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Authors

Jernigan, Terry L
Salmon, David P
Butters, Nelson
et al.

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Cerebral Structure on MRI, Part II:
Specific Changes in Alzheimer's and Huntington's Diseases

Terry L. Jernigan, David P. Salmon, Nelson Butters, and
John R. Hesselink

*Using magnetic resonance (MR) imaging and morphometric techniques, groups of patients
with Alzheimer's disease (AD) and Huntington's disease (HD) were compared with a
large group of normal control subjects. Measures of volume loss in specific subcortical
nuclei and eight cortical regions as well as an index of white matter abnormality were
obtained. Results indicated expected widespread cortical volume reductions in AD, which
were especially severe in mesial cortices; but comparable reductions were present in
subcortical structures, particularly the thalamus. In HD, the greatest reductions were in
striatal structures, but significant abnormalities were also detected in the thalamus and
inferior cortical areas, especially in mesial temporal lobe structures. Significant degen-
eration in white matter was present in both groups, but was more dramatic in the HD
patients. The significant diencephalic reduction in AD may make an important contribution
to early memory deficits in the disorder, which are usually attributed to hippocampal
damage. Similarly, damage to both the thalamus and mesial temporal lobe structures
may play a role in the memory deficits of HD.*

INTRODUCTION

Alzheimer's disease (AD) and Huntington's disease (HD) are both characterized by an
insidious onset of cognitive and intellectual impairments that progress inexorably until
the patient is completely disabled. Recent neuropsychological studies have demonstrated
that although superficially similar, the dementias associated with these two disorders
exhibit important neuropsychological distinctions (Butters et al 1988b; Cummings and
Benson 1983, 1984). For example, the severe anterograde amnesia of AD patients is
characterized by numerous intrusion errors (Fuld 1983; Fuld et al 1982; Butters et al
1987), a rapid rate of forgetting of what little verbal and figural information is learned
(Moss et al 1986; Butters et al 1988a), and some deterioration in the structure of semantic
knowledge (Butters et al 1987; Salmon et al 1988; Heindel et al 1989). In contrast, HD
patients' problems in acquiring new information have been linked to a deficiency in the
initiation of systematic retrieval processes (i.e., bradyphrenia) (Butters et al 1988b; Cum-
mings and Benson 1984; Albert 1978; Butters 1984; Caine et al 1978). Other studies

have reported double dissociations between AD and HD patients on skill learning and verbal priming tasks, respectively (for a review, see Butters et al 1988b). Although some caution is necessary in postulating specific brain–behavior relationships in progressive dementias, it is often assumed that the psychomotor slowing and bradyphrenia of HD are a consequence of basal ganglia dysfunction, whereas the failures in storage, intrusion errors, and impaired semantic knowledge of AD are due to damage to mesial temporal structures and association cortices.

Neuropathological studies do provide evidence of significant differences in the location, pattern, and extent of damage in AD and HD. For AD there is general agreement that neuritic placques and neurofibrillary tangles are present in widespread regions of the cerebral cortex (Blessed et al 1968; Tomlinson et al 1970; Terry et al 1981; Terry and Katzman 1983), probably in greater concentration in temporoparietal areas, hippocampus, and amygdala (Brun and Gustafson 1976; Herzog and Kemper 1980; Mann et al 1985; Brun and Englund 1986a, 1986b). These lesions are sometimes noted in hypothalamus and pons, but are relatively rare in the thalamus and basal ganglia. Histological studies suggest that substantial losses of large cortical neurons occur (Terry et al 1981; Terry and Katzman 1983), and that cell populations in basal forebrain nuclei (Whitehouse et al 1981) are also depleted. In some AD patients, similar losses occur in locus ceruleus (Bondareff et al 1982). Studies of glial populations suggest that although cortical glial cell numbers may not increase overall, a significant increase does occur in fibrous astrocytes (Terry at al 1981; Schechter et al 1981). Brun and Englund (1981, 1986a, 1986b) have emphasized the degeneration of cerebral white matter in AD.

