Selective Cortical and Hippocampal Volume Correlates of Mattis Dementia Rating Scale in Alzheimer Disease

Rosemary Fama, PhD; Edith V. Sullivan, PhD; Paula K. Shear, PhD; Laura Marsh, MD; Jerome A. Yesavage, MD; Jared R. Tinklenberg, MD; Kelvin O. Lim, MD; Adolf Pfefferbaum, MD

Objective: To examine whether each of the 5 Mattis Dementia Rating Scale (DRS) scores related to magnetic resonance imaging–derived volumes of specific cortical or limbic brain regions in patients with Alzheimer disease (AD).

Design: Relations between DRS measures and regional brain volume measures were tested with bivariate and multivariate regression analyses.

Setting: The Aging Clinical Research Center of the Stanford (Calif) University Department of Psychiatry and Behavioral Science and the Geriatric Psychiatry Rehabilitation Unit of the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif.

Patients and Other Participants: Fifty patients with possible or probable AD. Magnetic resonance imaging data from 136 healthy control participants, age 20 to 84 years, were used to correct brain volumes for normal variation arising from intracranial volume and age.

Main Outcome Measures: The DRS scores and volumes of regional cortical gray matter and of the hippocampus.

Results: Memory scores of the patients with AD were selectively related to hippocampal volumes. Attention and construction scores were related to several anterior brain volume measures, with attention showing a significantly greater association to right than left hemisphere measures. Initiation/perseveration scores were not significantly correlated with any measure of regional gray matter volume, but performance was related to prefrontal sulcal widening, with a greater association with the left than right sulcal volume.

Conclusions: Certain DRS subtests are predictably correlated with selective regional brain volumes in AD. The specific relation between memory and hippocampal volumes and the nonsignificant relations between memory and regional cortical volumes suggest a dissociation between cortical and hippocampal contributions to explicit memory performance.

Arch Neurol. 1997;54:719-728

From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif (Drs Fama, Sullivan, Shear, Marsh, Yesavage, Tinklenberg, Lim, and Pfefferbaum); the Psychiatry Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif (Drs Yesavage, Tinklenberg, and Lim); and the Neuropsychiatry Program, SRI International, Menlo Park, Calif (Drs Sullivan and Pfefferbaum). Dr Shear is now in the Department of Psychology, University of Cincinnati, Cincinnati, Ohio.

NEUROIMAGING studies of Alzheimer disease (AD) provide in vivo evidence for enlargement of ventricular and cortical sulcal volumes[1,2] and complementary deficits in cortical gray matter volume throughout much of the brain.[3,4] The regional pattern of brain volume abnormalities in patients with AD is distinct from that seen in normal aging and in another neurodegenerative disorder, Parkinson disease,[5] and the most marked deficits are in the medial temporal regions.[1-3,6-15] These neuroradiological findings are consistent with postmortem evidence of gray matter atrophy in the hippocampus and association cortices of AD brains.[16-19] Whether the extent of tissue-volume deficits in selective brain regions in AD is related to observable specific cognitive deficits is only sparsely established.[20-22]

The Mattis Dementia Rating Scale (DRS)[23,24] is widely used in clinical and research settings as a global measure of cognitive functioning in patients with AD. The DRS is composed of 5 subscales (memory, initiation/perseveration, attention, conceptualization, and construction), each of which assesses a different cognitive domain, and a total score, which provides an overall index of dementia severity. The DRS has greater sensitivity to longitudinal cognitive decline in AD than either of 2 other commonly used assessment tools, the Blessed Information-Memory-Concentration test and the Mini-Mental State Examination (MMSE).[25] The DRS has reasonably high power to discriminate AD from other dementing illnesses.[26-29] The indices thought to best discriminate patients with AD from healthy older individuals are the memory and initiation/perseveration subscales.[30]

METHODS AND PARTICIPANTS

METHODS

Participants in this study included 50 patients with AD recruited from the Geriatric Psychiatry Rehabilitation Unit and the National Institute of Mental Health Aging Clinical Research Center, both located at the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif. All patients with AD met the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association criteria for probable AD.[51,52] Normal control subjects spanning the adult age range (20-84 years of age) were used as a reference group for the MRI volumetric measures. These subjects, or a subset of them, have formed the norms for other studies from our laboratory.[37,53,54] The normal control group consisted of 95 men and 41 women for the axial protocol and 84 men and 28 women for the coronal protocol. Screening for all participants included a psychiatric interview and medical examination. Subjects were excluded if they had a history of psychiatric or neurological disorder unrelated to their diagnosis (eg, stroke, closed head injury), past or present alcohol or drug abuse or dependence, or a serious medical condition. Informed consent was obtained from all participants or their conservators. Demographic information for the AD group is as follows:

Characteristic	Mean (SD)	Range
Age, y	71.4 (7.4)	51-87
Education, y	14.7 (3.5)	6-22
Age at onset of symptoms, y	66.0 (8.0)	49-83
Premorbid IQ estimate*	105.8 (9.1)	89-122
MMSE score	17.6 (4.8)	8-28
Vocabulary age-scaled score†	8.8 (2.6)	2-12

* *National Adult Reading Test.*
† *Wechsler Adult Intelligence Scale–Revised.*

DEMENTIA RATING SCALE

The DRS is composed of 5 subscales: memory (recall and recognition of verbal and visual stimuli after immediate and short delays), initiation/perseveration (semantic [supermarket] fluency, motor fluency, and perseveration), attention (forward and backward digit span, ability to follow commands, and matching to sample stimuli with distractor), conceptualization (abstraction from verbally and visually presented stimuli), and construction (copy of geometric figures and signature writing).

MRI SCANNING AND QUANTIFICATION

Axial Protocol

Acquisition Parameters. Subjects were scanned with 1.5-T MRI scanners (Signa, General Electric, Milwaukee, Wis). Image acquisition procedures and parameters have been described in detail.[53,55,56] Axial MRI scans were 5 mm thick (2.5-mm skip) and were acquired in an oblique plane using a spin-echo sequence (20- and 80-millisecond echoes) with a 24-cm field of view and a 256×256 matrix. Acquisition was gated to every other cardiac cycle for an effective repetition time of more than 2400 milliseconds with 1 excitation for each of 256 phase encodes.

All images were stored on magnetic tape and transferred to optical disks for analysis. For each subject, the index slice was identified as the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally. Seven consecutive slices, beginning with the section inferior to the index slice and proceeding superiorly, were analyzed for each subject. The index slice or the slice below it was used for quantification of the third ventricle.

