < .05$] and showed trend-level differences for the factors parietal [$F(3,62) = 3.2$, $p = .08$] and occipital cortex [$F(3,62) = 3.6$, $p = .07$]. The diagnosis × test performance interaction was significant only for the factor right temporo-prefrontal areas [$F(3,62) = 4.2$, $p < .05$].

In further analyses, factor scores on factor 3, right temporo-prefrontal areas, were correlated with GMR for each pixel location on the slice images of the PET and MRI intensity, respectively. This provides a graphic image of the individual pixels where the factor score calculated for each subject has a significant correlation with the metabolic rate for each pixel in the group average image. The expected positive correlations with the right temporal area extending back into the occipital area (compare with factor 3 loadings in Table 1) can be seen. Negative correlations in the cingulate gyrus, thalamus, and insula indicate that subjects with low right temporal and frontal values have high values in these areas. As demonstrated in

Table 4. Means and SDs of Factor Scales in Good vs. Poor Performers on the Serial Verbal Learning Test among Alzheimer's Disease (AD) Patients and Healthy Control Subjects with the Results of a Two-Way Analysis of Variance

	AD patients		Healthy control subjects				
Factor	Good performance	Poor performance	Good performance	Poor performance	F_{diag}	F_{perf}	$F_{diag*perf}$
Parietal cortex	0.98 ± 0.13	0.90 ± 0.14	1.02 ± 0.15	0.97 ± 0.10	2.1	3.3[a]	0.2
Occipital cortex	1.13 ± 0.09	1.06 ± 0.15	1.17 ± 0.07	1.15 ± 0.06	5.8[b]	3.6[a]	1.1
R temporo-prefrontal cortex	1.16 ± 0.09	1.08 ± 0.08	1.19 ± 0.06	1.18 ± 0.06	16.6[c]	6.6[b]	4.2[b]
Frontal cortex	1.08 ± 0.09	1.10 ± 0.09	1.16 ± 0.08	1.14 ± 0.06	1.7	0.0	0.8
Motor strip	1.16 ± 0.10	1.20 ± 0.11	1.18 ± 0.10	1.19 ± 0.06	0.2	1.1	0.3
L temporal cortex	1.11 ± 0.08	1.11 ± 0.08	1.17 ± 0.07	1.17 ± 0.05	6.3[b]	0.0	0.0
Posterior temporal cortex	1.24 ± 0.23	1.24 ± 0.24	1.19 ± 0.23	1.26 ± 0.24	0.1	0.3	0.3

diag, diagnosis; perf, test performance; R, right; L, left.
[a] $p < .10$.
[b] $p < .05$.
[c] $p < .005$.