Autopsy studies of HD have revealed large decreases in populations of small neurons in the caudate and putamen, and loss of large neurons in globus pallidus (Bielschowsky 1922; Bruyn 1968, 1973; Dom et al 1973; Roos 1986, Vonsattel et al 1985). Although the ratio of striatal astroglial cells to neurons increases in HD, this appears to be due to relative sparing of the astroglial population rather than actual increases (Lange et al 1976). In the thalamus, there are significant losses of microneurons in the ventrolateral regions, and large neurons are shrunken in diameter (Forno and Jose 1973; Dom et al 1976). Bruyn (1973) also reported significant cell loss in the hypothalamus and degeneration in white matter. Pathology studies of HD have less frequently emphasized the cerebral cortex. Although atrophic changes have often been noted, there is little agreement concerning the usual extent or regional pattern of such changes (Bruyn 1973; Roos 1986; Bruyn et al 1979; McCaughey 1961; Vonsattel et al 1985).

With the availability of high-resolution in vivo brain images, it has become possible to examine brain structures in demented patients during life. Computed tomography (CT) studies of AD patients and controls have demonstrated differences in the average size of the cerebrospinal fluid (CSF) spaces (Earnest et al 1979; Gutzmann and Avdaloff 1980; Brinkman et al 1981; Jacoby and Levy 1980; Fox et al 1975; Wilson et al 1982; Gado et al 1982; Albert et al 1984; Luxenberg et al 1986; Bird 1982; Kido et al 1989), in the CT values of the parenchyma (Jernigan 1986; Naeser et al 1980; Bondareff et al 1981), and in cortical grey matter (Creasey et al 1986). However, overlap between dementia patients and controls is usually large, and little structural and regional specificity of the findings has been demonstrated.

Studies comparing the use of CT and magnetic resonance (MR) in the evaluation of dementia patients favor the latter (Erkinjuntti et al 1984; Johnson et al 1987) in terms of both sensitivity and specificity. Although studies of AD with MR have emphasized the prevalence and appearance of high signal abnormalities in cortical and subcortical struc-

Table 1. Subject Characteristics

	Controls (n = 55)	AD (n = 25)	HD (n = 11)
Age	54 ± 14.1	70 ± 4.1	49 ± 12.5
Sex	21 F, 34 M	11 F, 14 M	4 F, 7 M
Education (years)	14.8 ± 2.7	13.8 ± 2.8	13.8 ± 3.3
Handedness	51 R, 4 L	22 R, 2 L, 1 A	9 R, 2 L

tures (Johnson et al 1987; Fazekas et al 1987), the high incidence of these abnormalities in nonsymptomatic elderly controls (Fazekas et al 1987; Gerard and Weisberg 1986; Awad et al 1986a, 1986b, 1987; Kertesz et al 1988) complicates the interpretation of such changes in AD. Attempts to differentiate AD patients from controls and other patients using MR signal values within tissue, such as T_1 and proton density values, have met with mixed success (Besson et al 1983, 1985; Christie et al 1988). In spite of the greatly improved tissue contrast available with MR, few studies have measured individual brain structures in demented patients. One notable exception is the study by Seab et al (1988) in which cross-sectional measurements were made of hippocampus, lenticular nucleus, brain, and CSF spaces. AD patients differed from controls on a measure of hippocampal size normalized to lenticular nucleus size. The values on this measure showed no overlap between the groups, but they were unrelated to the severity of the AD patients' dementia. Although HD has not been studied extensively with MR, reports suggest that atrophy of basal ganglia is apparent on clinical inspection of images from these patients (Lukes et al 1983). No other changes have been noted.

The purpose of the present investigation is to provide an MR analog to the existing neuropsychological and neuropathological comparisons of AD and HD. Detailed MR analyses are performed with AD and HD patients, matched for overall level of dementia, and compared with those from control subjects.

Materials and Methods

Subjects

Twenty-five patients (11 women, 14 men) who met the NINCDS-ADRDA criteria (McKhann et al 1984) for AD, 11 patients (4 women, 7 men) with HD diagnosed on the basis of family history and the presence of chorea, and 55 normal volunteers (21 women, 34 men) participated as subjects in the present study. The controls were screened for any evidence of significant medical, neurological, psychiatric, or intellectual disorder. Table 1 summarizes the demographic characteristics of the groups. As expected, the AD patients were significantly older than both the HD and control groups; however, the groups did not differ in terms of handedness, education, or proportion of males and females. All patients were administered the Mattis Dementia Rating Scale (DRS) (Mattis 1976) to evaluate overall level of intellectual loss. The mean scores of the AD (107 ± 22) and the HD (113 ± 19) patients did not differ significantly ($p > 0.05$).