Regional Divisions and Segmentation of Images. Each MRI slice was segmented into cerebrospinal fluid (CSF), gray matter, and white matter compartments, using a semiautomated image analysis technique.[55,57] To separate the cerebral hemispheres, a midline was drawn manually on each slice. Each slice also was divided into an inner 55% region (to facilitate quantification of central CSF, which arose primarily but not exclusively from the lateral ventricles) and an outer 45% (to facilitate quantification of the cortical tissue volumes and sulcal CSF).[58,59]

The images were divided according to anatomical landmarks and a priori geometric rules to achieve standardized regional divisions of the brain images. The cortical tissue measure (the outer 45% of each image) was divided into 6 geometrically defined regions of interest, which roughly corresponded to lobar anatomy. The regions did not fully encompass the entire volume of the cortical lobes after which they were named but provided a reliable basis for dividing cortical sections.[60] To form these divisions, each MRI slice was divided into 4 regions by 3 coronal planes, which passed through the most anterior extreme of the genu of the corpus callosum, the most posterior extreme of the splenium of the corpus callosum, and midway between them. The first plane established a boundary for the prefrontal region. From these quadrants and slices, we devised 6 cortical regions, defined as follows: prefrontal—the most anterior quadrant of all 7 slices, which included most of the prefrontal cortex; frontal—the anterior middle quadrant of slices 3 to 7; anterosuperior temporal—the anterior middle quadrant of slices 1 and 2, which included the anterosuperior temporal gyrus and the most posterior extents of the frontal lobes at the level of the superior temporal gyrus; posterosuperior temporal—the posterior middle quadrant of slices 1 and 2, which included the posterosuperior temporal gyrus and a small portion of the anterior extents of the parietal lobes just above the superior temporal gyrus; anterior parietal—the posterior middle quadrant of slices 3 to 7; and posterior parietal-occipital—the most posterior quadrant of slices 3 to 7, which also included much of the occipital lobes (**Figure 1**).

Coronal Protocol

A detailed description of the acquisition methods, anatomical borders, and reliability used in our laboratory to examine the temporal lobes and hippocampus has been reported.[37,61] Summaries are presented below.

Acquisition Parameters. With this protocol, 22 contiguous 3-mm-thick coronal images were acquired using a multiecho, flow-compensated, cardiac-gated pulse sequence (echo time=40 and 80 milliseconds; effective repetition time, 2800 milliseconds) with a 24-cm field of view, 1 excitation, and a 256×256 matrix. The plane of image acquisition was oriented perpendicular to the anterior commissure–posterior commissure line. Image acquisition was specifically designed to encompass temporal-limbic structures, beginning 6 mm anterior to the anterior commissure and extending 66 mm posteriorly.

Hippocampal tissue could not be adequately segmented into gray matter and white matter compartments and, therefore, its volume reflected total tissue, ie, pixels represented gray matter and white matter. The hippocampus was outlined on each consecutive slice on each side of the brain and the volumes were derived by adding the areas of each measured slice.

Regional Divisions and Segmentation of Images. The anterior limit of the hippocampal measurement began where hippocampal tissue was clearly distinguished from amygdala, coinciding with the appearance of the digitations of Ammon's horn and consistent with the location of the pes hippocampus. This initial slice usually coincided with the visualization of ventricular temporal horn CSF over the digitations. Because the boundary between the subiculum and the amygdala cannot be distinguished at the medial aspect of the hippocampal formation at this slice level, a line was drawn from the most medial point of the subiculum to the most medial aspect of the temporal horn, thereby excluding amygdala from the measure. The posterior limit corresponded to the posterior temporal lobe image. This measure predominantly included portions of the head and body of the hippocampus, with exclusion of the most anterior portion of the pes (where it could not be distinguished from the amygdala) and the most posterior portion of the hippocampus (the ascending tail). The medial hippocampal boundary included the regional outline at the choroidal fissure. The inferior boundary was formed by, but did not include, the white matter of the parahippocampal gyrus. The fornix was not included in posterior slices unless it was inextricably embedded within the hippocampal structure. In the absence of histological confirmation, this measure presumably included hippocampal fields CA1 to CA4, the dentate gyrus, and portions of the subiculum.[62]

Temporal lobe measurement began anteriorly where a complete temporal lobe stem appeared at the level of or just caudal to the limen insulae. Because of variability in the gyri of the posterior temporal region, 3 anatomical landmarks were used as reference points to define the posterior boundary of the temporal lobe measure as consistently as possible. In general, the most posterior image measured was 1 slice (3 mm) anterior to the slice, showing the ascending portion of the hippocampal tail, the absence of the vertical fissures of the lateral sulcus, and the initial appearance of the ventricular trigone, fornix in the wall of the lateral ventricle, and splenium of the corpus callosum. These anterior and posterior boundaries excluded the temporal poles, which were not uniformly present on this scanning sequence, and the most posterior portion of the temporal lobes.

The temporal lobe area was delineated from adjacent brain regions by a line drawn from the most inferior point of the circular sulcus to the most lateral point of the transverse or choroidal fissure of the temporal lobe or the most medial border of the temporal horn at the fimbria, when present. Gyral outlines defined the lateral boundary. Unless the appearance of the anatomical landmarks warranted otherwise, the same number of sections was used for each hemisphere. The temporal lobe gray matter measure used in this study excluded the hippocampal volume.

Temporal horn measurements were made on all sections on which the structure was clearly present, beginning anterior to the hippocampus and lateral and inferior to the amygdala. The posterior limit corresponded to the hippocampal and temporal lobe measures. Limbic regions are shown in **Figure 2.**

SUBJECT DEMOGRAPHICS

Axial data for 49 and coronal data for 25 of the 50 subjects with AD were available. One subject had coronal but not axial data; otherwise, all subjects with coronal data also had axial data. Magnetic resonance imaging acquisition and cognitive testing had to have occurred within 3 months of each other for a person to be included in the study. The subjects with AD who had coronal studies (n=25) did not differ significantly from those who had only axial studies (n=25) on age at examination, age of disease onset, National Adult Reading Test IQ,[63] or age-scaled Wechsler Adult Intelligence Scale–revised vocabulary score.[64] A statistical trend was found for years of education and MMSE scores ($P<.10$), with the subjects with AD who had coronal studies having more years of education and higher MMSE scores than the subjects with AD who had only axial studies. This modest difference may reflect the greater difficulty that more severely demented patients had in successfully completing the coronal sequence, which required an additional 30 minutes to acquire.

All MRI films were reviewed by a neuroradiologist to eliminate subjects with gross structural lesions (eg, cysts), which would influence the diagnosis or volumetric analysis. Volume quantification was done blind to diagnosis. To minimize scoring bias due to knowledge of diagnosis, the MRIs of the patients with AD were mixed with MRIs of control subjects and patients with other diagnoses. In addition, all coronal images were reversed randomly in a left or right hemisphere orientation to prevent measurement bias for structures from 1 hemisphere relative to the other.

STATISTICAL ANALYSIS

The volumes of each region of interest in the patients with AD were corrected for variation attributable to intracranial volume (ie, head size) and age, using regression analyses. This regression approach has been described in detail in previous articles.[53,61,65,66] Briefly, a correction using a 2-step regression analysis to adjust for normal variation in head size and age based on normal control subjects yielded head size– and age-corrected z scores. All regional brain measures were expressed as z scores, where the expected mean of the control subjects at any age was 0 ± 1 SD. This correction method allows for analysis of disease-related changes that are independent of the known effects of normal aging and head size.[65,66] For the subjects with AD, these head size– and age-corrected z scores provide volume estimates relative to that which would be expected for normal control subjects of a particular head size and age. Low z scores for tissue measures and high z scores for CSF measures are in the direction of abnormality.