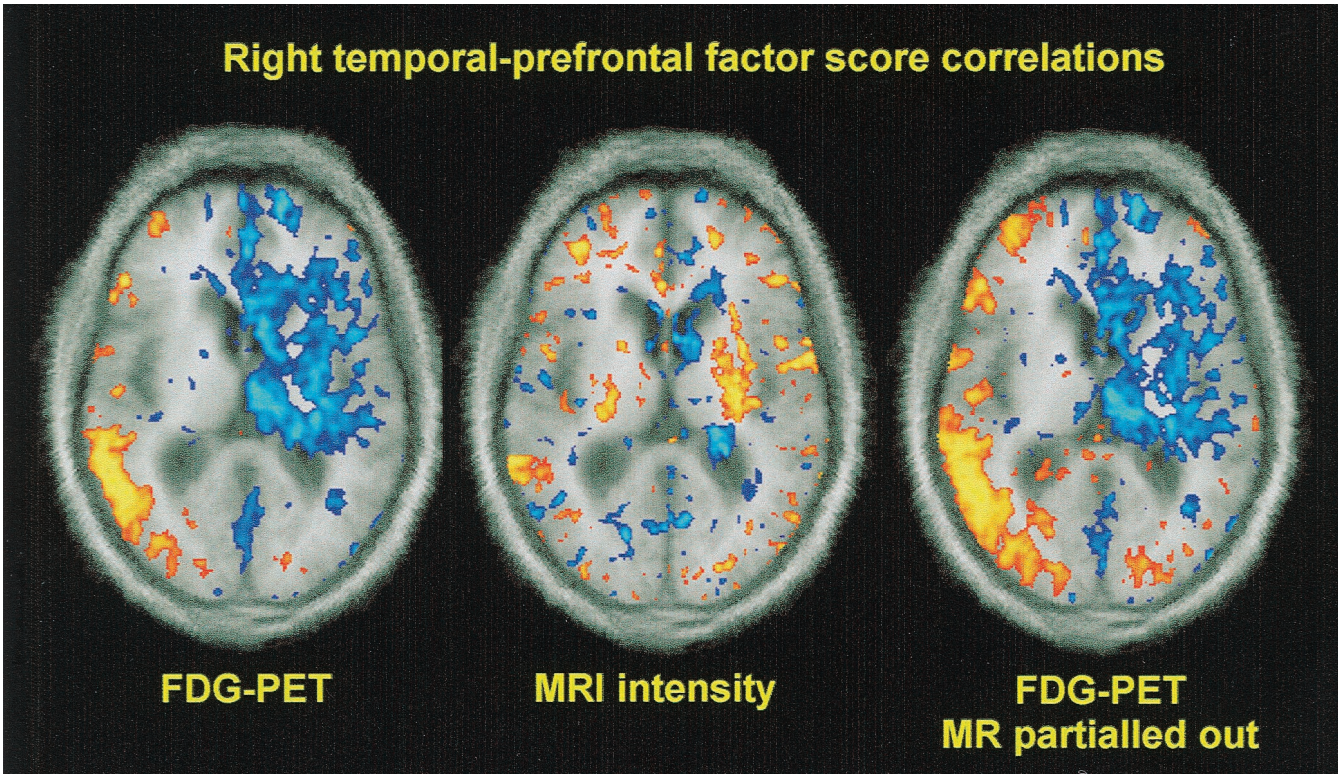

Figure 1. Effects of cerebral atrophy on metabolic correlation patterns. **(Left)** Correlation coefficients of factor 3 scores with metabolic rate at each pixel in patients with Alzheimer's disease. Orange areas in the right temporal cortex are positively correlated, whereas contralateral central and frontal areas are negatively correlated. Orange pixels mark where $p < .05$ for positive correlations and blue pixels mark where $p < .05$ for negative correlations for each r, and both are shown on a background of the mean shape-standardized structural magnetic resonance (MR) image. This illustration is analogous to a factor-loading table for each pixel and shows the anatomic distribution of the factor. It also indicates that individuals with low right temporal metabolic rates have higher rates in central gray, cingulate, and medial frontal areas. **(Middle)** Correlation of factor with MR image intensity. No region of correlation thresholded at $p < .05$ was sufficiently large to reach $p < .05$ significance on resampling (see Shihabuddin et al. 1998 for details on statistical methods). This illustration demonstrates that correlations in the image to the left are not largely due to anatomic variation or lowered metabolism due to sulcal widening and increased cerebrospinal fluid (CSF) space. **(Right)** Correlation between glucose metabolic rate and factor 3 with MR imaging (MRI) signal intensity value (low for CSF, intermediate for gray, and high for white) removed with partial correlation coefficient method. Note that metabolic correlations are mildly strengthened in the temporal cortex and little changed in medial blue regions. This second additional method also demonstrates that regions of factor correlation are not due to anatomic change represented in MRI signal values. FDG-PET, ^{18}F-2-deoxyglucose positron emission tomography.

Figure 1, factor score correlations with metabolic rate do not appear to be a function of cortical atrophy because the glucose factor does not show a correlation with MRI values. If sulcal widening were a major contributor to low metabolic rate, one would have expected a positive correlation between metabolic rate and MRI signal intensity values (low MRI values for CSF paired with low metabolic rate values). Further, when we used partial correlation coefficients to remove MRI values, factor correlations were unchanged or even slightly enhanced.

Discussion

Three main findings emerged from our factor-analytic study, which provided 1) further evidence that memory functions are not a highly localized process but involve different brain regions; 2) confirmation that occipital, temporal, and frontal cortical areas are all involved in AD; and 3) evidence that right prefrontal-temporal areas may establish a circuitry for declarative memory retrieval that distinguishes patients with AD from healthy control subjects.

First, cortical activity during a memory task was differentiated into seven dimensions of cortical activation, with occipital cortex, right temporo-prefrontal areas, frontal cortex, and left temporal cortex significantly differentiating AD patients from healthy control subjects. Second, when "good" and "poor" performers in the AD and control groups were compared, good performers tended to show higher activity values on the factors parietal cortex and occipital cortex and showed significantly higher values on the factor right temporo-prefrontal areas. Thus, altered

patterns of activity, rather than a single localized deficit, characterize AD and suggest that memory performance is not a unitary or highly localized phenomenon but involves different cortical areas in coordinated function. The SVLT is a complex task dependent upon several cognitive processes including visual processing, attention, identification of semantic categories, encoding, storage, and retrieval of information.