Magnetic Resonance Imaging

The imaging protocol and image analysis methods are described in detail in the companion article (Jernigan et al 1990).

Volume of the supratentorial cranium was estimated by summing supratentorial voxels

(including CSF, hyperintensities, and grey and white matter) over all sections. The grey matter voxels within each of three subcortical structures (caudate, lenticular nucleus, and diencephalic grey) and the cortical grey matter voxels within each of eight standard cerebral zones were summed separately. Eight regional volumes were also computed by summing all supratentorial voxels (including CSF, hyperintensities, and grey and white matter) within each region. An anterior diencephalic region, including septal nuclei and anterior hypothalamic grey, was examined separately from a measure of the posterior diencephalon, which consists almost entirely of thalamus. The volume of the total sub-cortical white matter region was estimated; and, finally, an index of signal alterations in the white matter was constructed by summing voxels within the subcortical white matter regions having signal characteristics meeting criteria for "grey matter" or for "signal hyperintensities", i.e., they had lengthened T_2 values. All subcortical measures were expressed as proportions of the supratentorial cranial volume, and all cortical measures as proportions of their respective regional volumes.

Statistical Analysis

Because the age ranges of the dementia groups are different, and the ages of the controls span the entire range of the combined dementia groups, group differences were evaluated with multiple linear hypothesis tests in which age was a factor. That is, both age and group membership were entered into a regression analysis in which the structural measure was the dependent (predicted) variable. In these analyses, the significance of the group effect is indicated by a significant regression coefficient for the group variable after effects on the structural measure attributable to age have been removed. The significance of the regression coefficient is assessed with a t statistic. Less powerful, but simpler, analyses comparing each patient group to an age-matched subgroup of the controls yielded virtually identical results.

Results

Routine clinical evaluations of the MR examinations were performed at the time of scanning. These evaluations were performed by clinical neuroradiology staff, usually with knowledge of the patient's diagnosis. Within the control subjects, occasional signal hyperintensities were noted within the cerebral white matter, especially among the older subjects. In one 59-year-old woman, a right cerebellar venous angioma was noted.

Among the 25 AD patients, volume loss was noted in 22 and high signal abnormalities in 18. In one 67-year-old female patient, a focal lesion was noted in the right cerebellopontine region, which was considered likely to represent a small meningioma or neuroma. An area of high signal surrounded by low signal was noted in the pons of one 69-year-old female patient, which was considered likely to be an old hemorrhage or arteriovenous malformation. A small extraaxial mass in the right middle cranial fossa was noted in a 68-year-old male patient. This was considered probably to be a meningioma.

Of the 11 HD patients, reduced size of caudate nuclei was noted in 7, volume loss in 11, and signal hyperintensities in 6. In two patients, low signal in the lenticular nuclei, presumed to be due to hemosiderin deposition, was noted. A focal area of encephalomalacia in the right occipital lobe was noted in one 47-year-old patient.

The comparisons of the AD patients with controls are summarized in Table 2. The AD patients show significant losses relative to controls in all cortical regions, and in all

Table 2. Comparisons of Cerebral Grey Proportions and White Matter Measures of AD Patients and Controls With Effects of Age Removed

	t	p
Caudate	−3.46	0.001
Lenticular	−4.15	0.000
Diencephalic	−5.29	0.000
Anterior	−0.84	0.404
Posterior	−5.14	0.000
Overall cortical grey	−4.48	0.000
Peripheral cortex		
Inferior anterior	−3.50	0.001
Inferior posterior	−3.91	0.000
Superior anterior	−1.96	0.054
Superior posterior	−2.98	0.004
Mesial cortex		
Inferior anterior	−4.46	0.000
Inferior posterior	−4.74	0.000
Superior anterior	−4.24	0.000
Superior posterior	−4.84	0.000
White matter volume	−1.26	0.211
White matter index	3.12	0.003

subcortical structures as well, with the exception of the anterior diencephalic measure. The regional pattern of grey matter changes does not suggest strong localization, either within the cortex, or in cortical relative to subcortical grey matter. The mesial cortices may be slightly more affected than peripheral cortices, but the discrepancies are not large. There is no significant reduction in white matter volume. The group difference on the white matter index suggests that white matter degeneration ₃ greater in AD patients than in elderly controls.