Relations between DRS measures and regional, bilateral, and lateralized (left and right) brain volume measures were examined with Pearson product-moment correlations; approximate P values are provided for descriptive purposes only. Multiple regression models were used to test our hypotheses and examined whether significant brain volume correlates independently contributed to the prediction of DRS subscale scores when the contributions of other relevant brain regions were considered. These analyses were conducted twice: the first set was based on head size– and age-corrected z scores; the second set was based on head size–corrected brain volumes and entered age as a separate predictor in each regression, and thus this analysis did not depend on modeling the effects of normal age on brain volumes but accounted for the age of the patients.

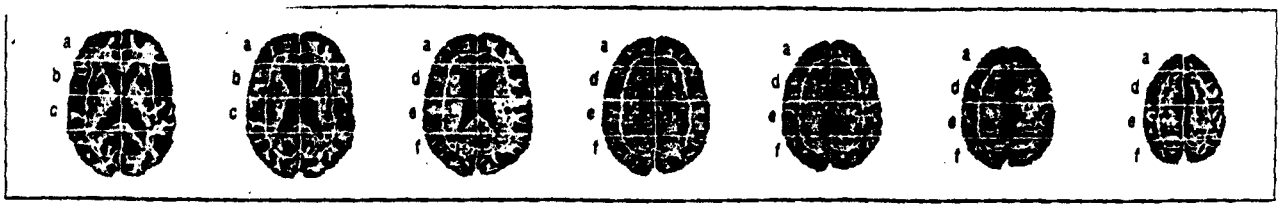

Figure 1. *Each measured magnetic resonance imaging slice was divided into an outer 45%, which represented cortical regions, and an inner 55%, which included ventricular regions. The cortical area was then divided into 6 regions that roughly corresponded to lobar anatomy. a indicates prefrontal, slices 1 to 7; b, anterosuperior temporal, slices 1 to 2; c, posterosuperior temporal, slices 1 to 2; d, frontal, slices 3 to 7; e, anterior parietal, slices 3 to 7; f, posterior parietal-occipital, slices 3 to 7. The volume of each cortical region was divided into gray matter (shown in dark gray), white matter (light gray), and cerebrospinal fluid (black).*

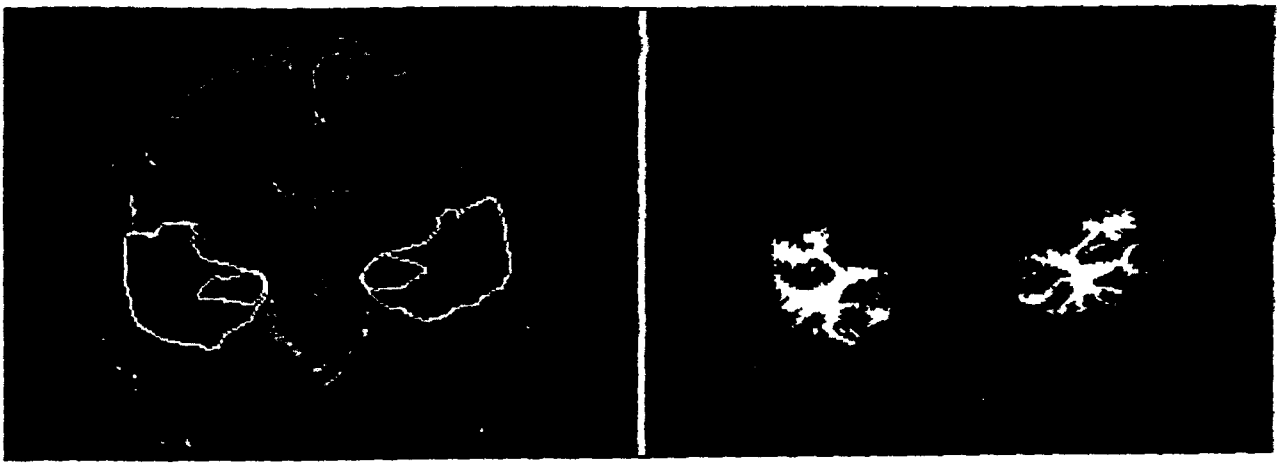

Figure 2. *Coronal magnetic resonance image of a 42-year-old normal, healthy man. Left, Outline of regions of interest—temporal lobes and hippocampi. Right, Segmentation of the image into gray matter (dark gray), white matter (light gray), and cerebrospinal fluid (black).*

The neuroanatomical abnormalities that may mediate impaired performance on the DRS subscales have not been fully explored. One postmortem study reported that the DRS memory score was significantly correlated with the number of neurofibrillary tangles found in several subfields of the hippocampus.[31] In addition to the relation between memory and hippocampal pathologic lesions, however, Samuel et al[31] found a number of other relations between other DRS subscales and neurofibrillary tangle counts of the subiculum and select regions of the hippocampal formation. Thus, the relation between memory and hippocampal pathologic lesions was not selective in their study.

An in vivo magnetic resonance imaging (MRI) study found that the DRS total and memory scores correlated significantly with volumes of the hippocampal formation but not of the amygdala or caudate nucleus in 18 patients with AD.[32] Although Deweer et al[32] investigated the selective relations between memory and medial brain structures, they did not investigate the relations between memory and cortical regions, some of which, like the hippocampus, are principal sites of AD pathology. Stout et al[33] recently reported that cortical gray matter volume deficits and white matter abnormalities observed with MRI make independent contributions to the prediction of overall dementia severity as assessed by the DRS and the MMSE. That study also showed that a measure of limbic volume, which included the hippocampus and other medial temporal lobe structures, was related to memory performance independent of any contribution from nonlimbic cortical or white matter abnormalities. In addition, attention scores were related to a global measure of nonlimbic, cortical gray matter volume and to white matter abnormalities. The study by Stout et al, however, neither examined the relations between cortical lobar gray matter volumes and DRS subscale scores nor used an anatomically defined measure of hippocampal volume, as was used in the present study. Thus, it remains unknown whether memory subscale performance is selectively correlated with hippocampal volume loss or whether it is also related to the significant shrinkage in cortical regions observable in vivo with MRI,[34,35] and whether performance on the remaining 4 subscales is selectively related to gray matter volumes in circumscribed regions.

The present study examined whether each of the 5 DRS subscale scores was predictably related to the MRI-derived volumes of specific cortical and limbic regions in patients with AD. Based on findings from human lesion studies, we tested a number of structure-function hypotheses. We expected that although overall cortical volumes may be associated with decline in general cognitive performance, scores on the memory subscale would be selectively correlated with hippocampal volumes, beyond the contributions made by the cortical regions. We examined whether memory scores were selectively correlated with temporal horn volume, which has been used as an indirect index of hippocampal volume loss.[12,36] Previously, we observed no relation between hippocampal and temporal horn volumes in healthy subjects, suggesting that temporal horn enlargement reflects extrahippocampal volume loss.[37] Thus, we expected that even if temporal horn volumes were related to the memory subscale scores, hippocampal volumes would be uniquely and significantly associated with the memory scores in patients with AD, beyond the contribution from the temporal horns.

