Volumetric Magnetic Resonance Imaging in Men with Dementia of the Alzheimer Type: Correlations with Disease Severity

D. G. M. Murphy, C. D. DeCarli, E. Daly, J. A. Gillette, A. R. McIntosh, J. V. Haxby, D. Teichberg, M. B. Schapiro, S. I. Rapoport, and B. Horwitz

Using magnetic resonance imaging (MRI), we measured the volumes of various brain structures and cerebrospinal fluid (CSF) in 19 men with dementia of the Alzheimer type (DAT) and 18 healthy age-matched control men. The mean (±S.D) Mini-Mental State exam score (MMSE) of the DAT men was 16 ± 7; 9 were mildly (MMSE > 20), 5 moderately (MMSE 10-20), and 5 severely (MMSE < 10) demented. Brain and CSF volumes were normalized as a percent of the traced intracranial volume to control for the relation of volumes of cerebral structures to head size, and analyzed statistically.

The whole group of DAT subjects had significantly smaller mean cerebral brain matter and temporal lobe volumes ($p < 0.05$), and significantly larger mean ventricular and temporal lobe peripheral CSF volumes than did controls. Mean volumes of the subcortical nuclei did not differ significantly between groups, and mean volume of temporal lobe brain matter decreased significantly more than whole brain, suggesting regional loss of brain matter in DAT. Mildly demented DAT patients had significantly smaller mean cerebral brain matter and temporal lobe volumes and significantly larger volumes of lateral ventricles, and of temporal lobe peripheral CSF, than did controls. Neuropsychological measures of disease severity in DAT patients were significantly ($p < 0.05$) and appropriately correlated to volumes of cerebral brain matter and right lateral ventricle.

These results suggest that in DAT: (i) significant brain atrophy is present early in the disease process, (ii) brain atrophy correlates with severity of cognitive impairment, and (iii) there is greater involvement of the telencephalic association system than whole brain, and there is relative sparing of the caudate, lenticular and thalamic nuclei.

Key Words: Magnetic resonance imaging, Alzheimer's disease, age, dementia severity, brain atrophy, cerebrospinal fluid, caudate nucleus, lenticular nucleus, thalamus

Introduction

Dementia of the Alzheimer type (DAT) is a progressive neurodegenerative disorder associated with neuron loss (Hansen et al 1988), and accumulation of neurofibrillary tangles and senile plaques (Khatchaturian 1985). There are significant correlations between global measures of de-

From the Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, MD
Address reprint requests to D.G.M. Murphy, M.D., Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bldg 10, Room 6C 414, Bethesda, MD 20892
Received October 15, 1992, revised July 7, 1993.

0006-3223/93/$06.00

mentia severity during life in DAT and postmortem neuropathological findings of neurofibrillary tangles (Wilcock and Esiri 1982), senile plaques (Delaere et al 1989), loss of cortical neurons in temporal and frontal lobes (Mann et al 1988; Neary et al 1986), and reduction of markers for acetylcholine (Mann et al 1988).

However, postmortem studies have several limitations (such as fixation artifacts, postmortem delay, and patient selection bias) which *in vivo* imaging studies avoid. Accordingly, attempts have been made to study brain morphometrics of DAT patients using *in vivo* techniques such as computerized X-ray tomography (CT) and magnetic resonance imaging (MRI).

Cross-sectional volumetric CT studies of patients with DAT (Gado et al 1982; George et al 1983; Ichimiya et al 1986) reported that their cerebrospinal fluid (CSF) volumes are significantly larger than healthy controls, but there was considerable overlap between the two groups (Drayer 1988). CT studies of DAT disagree whether CSF spaces increase in volume with increasing disease severity (Bigler et al 1985; Creasey et al 1986; Ichimiya et al 1986; Luxenberg et al 1987; Naugle et al 1985). CT scans are limited by their spatial resolution and tissue contrast differences, and by an artifactual elevation of brain CT numbers for pixels adjacent to the skull ('bone hardening artifact') (DiChiro et al 1978; Gado and Phelps 1975), making CT unreliable for measuring peripheral CSF. Unlike CT, MRI requires no ionizing radiation, repeated measures are without known risk, and MRI images are free of bone hardening artifacts (Andreasen 1989).

Volumetric MRI studies of DAT patients and controls found that DAT patients have significantly smaller volumes of cortical gray matter, caudate, lenticular and thalamic nuclei (Jernigan et al 1991), hippocampus and the parahippocampal gyrus (Kesslak et al 1991; Seab et al 1988). Brain volumes measured by MRI in DAT patients have been correlated with neuropsychological test scores, but no study factored out the confounding effect of age on brain volumes or neuropsychological test scores. This laboratory has previously reported a strong effect of age on brain volume (Murphy et al 1992b) and cognitive functioning (Koss et al 1991). We demonstrated, using quantitative MRI, significant age-related atrophy of total brain matter, and of the caudate and lenticular nuclei. Visuospatial ability in particular declines significantly with age (Koss et al 1991.)

In vivo imaging studies of regional brain glucose metabolism (Haxby et al 1988; Kumar et al 1991) suggest more involvement of the association than primary neocortical regions in Alzheimer's disease, and postmortem studies confirm that neuropathological changes are accentuated in association areas of the neocortex, as well as in regions of the hippocampal formation and amygdaloid complex (Ball 1977; Brun and Gustafson 1976; Lewis et al 1987; Mann et al 1985; Najlerahim and Bowen 1981; Pearson et al 1985); neurofibrillary tangles have greatest density in the temporal lobe and neocortical association areas, whereas they are less abundant in primary sensory and motor cortices, brain stem nuclei and the basal ganglia (Arnold et al 1991). Thus, Alzheimer's disease has a definite topographic distribution and regional brain atrophy in the areas most affected by the DAT process would be expected, but these have not been clearly demonstrated in pathological studies (Duyckaerts et al 1985; Shefer 1972). Contrary to the pathological literature, an MRI study of DAT has reported significant thalamic atrophy (Jernigan et al 1991). Given the distribution of the neuropathological findings in DAT, we would expect to find, using ***in vivo*** anatomical brain imaging such as MRI, more atrophy in neocortical and allocortical (temporal lobe) regions than in caudate, lenticular and thalamic nuclei.