In Table 3 the comparisons of HD patients and controls are summarized. Again, all subcortical grey matter structures are reduced in volume, with the exception of the anterior diencephalon. In this case, however, the effects on different subcortical structures are unequal, with the caudate nucleus clearly more affected, the lenticular nucleus less, and the thalamus, least. The results suggest that there are significant cortical reductions in HD as well, but they are considerably more circumscribed than in AD. All inferior cortical surfaces are significantly affected while in the superior regions the group effects do not even approach significance. The volume of subcortical white matter regions is also significantly reduced. Within this region, there is a striking increase in white matter signal abnormality in the HD patients relative to age-matched controls.

Results of comparisons of the two dementia groups are summarized in Table 4. To facilitate direct comparisons of the groups, and of each group to the controls, age-corrected z scores have been computed from formulas derived from the control data. These values, by definition, have an expected mean of 0 and a standard deviation of 1 in the controls. In the patients, they measure the deviation from an age-appropriate control mean in standard deviations of the control distribution. The means of the z scores are provided for each group. The results suggest that clear dissociations do exist. Although AD patients show significant losses in the caudate nucleus, the HD patients have significantly greater reductions in this structure relative to their age peers. This is shown clearly in Figure 1, in which the caudate volumes (expressed as proportions of the supratentorial cranium)

Table 3. Comparisons of Cerebral Grey Proportions and White Matter Measures of HD Patients and Controls With Effects of Age Removed

	t	p
Caudate	−12.67	0.000
Lenticular	−7.34	0.000
Diencephalic	−3.05	0.003
Anterior	−1.13	0.263
Posterior	−3.08	0.003
Overall cortical grey	−1.69	0.096
Peripheral cortex		
Inferior anterior	−2.51	0.015
Inferior posterior	−2.70	0.009
Superior anterior	−0.23	0.818
Superior posterior	−0.49	0.625
Mesial cortex		
Inferior anterior	−2.62	0.011
Inferior posterior	−3.22	0.002
Superior anterior	0.71	0.480
Superior posterior	−1.32	0.191
White matter volume	−2.65	0.010
White matter index	6.49	0.000

are plotted against age for all patients. Conversely, although cortical grey reductions are significantly greater in the AD patients, it is only in the superior cortices (both peripheral and mesial), unaffected in HD, that significant differences occur between the two dementia groups. In Figure 2, the cortical grey proportion in the peripheral SP region is plotted

Table 4. Comparisons of Cerebral Grey Proportions and White Matter Measures of AD and HD Patients With Effects of Age Removed