For the remaining 4 subscales, we predicted the following: that the initiation/perseveration subscale, with its emphasis on verbal fluency, would be associated with left posterior frontal and superior temporal gray matter volumes[38-41]; the attention subscale would be associated with prefrontal and posterior parietal gray matter volumes, possibly lateralized to the right[42-46]; the conceptualization subscale, assessing abstraction abilities, would be associated with prefrontal gray matter volumes[47,48]; and the construction subscale, because of its emphasis on visuospatial abilities, would be associated with posterior parietal gray matter volumes, especially of the right hemisphere.[49,50]

RESULTS

DRS PERFORMANCE

The AD group scored below the established cutoff, according to published norms,[24] on 3 of the 5 subscales and on the total score (**Table 1**). Almost all of the patients with AD scored in the impaired range on memory, but only 20% scored in the impaired range on the attention or construction subscale. About half of the group was impaired on the conceptualization subscale and about two thirds were impaired on the initiation/perseveration subscale.

MRI VOLUME ABNORMALITIES

Head size– and age-corrected z scores were used in these analyses. The volume of each brain region in the AD group was compared with that of subgroups of the controls who spanned the same age range as the patients with AD (for the axial measures, 70 controls, ages 50-81 years; for the coronal measures, 57 controls, ages 50-81 years). For the axial measures, the AD group showed the expected volume deficits in 5 of the 6 cortical gray matter measures in the following regions: prefrontal, $t(117)=2.7$, $P<.009$; frontal, $t(117)=2.9$, $P<.005$; anterosuperior temporal, $t(117)=3.9$, $P<.001$; posterosuperior temporal, $t(117)=5.2$, $P<.001$; and anterior parietal, $t(117)=2.0$, $P<.05$. The group difference between the AD group and controls was not significant for the measure of posterior parietal-occipital gray matter volume—$t(117)=1.1$, $P<.30$. The AD group had significantly larger lateral and third ventricular volumes than the control group: $t(86.3)=7.3$ and $t(81.9)=5.5$, respectively; $P<.001$ for both. Examination of the coronal and limbic measures indicated that the AD group showed volume deficits for all measures—hippocampus: left $t(80)=3.8$, $P<.001$ and right $t(80)=3.3$, $P<.002$; temporal lobe: left $t(80)=8.1$, $P<.001$ and right $t(80)=7.2$, $P<.001$; temporal horn: left $t(24.6)=5.0$, $P<.0001$ and right $t(24.6)=7.6$, $P<.001$.

REGIONAL BRAIN VOLUME CORRELATES OF THE DRS

Correlation coefficients between DRS subscales and regional brain volumes are given in **Table 2**. Head size– and age-corrected z scores were used in all of the following regression analyses.

Table 1. Dementia Rating Scale Performance of 50 Patients With Alzheimer Disease

Subscale	Maximum Score Possible	Mean	SD	No. (%) of Subjects in Impaired Range
Attention	37	33.6	2.8	10 (20)
Initiation/Perseveration	37	24.2	7.8	32 (64)
Construction	6	5.1	1.5	10 (20)
Conceptualization	39	30.9	6.0	21 (42)
Memory	25	12.5	4.2	46 (92)
Total score	144	106.3	16.8	42 (84)

Memory

As predicted, memory subscale scores showed the strongest bivariate correlations with hippocampal volumes (left, $r=0.61$, $P<.001$; right, $r=0.56$, $P<.01$) (**Figure 3**).

Multiple regression analyses were used to test the independent contribution of the hippocampus to the memory score over and above the contribution of several overall and regional cortical areas believed to be important in the mediation of memory functions (**Table 3**). The first set of analyses examined the relations of the hippocampal and temporal cortical volumes to the memory score. The incremental proportion of variance accounted for by the left hippocampal volume to the memory score, after accounting for the contribution of the left temporal cortical volume, was significant ($P=.001$). A corresponding multiple regression analysis examining the right hemisphere volumes of the hippocampal and temporal cortical volumes showed a similar pattern: the incremental proportion of variance accounted for by the right hippocampus to the memory score was significant ($P=.01$) after accounting for the contribution of the right temporal cortical volume.

Second, a multiple regression analysis examined the independent contributions of the bilateral hippocampal (obtained from the coronal MRIs) and total cortical gray matter volumes (obtained from the axial MRIs) to the memory score. The incremental proportion of variance accounted for by the combined volumes of both hippocampi to the memory score, after controlling for the contribution of total cortical gray matter volume, was significant ($P=.001$).

Last, multiple regression analyses examined the independent contributions of the hippocampal and temporal horn volumes to the memory score. The left hippocampal volume contributed significantly to the memory score ($P<.003$) after accounting for the contribution of the left temporal horn. A corresponding regression analysis examining the right hemisphere volumes of the hippocampus and temporal horn showed similar findings: the incremental proportion of variance accounted for by the right hippocampus to the memory score, after controlling for the contribution of the right temporal horn, was significant ($P<.02$).

Initiation/Perseveration

The hypothesis that prefrontal gray matter volume would be significantly correlated with initiation/perseveration scores was not supported. However, there was a trend

Coronal regions (n=25)						
Hippocampus						
Left	0.35	0.42*	0.06	0.11	0.62†	0.52‡
Right	0.24	0.07	0.02	0.10	0.57‡	0.29
Temporal lobe gray matter						
Left	0.06	0.32	−0.12	0.13	0.10	0.23
Right	0.34	0.32	−0.06	0.23	0.29	0.38
Temporal horn						
Left	−0.12	−0.48§	0.17	−0.26	−0.42*	−0.47§
Right	−0.15	−0.17	0.17	−0.07	−0.36	−0.23
Axial cortical gray matter regions (n=49)						
Total cortical gray matter	0.13	0.02	0.22	0.07	0.06	0.04
Total prefrontal	0.10	0.03	0.11	0.13	0.21	0.05
Left	0.09	0.01	0.06	−0.11	0.16	0.03
Right	0.09	0.04	0.13	−0.12	0.22	0.06
Total frontal	0.21	0.13	0.30*	−0.06	0.02	0.15
Left	0.16	0.09	0.25	0.02	0.01	0.10
Right	0.24	0.17	0.32*	0.11	0.03	0.20
Total anterosuperior temporal	0.25	0.11	0.38‡	0.04	0.16	0.18
Left	0.10	0.10	0.23	−0.02	0.13	0.11
Right	0.37‡	0.11	0.47†	0.09	0.17	0.23
Total posterosuperior temporal	0.34§	0.21	0.38‡	0.24	0.14	0.31*
Left	0.18	0.05	0.30*	0.14	0.14	0.17
Right	0.41‡	0.32*	0.36‡	0.28*	0.13	0.39‡
Total anterior parietal	0.06	0.00	0.19	−0.05	−0.07	−0.01
Left	0.10	0.00	0.14	−0.01	−0.06	0.01
Right	0.02	0.02	0.22	−0.09	−0.08	−0.02
Total posterior posterior-occipital	−0.01	−0.13	0.08	−0.20	−0.07	−0.15
Left	0.07	−0.04	0.14	−0.10	−0.05	−0.04
Right	−0.08	−0.21	0.01	−0.29	−0.08	−0.23
Total lateral ventricles	−0.41‡	−0.12	−0.36§	−0.07	−0.15	−0.22
Left	−0.33§	−0.14	−0.31*	−0.05	−0.13	−0.20
Right	−0.47†	−0.08	−0.40‡	−0.08	−0.15	−0.22
Third ventricle	−0.20	−0.08	−0.28	0.01	−0.23	−0.15

*P<.05.
†P<.001.
‡P<.01.
§P<.02.

toward a relation between the initiation/perseveration score and the bilateral prefrontal CSF sulcal volume ($r=-0.34$; $P<.02$) (**Figure 4**). To assess laterality of function, a multiple regression analysis was conducted using the left and right prefrontal CSF sulcal volume measures as independent variables. Results indicated that the left prefrontal CSF sulcal volume independently contributed to the initiation/perseveration score after accounting for the contribution of the right prefrontal CSF sulcal volume ($P<.003$), but that the contribution of the right prefrontal CSF sulcal volume, after accounting for the contribution of the left prefrontal CSF sulcal volume, did not reach significance ($P<.10$).