In the present study, we performed a quantitative MRI analysis of the human brain in DAT. Computerized approaches were employed to measure the volumes of subcortical gray matter nuclei, cerebral brain matter, temporal lobes, and ventricular and peripheral CSF in 19 men with DAT and in 18 age-matched healthy men. Our aims were: (i) to determine if there are significant volumetric differences between mildly demented DAT patients and healthy age/sex matched controls, (ii) to correlate brain volumes to severity of dementia in the patients, (iii) to test the hypothesis that brain atrophy, as measured by MRI, in DAT follows the previously described pathological distribution—affecting temporal lobes more than whole brain, caudate, lenticular, and thalamic nuclei. We examined one sex only (so no confounding gender effects are present), and factored out the effect of age on correlations between MRI volumes and neuropsychological test scores.

Portions of this work have been presented in abstract form to the Society for Neurosciences 23rd annual meeting, Anaheim, CA, Nov 1992 (Daly et al 1992).

Methodology

Subjects

All subjects were participants in a clinical program on brain metabolism and aging conducted by the Laboratory of Neuroscience of the National Institute on Aging. Nineteen men who met the NINCDS-ADRDA criteria (McKhann et al 1984) for probable Alzheimer's disease participated in the study. All patients had Hachinski Ischaemic Indices less than 5 (Hachinski et al 1975) and Hamilton depression scores less than 10 (Hamilton 1960). Patients were screened for medical illnesses that could affect brain function. No patient had any disease other than DAT, and no history of significant head injury, toxic exposure, di-

abetes, hypertension, cardiovascular disease, atherosclerosis, drug or alcohol abuse, or psychiatric disorder. In addition, no patient was taking any medications. All had normal routine urine, CSF, EKG and blood tests, including thyroid, Vitamin B_{12} and folate levels, HIV, cholesterol, glucose and negative syphilis serology. All patients and controls had a normal structured neurological exam (Kaye et al 1988), and routine CT and EEG showed no focal brain abnormalities. The age range of the patients was 53 to 81 years [mean ± S.D: 68 ± 9 yr)]. Cognitive dysfunction was evaluated by the Mini Mental State Exam Examination (MMSE) (Folstein et al 1975), Blessed Memory, Information and Concentration Test (BMICT) (Blessed et al 1968), Mattis Dementia Scale (MDSTOT) (Coblentz et al 1973), and the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1958). Of the 19 patients with DAT who underwent axial MRI, 13 also had coronal MRI for temporal lobe measurement. There was no significant mean difference between those who did and did not undergo coronal MRI in age, blood pressure, IQ, MMSE, or length of illness.

Healthy controls were recruited by advertisement from the local community, they consisted of 18 men age range 54-85 years [mean ± S.D: 70 ± 8 yr], and were screened in the same manner as the DAT patients to exclude primary brain disease and conditions that might be associated with brain disease (Duara et al 1983). Of the 18 healthy controls who underwent axial MRI, 12 also had coronal MRI for temporal lobe measurement. There was no significant mean difference between those who did and did not undergo coronal MRI in age, blood pressure, or IQ. Informed consent was obtained in all cases from patients and controls for NIH protocols 81-AG-10 (DAT) and 80-AG-26 (controls).

Magnetic Resonance Imaging

MRI of the brain was performed on a 0.5 Tesla scanner (Picker Instruments, Cleveland, OH). Temporal lobe volume was measured using coronal slices (Murphy et al 1992a), and all other brain volumes were determined using axial slices (Murphy et al 1992b).

To determine temporal lobe volume, 16 to 19, 6 mm thick, contiguous slices were obtained in the coronal orientation beginning anterior to the temporal pole and extending past the posterior aspect of the diencephalon. Data were acquired with a spin-echo sequence (TR 500/TE 12) with 192 views, and four repetitions. Voxel size was 6 mm^3.

Axial slices were analyzed, using the proton density (TR 2000 msec, TE 20 msec) portion of a double echo sequence (TR 2000/20/80) with 192 views and 2 repetitions. Thirty six, 7-mm thick, contiguous slices were obtained from the foramen magnum to the vertex, parallel to the inferior orbitomeatal line. Image acquisition time for the double echo sequence was 25 minutes. Data, stored on magnetic tape in digital form, were analyzed with a VAX 11/750 (Digital Equipment Corp, Landover, MD) computer system and a Gould 8400 Image Array Processor (Vicom Inc, Fairfax, VA), after being displayed on a television monitor. Scans were analyzed by operators after being loaded in random order by a research assistant; operators were blind to subject name, age, and group.

METHODS OF ANALYSIS. A region of interest (ROI) analysis (Murphy et al 1992b) was applied to determine the volumes of the cerebral ventricles, cerebral hemispheres, temporal lobes and subcortical nuclei. Subcortical nuclei were traced after employing a histogram equalization method to enhance the contrast between gray and white matter (Vicom Inc, Lips version 4.1, Oct 1985, Fairfax, VA). The cerebral ventricles, hemispheres, and temporal lobes were traced on unequalized images, and a segmentation analysis (DeCarli et al 1992) was used on the unequalized image to determine volumes of total CSF space and of cerebral brain matter (defined as cerebral white + gray matter). Peripheral CSF volume was calculated by subtracting ventricular CSF volume from total CSF volume determined by segmentation. Absolute volumes (in cm^3) were calculated, as well as volumes normalized as a percent of the traced intracranial volume (% vol), to control for the relation of volumes of cerebral structures to head size (Brinkman et al 1981). Intracranial volume was defined as volume of the cerebral hemispheres + brain stem + cerebellum.