|	Mean age-adjusted z-score		t	p
	AD	HD		
Caudate	−1.1	−3.8	−2.68	0.011
Lenticular	−1.4	−2.3	−0.98	0.332
Diencephalic	−1.6	−1.0	−0.89	0.378
Anterior	−0.2	−0.2	−0.02	0.985
Posterior	−1.6	−1.0	0.95	0.348
Overall cortical grey	−1.1	−0.5	2.05	0.049
Peripheral cortex				
Inferior anterior	−0.9	−0.8	0.97	0.341
Inferior posterior	−1.0	−0.9	0.85	0.401
Superior anterior	−0.5	−0.1	1.67	0.104
Superior posterior	−0.8	−0.2	2.15	0.039
Mesial cortex				
Inferior anterior	−1.1	−0.8	1.02	0.317
Inferior posterior	−1.2	−1.0	1.28	0.211
Superior anterior	−1.2	0.2	2.38	0.023
Superior posterior	−1.3	−0.5	1.36	0.183
White matter volume	−0.4	−0.9	−0.56	0.581
White matter index	0.7	2.1	2.21	0.034
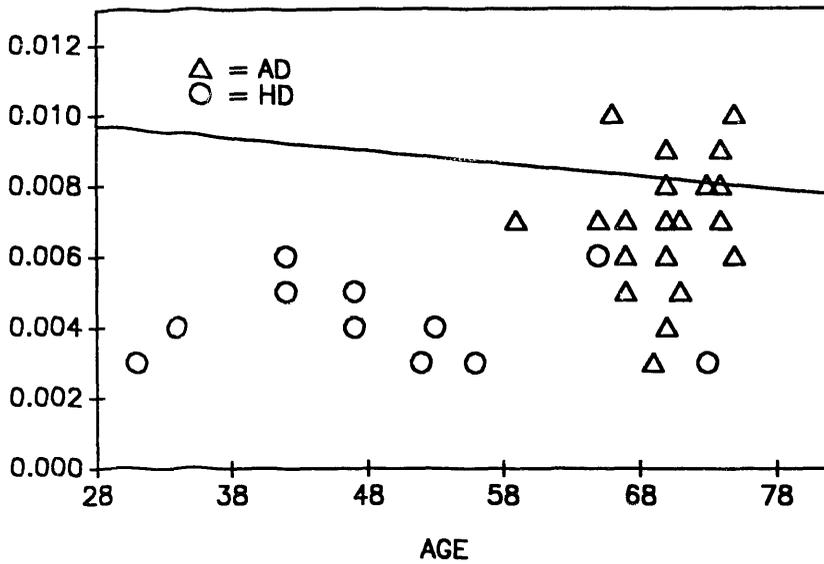
Figure 1. Scatterplot of values for the caudate volume expressed as a proportion of the supratentorial cranial volume by age for the HD patients (circles) and AD patients (triangles). The decline of the mean of this proportion in normal controls is indicated by the line.
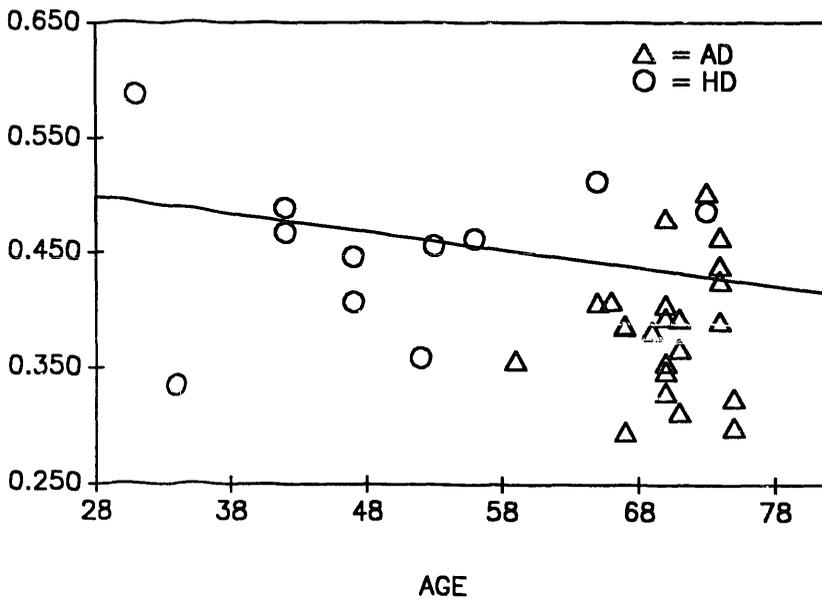