Attention

Attention subscale scores were significantly correlated with the bilateral volumes of the lateral ventricles ($r=-0.41$; $P<.004$), while a trend toward a relation was found between attention scores and the bilateral volumes of posterosuperior temporal gray matter ($r=0.34$; $P<.02$) (**Figure 5**). As Figure 5 shows, 1 subject scored substantially below the rest of the group on the attention subscale. When this subject was excluded from the correlational analyses, slightly stronger relations emerged between attention score and reported regional brain areas (lateral ventricles, $r=-0.45$, $P<.002$; posterosuperior temporal, $r=0.36$, $P<.02$).

Examination of lateralized brain volumes showed significant correlations between attention scores and right anterosuperior temporal ($r=0.37$; $P<.01$) and right posterosuperior temporal ($r=0.41$; $P<.004$) gray matter volumes. The attention score was also significantly correlated with right lateral ventricle volume ($r=-0.47$; $P<.001$), with a trend found with left lateral ventricle volume ($r=-0.33$; $P<.02$). Multiple regression analyses indicated that these right hemisphere regions (anterosuperior temporal, posterosuperior temporal, and lateral ventricles) contributed independently to the attention score after controlling for the contribution of the corresponding left hemisphere region (anterosuperior temporal: right, $P=.002$; left, $P=.07$; posterosuperior temporal: right, $P=.006$; left, $P\leq.47$; lateral ventricles: right, $P\leq.01$; left, $P\leq.46$).

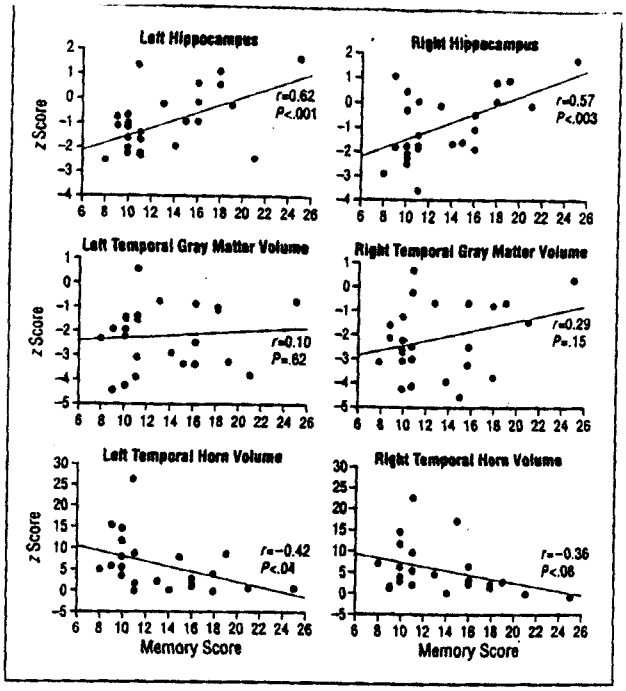

Figure 3. *Higher memory scores were significantly associated with larger hippocampal volumes. Multiple regression analyses disclosed selective relations between memory scores and left and right hippocampal volumes but not other global or regional cortical gray matter volumes.*

Table 3. Multiple Regressions Predicting Dementia Rating Scale Scores From Magnetic Resonance Imaging Regional Brain Volumes

Dependent Measure Predictors	β Coefficient	R^2 Change
Score		
Memory		
Left hippocampus	0.67*	0.39
Left temporal cortex	−0.14	0.02
Right hippocampus	0.58†	0.24
Right temporal cortex	−0.01	0.00
Bilateral hippocampus	0.67*	0.40
Total cortical gray matter	−0.08	0.00
Left hippocampus	0.55†	0.28
Left temporal horn	−0.28	0.07
Right hippocampus	0.55†	0.20
Right temporal horn	−0.04	0.00
Initiation/Perseveration		
Left prefrontal cerebrospinal fluid	−0.74‡	0.18
Right prefrontal cerebrospinal fluid	0.39	0.05
Attention		
Left anterosuperior temporal	−0.35	0.06
Right anterosuperior temporal	0.62‡	0.19
Left posterosuperior temporal	−0.13	0.01
Right posterosuperior temporal	0.50‡	0.15
Left lateral ventricle	0.18	0.01
Right lateral ventricle	−0.61†	0.12
Construction		
Left anterosuperior temporal	−0.23	0.03
Right anterosuperior temporal	0.64‡	0.20
Left posterosuperior temporal	0.12	0.01
Right posterosuperior temporal	0.29	0.05
Left lateral ventricle	0.10	0.00
Right lateral ventricle	−0.49	0.07

*P<.001.
†P<.05.
‡P<.01.

Conceptualization

Conceptualization subscale scores were not significantly correlated with any regional brain volume measure.

Construction

Construction subscale scores were significantly correlated with bilateral volumes of anterosuperior temporal (r=0.38; P<.01) and posterosuperior temporal (r=0.38; P<.01) gray matter, with a statistical trend found for lateral ventricle (r=−0.36; P<.02) volume (**Figure 6**). Examination of lateralized brain volume measures indicated significant correlations between construction score and right hemisphere volumes of anterosuperior temporal (r=0.47; P<.001), posterosuperior temporal (r=0.36; P<.01) gray matter and right lateral ventricle volume (r=−0.40; P<.005). Because of the restricted range of this subscale measure, Spearman correlations were conducted to confirm these correlations. These analyses yielded similar results, with the exception that the correlations between the construction score and bilateral (ρ=0.27; P<.06) and right (ρ=0.29; P<.05) posterosuperior temporal volume became only marginally significant.

A multiple regression analysis indicated that the right anterosuperior temporal volume uniquely contributed to the construction score after accounting for the contribution of the left anterosuperior temporal volume (P<.002), but that the contribution of the left anterosuperior temporal volume, after controlling for the contribution of the right anterosuperior temporal volume, did not reach significance (P=.22). Multiple regression analysis examining the unique contribution of the left and right posterosuperior temporal regions indicated that neither the left nor the right posterosuperior temporal volume contributed significantly to the construction score after the contribution of the other was accounted for (posterosuperior temporal: left, P=.49; right, P=.11). A third regression examined the unique contribution of the left and right lateral ventricles to the construction score, with the volume of the right lateral ventricle approaching significance (P=.05) as a unique predictor to the construction score, but the contribution of the left lateral ventricle to the construction score, after accounting for the contribution of the right lateral ventricle, was not significant (P=.69).

Total Score

The DRS total score, which reflects overall dementia severity, was significantly correlated with left hippocampal (r=0.52; P<.01) and right posterosuperior temporal gray matter (r=0.39; P<.01) volumes.