REGIONS OF INTEREST. Intracranial ROIs used for calculating temporal lobe volume were traced on each coronal MRI slice in which they were seen, from the anterior pole of the temporal lobe to the level of the Sylvian aqueduct in the midbrain. The medial temporal lobe boundary was defined as a straight line drawn from the angle of the medial temporal lobe where it is attached to the temporal stem, to the midpoint of the operculum (Murphy et al 1992a). The operator then traced the dura of the middle cranial fossa around each temporal lobe to complete the ROI.

In axial MRI slices, the operator traced the total cerebral hemispheric cross sectional area (cm^2), and outlined the right and left hemispheres (brain matter + CSF), lateral and third ventricles, cerebellum and brain stem. The medial surfaces of the cerebral hemispheres were bisected by following the dura into the interhemispheric fissure and then drawing a straight line connecting the anterior to the posterior interhemispheric fissure. ROI's were traced on each axial image in which they were present. The subcortical nuclei (right and left caudate and lenticular nuclei,

and thalamus) were traced after employing a histogram equalization method (Murphy et al 1992b).

The number of enclosed pixels (1 pixel = 1 mm^2) was determined for each ROI on every slice in which it was present. The volume of each ROI (in cm^3) was calculated by multiplying the summed pixel cross-sectional areas by slice thickness (6 mm for coronal, and 7 mm for axial slices).

Segmentation Analysis

To quantify CSF and brain matter in each slice, we used a semi-automated method based on mathematical modeling of MRI pixel intensity histograms (DeCarli et al 1992). On each coronal and axial image, the operator first outlined the intracranial area, and then used nonlinear modeling of the pixel intensity histogram to find an optimal threshold for separating CSF from brain matter pixels. The operator then returned to the image and outlined each cerebral hemisphere for segmentation of CSF from brain matter, using the global threshold value just obtained. With this method, the volumes of the following structures were calculated: total hemispheric brain matter, total CSF, right hemisphere brain matter, left hemisphere brain matter, right hemisphere CSF, left hemisphere CSF, right and left temporal lobe brain matter and CSF.

Derived Volumes

The volume of peripheral CSF was calculated by subracting the sum of the traced ventricular CSF volumes from the traced regional CSF volume obtained by segmentation [e.g. right peripheral CSF volume = right hemispheric CSF volume − right lateral ventricle volume − (III ventricle volume/2)].

Cerebral brain matter volume was defined as brain matter volume of the cerebral hemispheres. We present absolute volumes in cm^3 to allow comparison to previous studies, and volumes normalized to intracranial volume to control for the possible effect of head size on the volumes of the cerebral structures (Brinkman et al 1981).

Reliability

Each MRI scan was analyzed by one of two operators (DM, CD). Intra-rater and inter-rater reliabilities (Bartko and Carpenter 1986) for these operators have been previously published for this method (DeCarli et al 1992).

Statistics

Statistical analysis was only carried out on ROI volumes normalized to intracranial volume to control for the possible effect of head size on the volumes of the cerebral structures (Brinkman et al 1981). Three statistical comparisons were carried out between groups: (i) healthy controls vs all DAT men for all ROIs, (ii) healthy controls vs mildly demented DAT men for all ROIs, and (iii) a comparison of amount of atrophy in DAT in temporal lobe, cerebral hemispheric brain matter and subcortical nuclei. For the first two analyses all comparisons of means between DAT and control groups used unpaired students *t* tests; an F-test was used to assess within-group variance of all ROIs. To control for the two between-group statistical comparisons, level of statistical significance was defined as $p < 0.025$. To test the hypothesis that brain atrophy in DAT follows the previously described pathological distribution (affecting temporal lobes more than whole brain, caudate, lenticular, and thalamic nuclei), we performed a repeated measures ANOVA where the volume of sub cortical nuclei, whole brain and temporal lobe, were the repeated measures. Post hoc mean comparisons were performed using a Student-Newman-Keuls Multiple Range post hoc correction for multiple comparisons (SAS 1985) within the SAS ANOVA procedure (SAS 1985).

Correlations of MMSE, BMICT, MDSTOT and WAIS scores and cerebral volumes were carried out in the DAT group only. Because neuropsychological test scores may correlate with age (Botwink 1977; Duara et al 1983; Mataratzzo 1972; Schwartz et al 1985) and cerebral volumes also correlate with age (Murphy et al 1992b), if a cerebral volume and a test score correlated significantly, the correlation analysis was repeated with age partialed out. Only those correlations which remained significant when age was partialed out are presented.

Results

Mean pulse rate and blood pressure were not significantly different between the whole DAT group and controls (Table 1). The DAT group scored significantly lower ($p < 0.05$) on all dementia ratings than controls.

Absolute (unnormalized) volumes (in cm^3) of all measured ROI's are presented in Table 2. Statistical comparisons and neuropsychological correlations for all ROI's and derived parameters were carried out only on normalized values (Tables 3 and 4).