Figure 2. Scatterplot of values on the cortical grey proportion from the peripheral SP zone (cortical grey volume as a proportion of the regional volume) for the HD (circles) and AD (triangles) patients across the age range. The decline of the mean of this proportion in normal controls is indicated by the line.
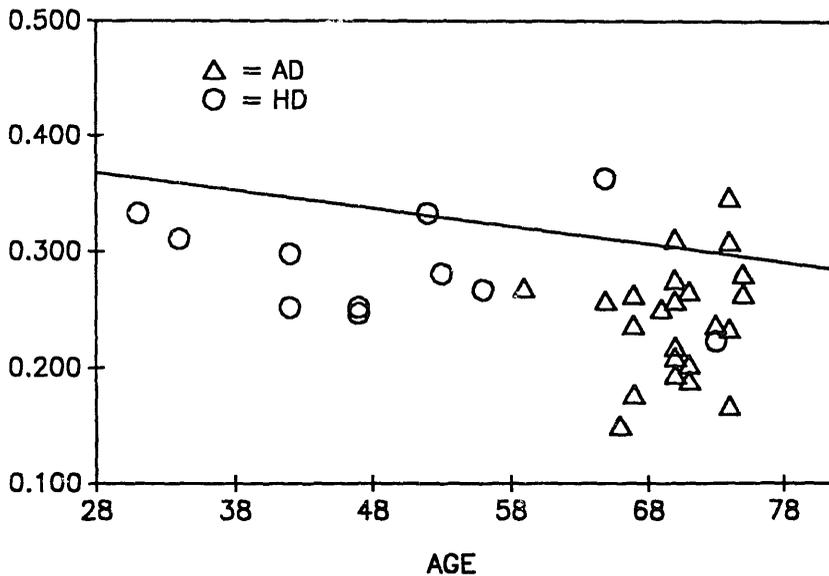
Figure 3. Scatterplot of values on the cortical grey proportion from the mesial IP zone (cortical grey volume as a proportion of the regional volume) for the HD (circles) and AD (triangles) patients across the age range. The decline of the mean of this proportion in normal controls is indicated by the line.

for each demented subject. This region appears to be affected in very few HD patients, but is frequently affected in the AD patients. No significant group differences were noted in the mesial temporal lobe structures (mesial inferior posterior), although these structures were reduced in volume in both groups relative to their age-peers. As there is a significant age-related decrease in the volume of these structures (Jernigan et al 1990), and the AD patients are older than the HD patients, the absolute volumes in this region are lower in the AD patients (Figure 3). The white matter abnormality in HD is also significantly more severe than that in AD (Figure 4).

Discussion

The present findings for the AD and HD patients demonstrate different patterns of cortical and basal ganglia losses in these two disorders. Consistent with neuropathological reports (Blessed et al 1968; Tomlinson et al 1970; Terry et al 1981; Terry and Katzman 1983; Brun and Gustafson 1976; Herzog and Kemper 1980; Mann et al 1985; Brun and Englund 1986a, 1986b; Bielschowsky 1922; Bruyn 1968, 1973; Dom et al 1973; Roos 1986; Vonsattel et al 1985), widespread cortical changes and severe reduction in the volume of the basal ganglia were noted in AD and HD, respectively. However, the HD patients also evidenced more limited cortical changes in orbitofrontal and temporooccipital cortical regions. In comparison with the controls, HD patients had little change in the superior regions, including dorsolateral frontal, mesial frontal, and parietal cortices. The present results are also consistent with reports of white matter changes on MRI in AD (Johnson et al 1987; Fazekas et al 1987) and confirm that these changes are greater in AD than in nondemented elderly individuals. Surprisingly, a significant degree of white matter ab-
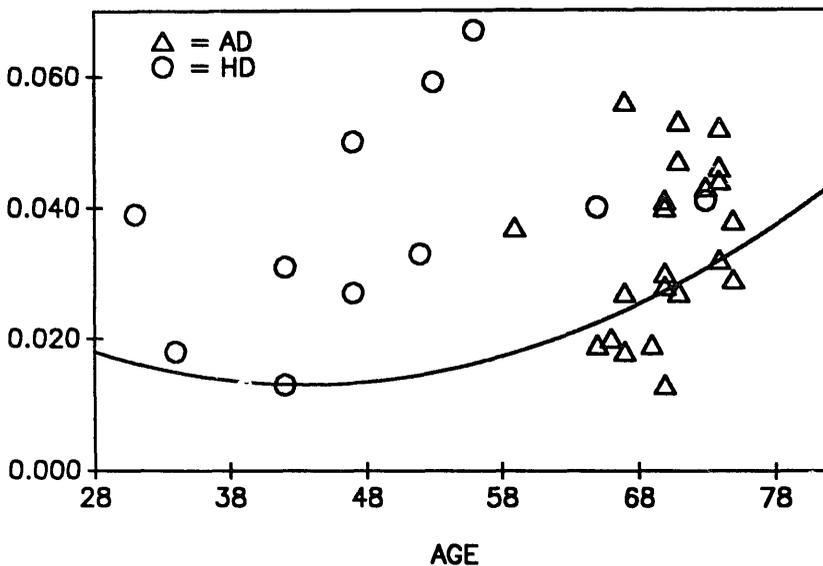
Figure 4. Scatterplot of values on the index of white matter abnormality (all white matter pixels with lengthened T_2 values expressed as a proportion of the supratentorial cranial volume) for the HD (circles) and AD (triangles) patients across the age range. The increase in the mean of this index in normal controls is indicated by the curve.