Multiple regression analyses based on head size–corrected MRI scores and using age as a separate predictor yielded the same pattern of results as those reported

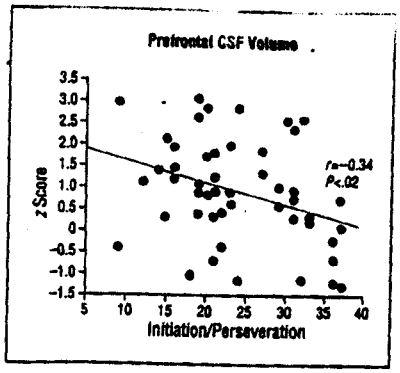

Figure 4. *Initiation/perseveration scores showed a significant negative correlation with prefrontal sulcal volume; lower scores were associated with larger prefrontal sulci. CSF indicates cerebrospinal fluid.*

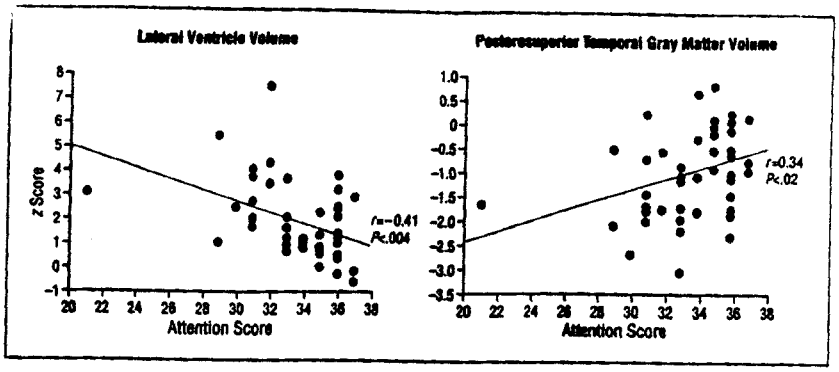

Figure 5. *Lower attention scores were significantly associated with larger lateral ventricles. A trend was found toward a relation between attention scores and posterosuperior temporal gray matter; better attention scores were related to larger posterosuperior temporal volumes.*

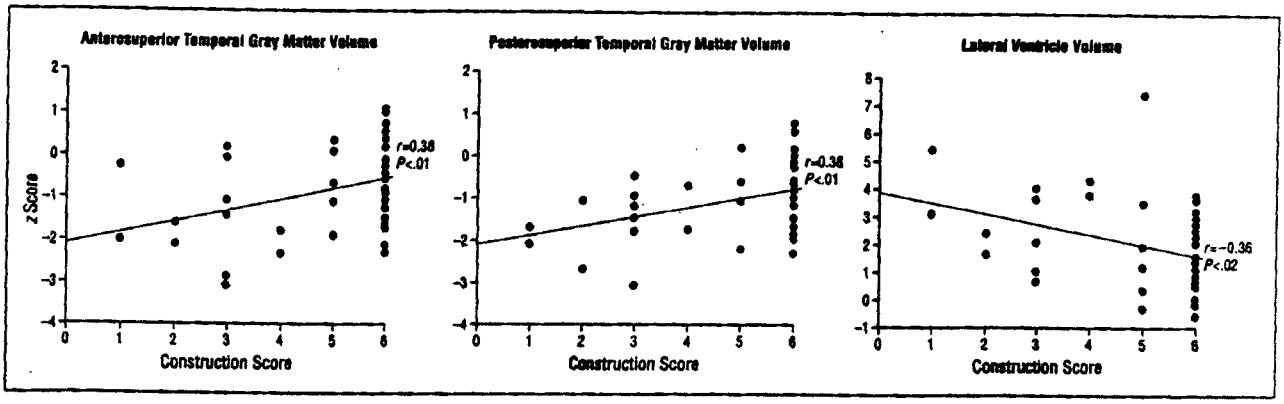

Figure 6. *Construction scores were significantly correlated with anterosuperior temporal and posterosuperior temporal volumes; higher construction scores were associated with more gray matter in these regions. A trend toward a negative relation was found between construction scores and lateral ventricle volume; lower construction scores were associated with larger lateral ventricles.*

above, which were based on head size– and age-corrected z scores.

COMMENT

These results show that selective subscales of the DRS are sensitive to the specific cognitive and regional brain volume deficits observed in AD. Although several structural neuroimaging studies have documented the association between overall dementia severity and general measures of cortical atrophy in AD,[67-70] this study provides evidence for associations between specific cognitive deficits and specific brain regions. Despite widespread loss of brain tissue volume, the performance of patients with AD on several DRS subscales was selectively and predictably related to regional brain volume measures quantified with MRI. Specifically, memory performance was related to hippocampal but not total or regional cortical gray matter volumes. Attention performance was related to temporal lobe gray matter and lateral ventricle volumes of the right hemisphere, but construction performance was related to these same brain regions in both hemispheres. Although regional gray matter volumes were not significantly correlated with the initiation/perseveration or conceptualization subscale scores, sulcal dilation in the prefrontal region was related to initiation/perseveration scores, with a greater association to the left than right prefrontal sulcal CSF volume. Stout et al[33] observed an independent contribution to DRS performance from presence of abnormal white matter intensities beyond the gray matter contribution; however, the present study did not quantify white matter signal hyperintensities.

CORRELATES OF MEMORY PERFORMANCE

This study provides further evidence of the importance of hippocampal integrity to memory functioning in AD.[14,32,33] Our findings extend the observations of Deweer et al,[32] who reported a relation between hippocampal formation and memory in patients with AD, because we examined overall and regional cortical contributions and hippocampal contribution to memory performance. The selective relation between memory and hippocampal volumes found in the present study, with the nonsignificant relations between memory and regional cortical volumes suggests a dissociation between cortical and hippocampal functions as they contribute to explicit memory performance in AD. Our results are consistent with the observations of Stout et al,[33] who found a relation between limbic gray matter volume and DRS memory performance, and confirm this association using an anatomically defined measure of hippocampal volumes. Thus, explicit memory functioning in AD seems to be more related to reduction of hippocampal region volume than

to general or specific reduction of regional cortical gray matter, which itself was quite striking.

Hippocampal volume was a significant independent predictor of the memory subscale score, but temporal horn volume was not. Although it is tempting to assume that the change in the hippocampus and adjacent temporal horn are directly associated, other extrahippocampal volume loss (specifically the amygdala and temporal lobe) may play a role in temporal horn enlargement.[2] Thus, conclusions based on brain-behavior relations using temporal horn volume cannot necessarily be generalized to reflect hippocampal integrity.[37]

CORRELATES OF NONMNEMONIC PERFORMANCE

The relations between attention subscale performance and the right superior temporal gray matter and lateral ventricle volumes are consistent with previous findings implicating the right hemisphere in attentional demands.[43] Although this study was not designed to address specific attentional component processes, it provides evidence that directed attention necessary for successful task completion may depend preferentially on the integrity of the right, not the left hemisphere.