As a group the DAT men had significantly smaller cerebral brain matter and temporal lobe volumes, and significantly larger CSF volumes in each ventricular CSF measure than controls (Tables 3 and 4). Cerebral hemispheric peripheral CSF did not differ significantly between groups, but temporal lobe peripheral CSF volume was significantly larger in DAT men than controls. The volumes of the subcortical nuclei did not differ significantly between DAT and controls. When these regional brain volume differences were compared using the repeated

Table 1. Characteristics of Healthy Male Controls and Men with Dementia of the Alzheimer Type

	Controls (N = 18)	All DAT (N = 19)	Mild DAT (N = 9)
Age (yr)	70 ± 8#	68 ± 9	68 ± 10
Education (yr)	18 ± 2	16 ± 2	19 ± 1
Duration ill (yr)	0 ± 0	7 ± 3	6 ± 3
MMSE	30 ± 0.24	16 ± 6.9*	22 ± 0.9*
WFSIQ	132 ± 7	93 ± 19*	105 ± 14*
Mattis Dementia Scale	138 ± 6	95 ± 31*	117 ± 5*
Systolic blood press (mmHg)	136 ± 9	134 ± 10	135 ± 7
Diastolic blood press (mmHg)	76 ± 8	78 ± 7	77 ± 8
Heart rate (beats/min)	68 ± 11	66 ± 12	68 ± 11

= all values are mean ± S.D.
* = mean value is significantly different than age matched male controls.
MMSE = Mini Mental State Exam score (Folstein et al 1975).
WFSIQ = Wechsler Full Scale IQ (Wechsler 1958).

Table 2. Absolute Volumes (cm^3) of Cerebral Brain Matter, Subcortical Nuclei, and CSF in Control Men and Men with DAT, as Measured by MRI

Structure	Control Men (N = 18)	All DAT Men (N = 19)
Total intracranial volume*	1400 ± 157†	1495 ± 164
Total cerebral hemi volume‡	1238 ± 149	1302 ± 143
R cerebral hemi volume‡	618 ± 63	644 ± 63
L cerebral hemi volume‡	621 ± 61	643 ± 70
Brain stem + cerebellum	161 ± 31	193 ± 89
Cerebral hemisphere brain matter volumes		
Total brain matter	1075 ± 133	1061 ± 121
R brain matter	542 ± 58	531 ± 55
L brain matter	542 ± 60	520 ± 57
CSF volumes		
Total CSF	159 ± 41	241 ± 62
R total CSF	76 ± 20	112 ± 30
L total CSF	83 ± 21	123 ± 34
Total periph CSF	138 ± 37	182 ± 64
R periph CSF	66 ± 18	84 ± 30
L periph CSF	73 ± 18	92 ± 31
R lateral ventricle	9.3 ± 5.1	27 ± 11.3
L lateral ventricle	9.7 ± 5.2	20 ± 10.9
Third ventricle	1.2 ± 0.4	1.9 ± 0.8
Subcortical nuclei volumes		
R thalamus	7.2 ± 0.7	7.7 ± 1.1
L thalamus	7.4 ± 0.8	7.9 ± 1.2
R lenticular nucleus	6.7 ± 1.6	5.9 ± 2.0
L lenticular nucleus	6.4 ± 1.6	5.8 ± 2.0
R caudate	5.1 ± 1.0	5.3 ± 1.8
L caudate	5.3 ± 0.8	5.7 ± 1.8

*Total intracranial volume = Total CSF volume + Total cerebral brain matter volume, †Brainstem volume + cerebellar volume.
†All volumes are mean ± S.D.
‡Cerebral hemisphere volume = brain matter volume + CSF volume.

measures ANOVA, a significant ($p < 0.0001$, F = 14.2) regions by group effect was found. Post hoc analysis of mean differences revealed that this significant group by region effect was due to significant differences in temporal lobe vs whole brain volumes (F 10.4, $p < 0.004$).

The group of mildly demented DAT subjects had a significantly smaller volume of cerebral brain matter and temporal lobe, and significantly larger lateral ventricles, temporal pole of the lateral ventricles, and temporal lobe peripheral CSF, than did controls. The group of mildly demented DAT subjects had a significantly smaller volume of cerebral brain matter and temporal lobe, and significantly larger lateral ventricles, temporal pole of the lateral ventricles, and temporal lobe peripheral CSF, than did controls. However, volumes of third ventricle, cerebral hemispheric peripheral CSF, and of subcortical nuclei did not differ from control volumes.

In DAT patients the Mattis Dementia Scale, Mini Mental State Exam, Wechsler full scale, performance, and verbal IQ score were each significantly ($p < 0.05$) and appropriately correlated to the normalized volumes of total, right and left cerebral brain matter (Table 5, Figure 1). Correlations of dementia severity and CSF measures were less clear; the only significant correlation was the Mattis Dementia Scale with volume of right lateral ventricle.

Discussion

The principle findings of this cross-sectional study are that: (i) there are significant brain volumetric differences between mildly demented DAT men and healthy age matched male controls, (ii) brain matter volumes correlate significantly with severity of dementia in patients with DAT, (iii) in DAT temporal lobe brain matter volume is decreased significantly more than cerebral hemispheric brain matter and the subcortical nuclei, and (iv) volume of subcortical nuclei is not significantly decreased in DAT.

Like other CT and MRI studies (Albert et al 1984; Arai et al 1983; Brinkman et al 1981; Creasey et al 1986; Gado et al 1982; Jernigan et al 1991), we found an overlap of brain volumes in DAT patients and controls. A cross-sectional quantitative CT study from this laboratory (Creasey et al 1986) reported that male DAT patients with mild dementia only had a larger mean third ventricle volume, and larger bilateral anterior horn cross sectional areas, than controls. The reasons we obtained more volumetric differences between mildly demented patients with DAT and controls in our current MRI study include intrinsic differences in MRI and CT, and different imaging protocols. A previous comparison (Murphy et al 1992b) showed that MRI provides ROI volumes which are more consistent

Table 3. Normalized Volumes[(i)] of Cerebral Brain Matter, Subcortical Nuclei, and CSF of Control Men and Men with DAT[(ii)], Expressed as a Percent of Intracranial Volume