Relative to healthy control subjects, AD patients showed significantly reduced activity values on the factor occipital cortex, which included Brodmann areas 19 (left), 17 (right and left), 21 (right and left), and 18 (right and left). Neuropathologic studies in AD (Pearson et al 1985) indicate maximal involvement of association areas and minimal involvement of primary sensory areas. However, an ophthalmologic study found evidence for a widespread visual dysfunction in AD (Cronin-Golomb et al 1991). In two PET studies of AD, decreased metabolic activity in occipital areas was reported (Mielke et al 1994; Smith et al 1992); and occipital area metabolic rate was correlated with dementia ratings in AD patients during visual stimulation but not resting (Pietrini et al 1999, 2000). Whereas Smith et al (1992) found occipital metabolism unchanged at follow-up, Mielke et al (1994) reported a further decline in occipital metabolism with disease progression. A similar pattern of deficits was identified in our study, with significantly lower levels of metabolic activity being found in occipital areas in the moderately impaired patients—but not in the mildly impaired patients—than in the healthy control subjects. That the decreased occipital activity in AD may reflect functional rather than structural changes was demonstrated by Kessler et al (1991), who investigated 21 patients with AD and nine healthy control subjects in a resting condition and during performance of a continuous visual recognition task using FDG PET. Whereas glucose uptake in the primary visual cortex did not differ between groups in the resting condition, patients with AD showed a significantly reduced activation in the visual cortex while executing the visual recognition task.

The right inferior frontal gyrus area, right superior and middle temporal gyrus areas, and right occipital area 19 (factor 3, right temporo-prefrontal areas) have been implicated in episodic memory retrieval. Using $[^{15}O]H_2O$ PET, Squire et al (1992) studied rCBF in 18 subjects in a baseline condition and during the performance of semantic priming and episodic memory retrieval tasks. Both tasks induced significant activity changes in right prefrontal and midtemporal regions. Tulving et al (1994) reported right dorsolateral prefrontal cortex, adjacent premotor cortex, left anterior cingulate sulcus, and bilateral parietal areas to be activated during an auditory task that required subjects to distinguish previously learned sentences from novel ones. A right hemispheric network of temporal, cingulate, and prefrontal areas engaged in the retrieval of autobiographic information was also identified by Fink et al (1996) in an FDG PET study of seven healthy volunteers. The cingulate and prefrontal parts of this network appear especially activated in patients with right temporal decreases, perhaps as a compensatory adaptation as may occur in successful aging (Hazlett et al 1998). These reports are generally consistent with the findings of Andreasen et al (1995) that large right frontal regions, biparietal areas, and the left cerebellum were involved in both long- and short-term retention.

Changes in the temporal lobe and the medial temporal substructures are a well-established finding in AD. Using quantitative MRI, Pantel et al (1997) compared the volumes of the temporal lobes, the frontal lobes, and the amygdala-hippocampus complex in 20 AD patients and 10 healthy control subjects. The AD patients were characterized by significant volume reductions in the temporal lobes and the amygdala–hippocampus complex, deficits that were already detectable in the mildly demented. Moreover, temporal atrophy was significantly correlated with CSF concentrations of β-amyloid 1-42, a peptide that is generally considered to play an important role in the formation of senile plaques in AD (Schröder et al 1997). In a computed tomography study, Jobst et al (1994) estimated the average rate of atrophy of the medial temporal lobe to be 15.1% per year in 20 patients with histopathologically confirmed AD but 1.5% per year in 47 healthy aging control subjects. FDG PET studies revealed consistent results: Haxby et al (1988) reported significant activity decreases in the right and left lateral temporal cortices in 32 AD patients relative to 29 healthy control subjects. Again, these changes were prominent even in the mildly demented. A similar pattern of temporal changes among patients with mild and moderate/severe AD was reported by Kessler et al (1991) and in this study. In a prospective study, Smith et al (1992) examined glucose uptake in the temporal cortex in 14 AD patients and 15 healthy control subjects longitudinally over a period of 36 and 42 months, respectively. Although the healthy control subjects did not show any significant activity changes, temporal lobe activity values of the AD patients declined significantly over the follow-up period.