The hypothesis that verbal fluency performance and associated items (initiation/perseveration subscale) would be related to prefrontal gray matter volume was not directly supported. Performance on this subscale was, however, significantly related to prefrontal sulcal CSF volume, with a greater association with left than right hemisphere volume. One speculation is that sulcal volume enlargement may precede gray matter volume shrinkage, and, if so, a stronger relation between the behavioral tasks and prefrontal gray matter volume may be detected as the disease progresses. The prediction of lateralized findings (left more than right involvement) was supported and may be attributed primarily to the large contribution of the fluency item (20 of the possible 37 points) to the total initiation/perseveration score.

The interpretation of the structure-function relations based on construction performance requires caution because of the restricted range of scores on this subscale. Although the results of this study suggest that the right anterosuperior temporal and lateral ventricle regions are important in the mediation of the visuospatial abilities necessary to successfully copy geometric figures, further study with measures providing greater variability is needed to confirm this interpretation.

In conclusion, these results are consistent with other studies[25,30] reporting severely impaired DRS memory performance in AD. It has been suggested that brain-behavior relations between memory performance and specific limbic regions would be difficult to document because patients with AD are severely impaired on memory tasks (ie, floor effect) and the volume deficits associated with the medial temporal region are marked.[33] However, the present study showed that the DRS memory subscale affords the variability in performance necessary to examine brain-behavior relations, at least in moderately demented patients with AD. Most striking was the relation observed between memory performance and regional hippocampal volume reduction. These results highlight the sensitivity of the DRS to selective cognitive processes and to the integrity of their underlying anatomical structures in AD.

Accepted for publication January 28, 1997.

This research was supported by grants MH18905, MH40041, MH30854, AA05965, and AA10723 from the National Institute of Mental Health and the National Institute of Alcoholism and Alcohol Abuse, Bethesda, Md, and the Department of Veterans Affairs, Washington, DC.

Portions of this research were presented at the International Neuropsychological Society meeting, Chicago, Ill, February 16, 1996.

We thank Kenneth Chow, MA, for his statistical assistance; Brian Matsumoto, MS, for image analyses; Deborah A. Cahn, PhD, Daniel H. Mathalon, PhD, MD, and Margaret J. Rosenbloom, MA, for helpful comments on the manuscript; and Jennifer Johnson, Maria Stein, Linda Davis, and other members of the Laboratory of Physiology and Structural Brain Imaging at the Veterans Affairs Palo Alto Health Care System for their invaluable work in subject recruitment and in data collection, scoring, and computer entry.

Reprints: Edith V. Sullivan, PhD, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5548.

REFERENCES

1. Rusinek H, De Leon MJ, George AE, et al. Alzheimer disease: measuring loss of cerebral gray matter with MR imaging. *Radiology.* 1991;178:109-114.
2. Killiany RJ, Moss MB, Albert MS, Sandor T, Tieman J, Jolesz F. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. *Arch Neurol.* 1993;50:949-954.
3. Jernigan TL, Salmon DP, Butters N, Hesselink JR. Cerebral structure on MRI, II: specific changes in Alzheimer's and Huntington's diseases. *Biol Psychiatry.* 1991;29:68-81.
4. Sullivan EV, Shear P, Lim KO, et al. Age-related cortical gray matter deficits in Alzheimer's disease. *J Int Neuropsychol Soc.* 1995;17:185.
5. Mathalon D, Sullivan EV, Shear PK, et al. Discrimination of Alzheimer's and Parkinson's disease by analysis of regional CSF profiles using quantitative CT brain imaging. Presented at the Society for Neuroscience 25th Annual Meeting; November 11-16, 1995; San Diego, Calif.
6. Jagust WJ, Eberling JL, Richardson BC, et al. The cortical topography of temporal lobe hypometabolism in early Alzheimer's disease. *Brain Res.* 1993;629:189-198.
7. Pearlson GD, Harris GJ, Powers RE, et al. Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. *Arch Gen Psychiatry.* 1992;49:402-408.
8. Laherley S, Baulac M, Chiras J, et al. Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. *Am J Neuroradiol.* 1994;15:929-937.
9. Seab JP, Jagust WJ, Wong STS, Roos MS, Reed BR, Budinger TF. Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. *Magn Reson Med.* 1988;8:200-208.
10. De Leon MJ, George AE, Reisberg B, et al. Alzheimer's disease: longitudinal CT studies of ventricular change. *Am J Neuroradiol.* 1989;10:371-376.
11. De Leon MJ, Golomb J, Convit A, Desanti S, McRae TD, George AE. Measurement of medial temporal lobe atrophy in diagnosis of Alzheimer's disease. *Lancet.* 1993;341:125.
12. Golomb J, De Leon MJ, Kluger A, George AE, Tarshish C, Ferris SH. Hippocampal atrophy in normal aging: an association with recent memory impairment. *Arch Neurol.* 1993;50:967-973.
13. Jack CR, Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology.* 1992;42:183-188.
14. Laakso MP, Soininen H, Partanen K, et al. Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. *J Neural Transm Park Dis Dement Sect.* 1995;9:73-86.
15. Jagust WJ. Neuroimaging in normal aging and dementia. In: Albert ML, Knoefel JE, eds. *Clinical Neurology of Aging.* New York, NY: Oxford University Press Inc; 1994:190-213.