Structure	Controls (N = 18)	All DAT (N = 19)	MILD DAT (N = 9)
R hemisphere (iii)	44.23 ± 1.58	43.18 ± 2.87	43.6 ± 1.16
L hemisphere (iii)	44.43 ± 1.75	43.12 ± 2.98	43.5 ± 2.17
Cerebral brain matter volumes (%)			
Total brain matter	76.8 ± 3.18	71.1 ± 4.64***	73.1 ± 3.10**
R brain matter	38.8 ± 1.80	35.6 ± 2.53**	36.6 ± 1.62**
L brain matter	38.7 ± 1.56	34.8 ± 2.37***	35.8 ± 1.43***
CSF volumes (%)			
Total CSF	11.4 ± 2.78	16.2 ± 3.87**	15.0 ± 3.60**
R hemisphere CSF	5.43 ± 1.38	7.55 ± 1.98***	7.04 ± 1.68**
L hemisphere CSF	5.98 ± 1.48	8.25 ± 2.18***	7.76 ± 2.23**
Total periph CSF	9.90 ± 2.50	12.3 ± 4.12	11.6 ± 3.93
R periph CSF	4.72 ± 1.26	5.71 ± 2.05	5.47 ± 1.73
L periph CSF	5.24 ± 1.30	6.20 ± 2.40	5.84 ± 2.50
Total lateral ventricle	0.15 ± 0.09	0.38 ± 0.13***	0.33 ± 0.12***
R lateral ventricle	0.66 ± 0.34	1.77 ± 0.68***	1.52 ± 0.56***
L lateral ventricle	0.69 ± 0.35	1.99 ± 0.67***	1.90 ± 0.70***
Third ventricle	0.08 ± 0.03	0.12 ± 0.05**	0.11 ± 0.05**
Subcortical nuclei volumes (%)			
R thalamus	0.52 ± 0.07	0.52 ± 0.07	0.51 ± 0.04
L thalamus	0.53 ± 0.06	0.53 ± 0.09	0.52 ± 0.07
R lenticular nucleus	0.48 ± 0.12	0.40 ± 0.16	0.41 ± 0.15
L lenticular nucleus	0.46 ± 0.11	0.39 ± 0.15	0.40 ± 0.15
R caudate	0.37 ± 0.08	0.36 ± 0.13	0.34 ± 0.10
L caudate	0.39 ± 0.07	0.39 ± 0.13	0.37 ± 0.08

** = DAT are significantly different than controls by unpaired two tailed Student's t test $p < 0.025$, **$p < 0.01$, and *** = $p < 0.001$.
(i): All volumes are: 100× (cm^3 structure/cm^3 total cranium), mean ± S.D.
(ii): mild DAT MMSE >20.
(iii): Cerebral hemisphere volume = brain matter + CSF.

Table 4. Normalized Temporal Lobe Brain Matter and CSF Volumes in Control Men and Men with DAT, Expressed as a Percent of Intracranial Volume

Structure	Controls (N = 12)	All DAT (N = 13)	MILD DAT (N = 7)[(i)]
Temporal lobe Brain matter volumes (%)			
Total temporal lobe	9.50 ± 1.10	8.00 ± 0.90***	7.74 ± 0.93**
Right temporal lobe	4.90 ± 0.61	4.30 ± 0.60*	4.23 ± 0.55
Left temporal lobe	4.60 ± 0.56	3.70 ± 0.51***	3.51 ± 0.56**
Temporal lobe CSF volumes (%)			
Right total CSF	0.78 ± 0.20	1.50 ± 0.53***	1.58 ± 0.60*
Left total CSF	0.70 ± 0.20	1.40 ± 0.45***	1.43 ± 4.75**
Right temporal pole lat vent	0.02 ± 0.05	0.14 ± 0.08***	0.14 ± 0.09*
Left temporal pole lat vent	0.02 ± 0.05	0.11 ± 0.06***	0.12 ± 0.07**
Right peripheral CSF	0.80 ± 0.02	1.35 ± 0.05***	1.44 ± 0.53**
Left peripheral CSF	0.70 ± 0.02	1.30 ± 0.42***	1.32 ± 0.52**

* = DAT are significantly different than controls by unpaired two tailed Student's t test $p < 0.025$, ** = $p < 0.01$, and *** = $p < 0.001$.
(i): mild DAT MMSE > 20.

Table 5. Significant Correlations Between Corrected Brain Volumes in DAT Patients and Disease Severity, when Age is Factored Out

Structure	MMSE	Mattis	WFSIQ	WVIQ	WPIQ
Total brain matter	0.53	0.54	0.55	0.59	0.53
p = <	0.02	0.02	0.02	0.01	0.03
n = ( )	(19)	(19)	(17)	(18)	(17)
Right brain matter	0.49	0.57	0.47	0.50	0.50
p = <	0.04	0.02	0.05	0.04	0.03
n = ( )	(19)	(19)	(17)	(18)	(17)
Left brain matter	0.52	0.53	0.54	0.70	0.55
p = <	0.03	0.02	0.03	0.01	0.03
n = ( )	(19)	(19)	(17)	(18)	(17)
R Lateral ventricle		−0.46			
p = <		0.05			
n = ( )		(19)			

MMSE = Mini Mental exam score (Folstein et al 1975).
Mattis = Mattis Dementia Scale score (Coblentz et al 1973).
WFSIQ = Wechsler full scale IQ (Wechsler 1958).
WVIQ = Wechsler verbal IQ.
WPIQ = Wechsler performance IQ.