normality was also noted in HD patients and both the volume and the tissue values were affected. Although white matter changes in HD have been reported by Bruyn (1973), little attention has been given to such changes in this disorder.

Some of the present MR findings were not anticipated. For instance, the significant changes noted in the thalamus and basal ganglia in AD were unexpected given the lack of previous reports of pathology in these structures. It is possible that the classical lesions of AD are not typically found in these subcortical nuclei, but the neuropil is nonetheless affected by altered neuronal interaction with damaged cortical projection areas. Such changes may ultimately lead to subcortical neuronal loss and shrinkage. From a behavioral perspective, this loss of thalamic volume in AD has important implications. Because damage to the mesial diencephalon is associated with amnesic symptoms (for review, see Butters and Stuss 1989), the present results suggest that the severe anterograde and retrograde memory deficits of AD patients may reflect destruction of critical thalamic (e.g., dorsomedial nucleus) as well as of mesial temporal lobe structures.

A second unexpected result concerns the significant changes noted in HD patients' mesial temporal lobes (i.e., the mesial inferior posterior measure). Given that this region is presumed to be involved in the processing of new information for storage (Squire 1987), it is possible that current retrieval explanations of HD patients' memory disorders may be incomplete (Cummings and Benson 1983; Caine et al 1978; Butters et al 1985, 1986). That is, in addition to their bradyphrenia, which is usually attributed to their striatal damage, HD patients may also have significant impairments in storage because of damage to limbic structures. The tendency for the HD patient's retrieval problems to be more apparent than their storage deficiencies on neuropsychological examinations may be due to the relatively greater deterioration of striatal than of limbic structures (Table 3).

The present findings provide little evidence that the hippocampal region is the most

affected area in AD. Although the region containing the hippocampus evidenced significant volume reductions, losses in regions containing the amygdala, orbitofrontal cortex, insula, and cingulate were comparable, and nearly equal changes were noted in the posterior temporooccipital convexity. These diffuse changes may be related to the AD patients' stage of illness. Although the patients included in this investigation were in the relatively early stages of AD, they did demonstrate cognitive deficits in problem solving, language, and visuoperceptual capacities as well as in memory. Thus, an MR study focusing on very early AD patients who manifest primarily amnesic symptoms might result in MR changes more restricted to the hippocampal (and perhaps thalamic) area.

In considering this lack of primacy of the hippocampal region in AD, it should be stressed that these MR regional patterns describe only the measurable volume reductions in the regions. Thus, if gliosis is particularly severe in an affected area, the volume in this region may not be reduced in proportion to the pathology present. This explanation may account for the relatively even distribution of cortical reductions noted in the present findings (i.e., the measures used here for detecting changes in the hippocampus were not more reduced because of extensive gliosis in this area). Also, our measure of mesial inferior–posterior cortex is not specifically a hippocampal index, as a small portion of the amygdala and posterior insula and most of the parahippocampal gyrus are typically included, and some variability in the boundaries is inevitable using our methods. Perhaps a more specific measure of hippocampal volume would have yielded larger group differences.

The present findings demonstrate the feasibility of describing localized changes in specific structures in living patients. It may be possible to gain increased sensitivity to changes in specific structures by optimizing the MR protocol for measurement of those structures (Naidich et al 1987a, 1987b). The advantage of the methods used here, however, is that multiple structures are measured with comparable measurement sensitivity using standardized, blindly applied techniques. This provides an opportunity to establish not only simple correlations between structural abnormalities and function, but dissociable neurobehavioral relationships between the different abnormalities and specific functional dimensions.

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