16. Mann DMA. The neuropathology of Alzheimer's disease: a review with pathogenetic, aetiological and therapeutic considerations. *Mech Aging Dev.* 1985; 31:213-255.
17. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry.* 1968;114:797-811.
18. Flood DG, Coleman PD. Hippocampal plasticity in normal aging and decreased plasticity in Alzheimer's disease. In: Storm-Mathisen J, Zimmer J, Otterson OP, eds. *Progress in Brain Research: Understanding the Brain Through the Hippocampus.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1990; 83:435-443.
19. Kemper TL. Neuroanatomical and neuropathological changes during aging and dementia. In: Albert ML, Knoefel JE, eds. *Clinical Neurology of Aging.* New York, NY: Oxford University Press Inc; 1994:3-67.
20. Lezak MD. *Neuropsychological Assessment.* 3rd ed. New York, NY: Oxford University Press Inc; 1995.
21. Albert MS, Moss MB. *Geriatric Neuropsychology.* New York, NY: Guilford Press; 1988.
22. Bondi MW, Salmon DP, Kaszniak AW. The neuropsychology of dementia. In: Grant I, Adams KM, eds. *Neuropsychological Assessment of Neuropsychiatric Disorders.* New York, NY: Oxford University Press Inc. In press.
23. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellack L, Karasu TB, eds. *Geriatric Psychiatry.* New York, NY: Grune & Stratton Inc; 1976:77-120.
24. Mattis S. *Dementia Rating Scale (DRS) Professional Manual.* Odessa, Fla: Psychological Assessment Resources Inc; 1988.
25. Salmon DP, Thal LJ, Butters N, Heindel WC. Longitudinal evaluation of dementia of the Alzheimer type: a comparison of 3 standardized mental status examinations. *Neurology.* 1990;40:1225-1230.
26. Salmon DP, Kwo-on-Yuen P, Heindel WC, Butters N, Thal LJ. Differentiation of Alzheimer's disease and Huntington's disease with the Dementia Rating Scale. *Arch Neurol.* 1989;46:1204-1208.
27. Paulsen JS, Butters N, Sadek JR, et al. Distinct cognitive profiles of cortical and subcortical dementia in advanced illness. *Neurology.* 1995;45:951-956.
28. Rosser AE, Hodges JR. The Dementia Rating Scale in Alzheimer's disease, Huntington's disease and progressive supranuclear palsy. *J Neurol.* 1994;241: 531-536.
29. Paolo AM, Troster AI, Glatt SL, Hubble JP, Koller WC. Differentiation of the dementias of Alzheimer's and Parkinson's disease with the Dementia Rating Scale. *J Geriatr Psychiatry Neurol.* 1995;8:184-188.
30. Monsch AU, Bondi MW, Salmon DP, et al. Clinical validity of the Mattis Dementia Rating Scale in detecting dementia of the Alzheimer type: a double cross-validation and application to a community-dwelling sample. *Arch Neurol.* 1995; 52:899-904.
31. Samuel W, Masliah E, Hill LR, Butters N, Terry R. Hippocampal connectivity and Alzheimer's dementia: effects of synapse loss and tangle frequency in a two-component model. *Neurology.* 1994;44:2081-2088.
32. Deweer B, Lehericy S, Pillon B, et al. Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. *J Neurol Neurosurg Psychiatry.* 1995;58:590-597.
33. Stout J, Jernigan T, Archibald SL, Salmon DP. Association of dementia severity with cortical gray matter and abnormal white matter volumes in dementia of the Alzheimer type. *Arch Neurol.* 1996;53:742-749.
34. Hyman BT, Arriagada PV, Van Hoesen GW, Damasio AR. Memory impairment in Alzheimer's disease: an anatomical perspective. In: Parks RW, Zec RF, Wilson RS, eds. *Neuropsychology of Alzheimer's Disease and Other Dementias.* New York, NY: Oxford University Press Inc; 1993:138-150.
35. Jernigan TL, Cermak LS. Structural basis of memory. In: Kertesz A, ed. *Localization and Neuroimaging in Neuropsychology.* New York, NY: Academic Press Inc; 1994:599-620.
36. DeCarli C, Murphy DGM, McIntosh AR, Horwitz B. Discriminant analysis of Alzheimer's disease. *Arch Neurol.* 1994;51:1088.
37. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging.* 1995;16:591-606.
38. Parks RW, Loewenstein DA, Dodrill KL, et al. Cerebral metabolic effects of a verbal fluency test: a PET scan study. *J Clin Exper Neuropsychol.* 1988;10: 565-575.
39. Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR. Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behav Neurosci.* 1989;103:548-560.
40. Newcombe F. *Missile Wounds of the Brain: A Study of Psychological Deficits.* New York, NY: Oxford University Press Inc; 1969.
41. Kertesz A, Naeser MA. Anatomical asymmetries and cerebral lateralization. In: Kertesz A, ed. *Localization and Neuroimaging in Neuropsychology.* New York, NY: Academic Press Inc; 1994:213-244.
42. Posner MI, Petersen SE. The attention system of the hur *Neurosci.* 1990;13:25-42.
43. Mesulam M-M. Attention, confusional states, and neglect. ed. *Principles of Behavioral Neurology.* Philadelphia, Pa: F. ers; 1985:125-168.
44. Stuss DT, Benson DF. Neuropsychological studies of the *chol Bull.* 1984;95:3-28.
45. Heilman KM, Watson RT, Valenstein E. Localization of les related disorders. In: Kertesz A, ed. *Localization and Neur psychology.* New York, NY: Academic Press Inc; 1994:49
46. Shimamura AP, Jurica PJ, Mangels JA, Gershberg FB. Susc interference effects following frontal lobe damage: findings f associate learning. *J Cogn Neurosci.* 1995;7:144-152.
47. Stuss DT, Benson DF. *The Frontal Lobes.* New York, NY: I
48. Lezak MD. *Neuropsychological Assessment.* 2nd ed. Nev University Press Inc; 1983.
49. Corkin S, Rosen J, Sullivan EV, Clegg RA. Penetrating he adulthood exacerbates cognitive decline in later years. J 3876-3883.
50. Kirk A, Kertesz A. Localization of lesions in constructional imp A, ed. *Localization and Neuroimaging in Neuropsychology.* demic Press Inc; 1994:525-544.
51. McKhann G, Drachman D, Folstein M, Katzman R. Clinica heimer's disease: report of the NINCDS-ADRDA Work Gr pices of Department of Health and Human Services Task Fo disease. *Neurology.* 1984;37:939-944.
52. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch* 1097-1105.
53. Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zip A quantitative magnetic resonance imaging study of chan phology from infancy to late adulthood. *Arch Neurol.* 199
54. Lim KO, Zipursky RB, Sullivan EV, Pfefferbaum A. Cortical deficits in schizophrenia: a replication. *Schizophr Res.* 19
55. Lim KO, Pfefferbaum A. Segmentation of MR brain images fluid spaces, white and gray matter. *J Comput Assist Tom* 593.
56. Zipursky RB, Lim KO, Sullivan EV, et al. Widespread cerebr ume deficits in schizophrenia. *Arch Gen Psychiatry.* 1992;
57. Lim KO, Zipursky RB, Watts MC, Pfefferbaum A. Decrea normal aging: an in vivo magnetic resonance study. *J Geri Soc Sci.* 1992;47:26-30.
58. Pfefferbaum A, Lim KO, Zipursky RB, et al. Brain gray and ume loss accelerates with aging in chronic alcoholics: a qua *Alcohol Clin Exp Res.* 1992;16:1078-1089.
59. Pfefferbaum A, Zatz L, Jernigan TL. Computer-interactive fying cerebrospinal fluid and tissue in brain CT scans: effect *put Assist Tomogr.* 1986;10:571-578.
60. Zipursky R, Lim KO, Dement S, Marsh L, Murphy GM, Pf metric MRI assessment of temporal lobe morphology in tients with widespread gray matter volume deficit. *Biol Ps* 124. Abstract.
61. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum campal volume deficits in nonamnesic, aging chronic alcol *Exp Res.* 1995;19:110-122.
62. Amaral DG, Insausti R. Hippocampal formation. In: Paxinos *Nervous System.* New York, NY: Academic Press Inc; 199
63. Nelson HE. *The National Adult Reading Scale (NART).* Win son Publishing Co; 1982.
64. Wechsler D. *Manual for the Wechsler Adult Intelligence S* York, NY: The Psychological Corp; 1981.
65. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Corr in brain-imaging measurements. *Psychiatry Res.* 1993;50:
66. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Corr in brain-imaging measurements: letter to editor. *Psychiatry*
67. Shear PK, Sullivan EV, Mathalon DH, et al. Longitudinal vol tomographic analysis of regional brain changes in normal mer's disease. *Arch Neurol.* 1995;52:392-402.
68. Sullivan EV, Shear PK, Mathalon DH, et al. Greater abnorm rebrospinal fluid volumes in younger than older patients wi ease. *Arch Neurol.* 1993;50:359-373.
69. Murphy DGM, DeCarli CD, Daly E, et al. Volumetric magn aging in men with dementia of the Alzheimer type: correla severity. *Biol Psychiatry.* 1993;34:612-621.
70. Creasey H, Schwartz M, Frederickson H, Haxby JV, Rapop computed tomography in dementia of the Alzheimer type. 36:1563-1568.