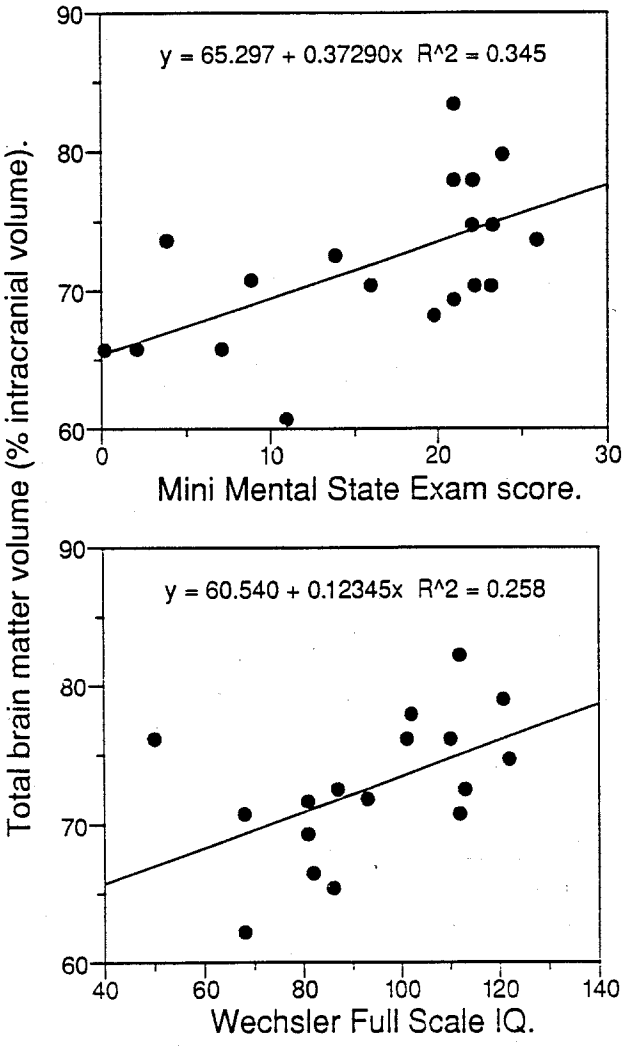

Figure 1. Correlation of Mini Mental State Exam score and Wechesler Full Scale IQ with total brain matter volume (%) in DAT.

with autopsy derived volumes of cerebral structures than does CT.

CT studies disagree whether CSF spaces increase with increasing severity of DAT (Bigler et al 1985; Ichimiya et al 1986; Naugle et al 1985). However, quantitative CT studies from this laboratory reported (Creasy et al 1986; Luxenberg et al 1987) that severity of dementia in DAT patients correlated with brain matter and CSF volumes (Creasy et al 1986), and that yearly rates of change in cognitive performance correlated significantly with rates of change in ventricular CSF volumes (Luxenberg et al 1987).

In contrast to our previous CT studies, global loss of brain matter volume but not global expansion of CSF correlated significantly with loss of cognitive ability within DAT patients. The only significant CSF-neuropsychological test score correlation as between right lateral ventricle and the MDSTOT score. Neuropsychological test scores in DAT patients may correlate better with brain matter volume than CSF volumes because changes in CSF volumes only indirectly reflect cerebral atrophy, whereas measurement of brain matter volume provides a more direct measure of tissue loss.

We found that ventricular CSF volume was significantly larger in DAT patients but peripheral CSF volume was not. This finding suggests relatively more atrophy of cerebral white matter than of cortical gray matter, and this may reflect a relatively moderate loss of large pyramidal neurons, whereas central CSF enlargement may reflect loss of the axons of these cell bodies. This interpretation is supported by postmortem (De La Monte 1989; Shefer 1972) and CT (Massman et al 1986) studies. However, MRI does have some technical limitations which may have affected our measurement of peripheral CSF. For example, radio-frequency inhomogeneities can affect CSF-brain segmentation, and may have affected our measurement of peripheral CSF volume (DeCarli et al 1992). In addition, as the shape of compartments containing ventricular and peripheral CSF differ, partial voluming may influence the measurement of these CSF volumes.

Jernigan *et al* (Jernigan et al 1991) reported a significant reduction in volumes of cortical gray matter, and caudate, lenticular and thalamic nuclei, in male and female DAT patients compared to controls. They suggested: (i) that the neuropil of the subcortical nuclei is affected by damage in cortical projection areas, and (ii) severe anterograde and

retrograde memory deficits of DAT patients reflect destruction of thalamic as well as mesial temporal lobe structures. However, we found no significant difference between groups in the volume of any of these nuclei. Our study differed from that of Jernigan *et al* (Jernigan et al 1991) in a number of ways. They examined men and women, and had a 2.5 mm gap between successive MRI slices. The globus pallidus has iron depositions (Drayer 1988) which would reduce signal values on the T2-weighted images that they analyzed, and interslice gaps reduce measurement sensitivity, particularly of small irregularly shaped structures. We examined only men, used a proton density image acquisition protocol at 0.5 Telsa which is minimally affected by iron deposition, and left no gap between slices. We only examined men to remove any confounding gender effects on brain structure and function, thus this our conclusions are limited to males with DAT, and they may not be applicable to females with DAT.

It is possible that we found significant group differences in volume of cerebral hemispheric and temporal lobe brain matter, but not subcortical nuclei due to our relatively small DAT sample size, or because our method for measuring volume of subcortical nuclei is insensitive compared to our method for measuring cerebral hemispheric brain matter. However, a previous MRI study by this laboratory using the same MRI analysis technique (Murphy et al 1992b) reported significant age-related decreases in volume of subcortical nuclei and autopsy studies report (Hubbard and Anderson 1981) that gray matter loss is primarily cortical in Alzheimer's disease patients under 80 years of age, and that the volumes of the subcortical nuclei are not significantly different between patients and controls (De La Monte 1989). In addition, we found no significant difference in volume of subcortical nuclei between DAT patients and controls, and no significant correlation between any neuropsychological test score and any volume of the subcortical nuclei. In addition, we previously reported (Kumar et al 1991) no significant difference in regional cerebral glucose metabolism of the subcortical nuclei between mildly and severely demented DAT patients, using positron emission tomography and 18 F-2-fluoro-2-deoxy-D-glucose. Thus, we find no evidence that severe anterograde and retrograde memory deficits of DAT patients reflect destruction of thalamic as well as mesial temporal lobe structures.