In addition to the occipital and right temporal–prefrontal changes described above, the moderately impaired AD patients showed significantly lower activity values on the factor frontal cortex relative to healthy control subjects. This finding parallels the quantitative MRI study of Pantel et al (1997), who reported significantly reduced frontal lobe volumes in moderately impaired AD patients relative to healthy control subjects. Further evidence that the frontal cortex is involved in AD comes from PET studies that found reduced activity values in the frontal cortex of

AD patients (Haxby et al 1988; Kessler et al 1991; Smith et al 1992). One interpretation of these findings is that the frontal cortex may be spared at the onset of the disease but is affected in the later stages (Haxby et al 1988). An alternative explanation is that frontal changes may be characteristic for a subgroup of patients with relatively fast progression of the disease (Mann et al 1992). The involvement of the frontal cortex may be reflected in working memory dysfunction, as demonstrated in our study by the reduced number of semantic categories identified in the SVLT by the AD patients.

Moreover, the AD patients were characterized by significantly reduced activity values on the factor left temporal cortex. These changes were already detectable in the early stages of the disease. Similar findings were reported by Mann et al (1992), Nybäck et al (1991), and Kessler et al (1991). In the longitudinal study cited above, Smith et al (1992) found left temporal activity continued to decline with disease progression. According to Kapur et al (1996), left temporal cortex function reflects encoding processes. Moreover, left temporal changes may also be related to aphasic symptoms—in particular, word-finding difficulties, which are often present even in the early stages of AD (Pantel et al 1997).

In contrast to the significant differences for the regions reviewed above, the factors parietal cortex, motor strip, and posterior temporal cortex did not vary significantly between patients and control subjects. Significant activity reductions in the parietal cortex of AD patients were reported by Haxby et al (1988), Nybäck et al (1991), and Smith et al (1992). This discrepancy may reflect methodological differences because the studies cited above investigated patients in a resting condition, whereas the SVLT used in our study does not particularly address parietal lobe functions such as visuospatial processing. That neither the activity in the sensorimotor cortex nor the activity in the primary visual association areas such as the posterior temporal gyri varied significantly between the diagnostic groups is consistent with earlier findings (e.g., Kessler et al 1991; for a review, see Stein et al 1998). However, significantly reduced sensorimotor cortex activity values were described by Haxby et al (1988) for the severely demented. Smith et al (1992) found a reduced sensorimotor cortex activity even in the mildly impaired, although this alteration did not progress at follow-up 36 months later.

Our factor structure shows an organization into lobes and fronto-temporal factors like that of Ichimiya et al (1994), but with a different ordering of factors. Their factor 3, which showed fronto-temporal–parietal weighting, was their best correlate of patients' MMSE scores, a result not entirely unlike our right temporal–prefrontal factor showing patients different from control subjects. Interestingly, our temporal–prefrontal factor was significantly related to the quality of memory performance in the patient group itself as well, probably reflecting task-associated variance.

Partial volume effects due to sulcal atrophy in AD (e.g., Wahlund et al 1999) and the ability of patients to execute the SVLT need to be discussed as potential confounding variables. Partial volume effects were minimized by the high spatial resolution capacity of the imaging techniques employed; moreover, statistical control of the effect of sulcal CSF regions on PET metabolic rate (by partialing out the MRI values in the coregistered MRI on a pixel-by-pixel basis) did not substantially affect the correlations obtained between the activity measures (Figure 1). Positron emission tomography measures were restricted to cortical areas because neuroimaging in healthy volunteers (Andreasen et al 1995; Squire et al 1992; Tulving et al 1994) mainly showed significant cerebral activity changes in the cortex in declarative memory tasks. That patients were able to comprehend the task demands is indicated by the mean number of correct answers, which ranged well above zero even in the poor performers among the AD patients and differed significantly between good and poor performers within the diagnostic groups. Hence, floor effects are unlikely. That both patients and control subjects were executing the task according to their mental abilities is further demonstrated by the significant interaction between diagnosis and test performance that was found for the factor right temporo-prefrontal areas.

Our study confirms reductions in metabolic activity in the occipital, temporal, and frontal cortices in AD and supports the hypothesis that right temporo-prefrontal areas constitute a circuitry important for memory retrieval. Amnestic dysfunction in AD appears to involve a deviant pattern of cortical activity, rather than a specific deficit in a single location, and the findings emphasize the potential role of the right prefrontal–temporal circuitry for understanding AD-related memory deficits.

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