Our finding of relatively greater atrophy of temporal lobes than cerebral hemispheric brain matter, together with the preservation of the volume of the caudate, lenticular and thalamic nuclei, provides the first **in vivo** structural imaging support for the topographic distribution of DAT Alzheimer's disease found at autopsy (Ball 1977; Brun and Gustafson 1976; Lewis et al 1987; Mann et al 1985; Najlerahim and Bowen 1981; Pearson et al 1985).

In summary, we found that differences in volume between DAT men and controls occur early in the disease process, and are not homogeneous over various brain structures. Temporal lobe brain volume is decreased significantly more than whole cerebral hemispheric volume. Central CSF volume is enlarged with increasing dementia severity, but volumes of the subcortical nuclei are unchanged, consistent with postmortem studies (De La Monte 1989) and with preserved **in vivo** glucose metabolism measured by positron emission tomography (Kumar et al 1991). These results suggest that in DAT: (i) significant brain atrophy is present early in the disease process, (ii) brain atrophy correlates with severity of cognitive impairment, and (iii) there is greater involvement of the telencephalic association system than whole brain, and there is relative sparing of the caudate, lenticular and thalamic nuclei.

References

Albert M, Naesser MA, Levin HL, et al (1984): Ventricular size in patients with presenile dementia of the Alzheimer's type. *Arch Neurol* 41:1258–63.

Andreasen NC (1989): Nuclear Magnetic Resonance Imaging, Brain Imaging: Applications in Psychiatry. Washington, DC, U.S.A., American Psychiatric Press Inc.

Arai H, Kobayashi K, Ikeda K, et al (1983): A computed tomography study of Alzheimer's disease. *J Neurol* 229:69–77.

Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW (1991): The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex* 1:103–116.

Ball MJ (1977): Neuronal loss, neurofibrillary tangles and granulovacular degeneration in the hippocampus with aging and dementia: a quantitative study. *Acta Neuropathol (Berl)* 37:111–1118.

Bartko J, Carpenter WT (1986): On the methods and theory of reliability. *J Nerv Ment Dis* 163: 307–317.

Bigler ED, Hubler DW, Cullum CM, et al (1985): Intellectual and memory impairment in dementia. Computerized axial tomographic volume correlations. *J Nerv Ment Dis* 173:347–362.

Blessed G, Tomlinson BE, Roth M (1968): The association between measures of dementia and of senile change in the cerebral gray matter of elderly subjects. *Br J Psychiatry* 114:797–811.

Botwink J (1977): Intellectual abilities, The handbook of psychology of aging. New York, Van Nostrand Reinhold.

Brinkman SD, Sarwar M, Levin HS, et al (1981): Quantitative

indexes of computed tomography in dementia and normal aging. *Radiology* 138:89–92.

Brun A, Gustafson L (1976): Distribution of cerebral degeneration in Alzheimer's disease. A clinico-pathological study. *Arch Psychiatr Nervenkr* 223:15–33.

Coblentz JM, Mattis S, Zingesser LH, et al (1973): Presenile dementia: clinical aspects and evaluation of cerebrospinal fluid dynamics. *Arch Neurol* 29:299–308.

Creasey H, Schwartz M, Frederickson H, et al (1986): Quantitative computed tomography in dementia of the Alzheimer type. *Neurology* 36:1563–1568.

Daly E, DeCarli CD, Haxby JV, Soncrant T, Schapiro MB, Rapoport SI, Horwitz B, Murphy DGM (1992). Volumetric Magnetic Resonance Imaging in Alzheimer's disease: Correlations with Disease Severity. Society for Neuroscience 22nd annual meeting. 18:567.

De La Monte SM (1989): Quantification of cerebral atrophy in preclinical and end-stage Alzheimer's disease. *Ann Neurol* 25:450–459.

DeCarli CD, Maisog J, Murphy DGM, Teichberg D, Rapoport SI, Horwitz B (1992): A simple method for quantification of brain, central and peripheral CSF volumes from magnetic resonance images. *JCAT* 16:274–284.

Delaere P, Duckaerts C, Brion JP, et al (1989): Tau, paired helical filaments and amyloid in the neocortex: a morphometric study of 15 cases with graded intellectual status in aging and senile dementia of the Alzheimer type. *Acta Neuropathol (Berl)* 77:645–653.

DiChiro G, Brooks RA, Dubal L, et al (1978): The apical artifact: elevated attenuation values toward the apex of the skull. *J Comput Assist Tomogr* 2:65–70.

Drayer BP (1988): Imaging of the human brain. Part 1. Normal findings. *Radiology* 166:785–796.

Duara R, Margolin RA, Robertson-Tchabo EA, et al (1983): Cerebral glucose utilization, as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. *Brain* 106:761–75.

Duyckaerts C, Hauw JJ, Piette F, et al (1985): Cortical Atrophy in senile dementia of the Alzheimer type is mainly due to a decrease in cortical length. *Acta Neuropathol (Berl)* 66:72–74.

Folstein MF, Folstein SE, McHugh PR (1975): "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–98.

Gado M, Hughes CP, Danziger W (1982): Volumetric measurements of the cerebrospinal fluid in demented subjects and controls. 144:535–538.

Gado M, Phelps M (1975): The peripheral zone of increased density in cranial computed tomography. *Radiology* 117:71–74.

George AE, deLeon MJ, Rosenbloom S, et al (1983): Ventricular volume and cognitive deficit: a computed tomographic study. *Radiology* 149:493–498.

Hachinski VC, Iliff LD, Zilhka E, et al (1975): Cerebral blood flow in dementia. *Arch Neurol* 32:632–7.

Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Hansen LA, DeTerasa R, Davies P, Terry RD (1988): Neocortical morphometry, lesion counts, and choline acetyltransferase levels in the age spectrum of Alzheimer's disease. *Neurology* 38:48–54.

Haxby JV, Grady CL, Koss E, Horwitz B, Schapiro MB, Friedland RP, Rapoport SI (1988): Heterogenous anterior-posterior metabolic patterns in Alzheimer's type dementia. *Neurology* 38:1853–1863.

Hubbard BM, Anderson JM (1981): A quantitative study of cerebral atrophy in old age and senile dementia. *J Neurol Sci* 50:135–145.

Ichimiya Y, Kobayashi K, Arai H, et al (1986): A computed tomography study of Alzheimer's disease by regional volumetric and parenchymal density measurements. *J Neurol* 233:164–167.

Jernigan TL, Salmon D, Butters N, et al (1991): Cerebral Structure on MRI, Part II: Specific Changes in Alzheimers and Huntington's diseases. *Biol Psychiatry* 29:68–81.

Kaye JA, May M, Atack JR, Daly E, Sweeney DL, Beal MF, Kaufman S, Milstien S, Friedland RP, Rapoport SI (1988): Cerebrospinal fluid neurochemistry in the myoclonic subtype of Alzheimers Disease. *Annals Neurology* 24:647–650.

Kesslak PJ, Nalcioglu O, Cotman CW (1991): Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimers disease. *Neurology* 41:51–54.

Khatchaturian ZS (1985): Diagnosis of Alzheimer's disease. *Arch Neurol* 42:1097–1104.

Koss E, Haxby JV, DeCarli CD, Schapiro MB, Friedland RP, Rapoport SI (1991): Patterns of Performance Preservation and Loss in Healthy Aging. *Developmental Neuropsychology* 7:99–113.

Kumar A, Schapiro MB, Grady CL, Haxby JV, Wagner E, Salerno JA, Friedland RP, Rapoport SI (1991): High-Resolution PET studies in Alzheimer's Disease. *Neuropsychopharmacology* 4:35–46.

Lewis DA, Cambell MJ, Terry RD, et al (1987): Laminar and regional distributions of neurofibrillary tangles and neuritic plaques in Alzheimers Disease: a quantitative study of visual and auditory cortices. *J Neursci* 7:1799–1808.

Luxenberg JS, Haxby JV, Creasey H, et al (1987): Rate of ventricular enlargement in dementia of the Alzheimer type correlates with rate of neuropsychological deterioration. 37:1135–1140.

Mann DM, Marcyniuk B, Yates PD, et al (1988): The progression of the pathological changes of Alzheimer's disease in frontal and temporal neocortex examined both at biopsy and at autopsy. *Neuropathol Appl Neurobiol* 14:177–195.

Mann DMA, Yates PO, Marcyniuk B (1985): Some morphometric observations on the cerebral cortex and hippocampus in presenile Alzheimer's disease, dementia of the Alzheimer type and Down's syndrome in middle age. *J Neurol Sci* 69:139–159.

Massman PJ, Bigler ED, Cullum CM, et al (1986): The relationship between cortical atrophy and ventricular volume. *Int J Neurosci* 30:87–99.

Mataratzo JD (1972): Wechslers's Measurement and Appraisal of Adult Intelligence. Baltimore, Williams & Wilkins.

McKhann G, Drachman D, Folstein M, et al (1984): Clinical diagnosis of Alzheimer's Disease. Report of the NINCDS-

ADRA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944.

Murphy DGM, DeCarli CD, Gillette JA, Haxby JV, Teichberg D, Schapiro MB, Rapoport SI, Horwitz B (1992a): Lack of age-related reduction in temporal lobe volume in very healthy subjects aged 21-93 years. *Neurology* (suppl 3) 42:175.

Murphy DGM, DeCarli CD, Schapiro MB, Rapoport SI, Horwitz B (1992b): Age related differences in volumes of subcortical nuclei, brain matter, and cerebrospinal fluid in healthy men as measured with MRI. *Arch Neurol* 49:839–849.

Najlerahim A, Bowen D (1981): Biochemical measurements in Alzheimer's disease reveal a necessity for improved neuroimaging techniques to study metabolism. *Biochem J* 251:305–308.

Naugle RI, Cullum CM, Bigler ED, et al (1985): Neuropsychological and computerized axial tomography volume characteristics of empirically derived dementia subgroups. *J Nerv Ment Dis* 173:596–604.

Neary D, Snowden JS, Mann DMA, et al (1986): Alzheimer's disease: a correlative study. *J Neurol Neurosurg Psychiatry* 49:229–237.

Pearson RCA, Esiri MM, Hiorns RW, et al (1985): Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimers Disease. *Proc Natl Acad Sci* 82:4531–4534.

SAS I (1985): *SAS Users guide: Basics version 5*. SAS Users Guide. Cary, N.C.

Schwartz M, Creasey H, Grady CL, et al (1985): Computed tomographic analysis of brain morphometrics in 30 healthy men, aged 21 to 81 years. *Ann Neurol* 17:xx.

Seab JP, Jagust WJ, Wong STS, et al (1988): Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. *Magn Reson Med* 8:200–208.

Shefer VF (1972): Absolute number of neurons and thickness of the cerebral cortex during aging, senile and vascular dementia, and Pick's and Alzheimer's disease. *Zhurnal Nevropathologii i Psikhiatrii imeni S.S. Korsakova* 72:1024–1029.

Wechsler D (1958): The Measurement and Appraisal of Adult Intelligence. Baltimore, Williams & Wilkins.

Wilcock GK, Esiri MM (1982): Plaque, tangles and dementia: a quantitative study. *J Neurol Sci* 56:343–356.