Temporal Lobe Regions on Magnetic Resonance Imaging Identify Patients with Early Alzheimer's Disease

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Abstract

The goal of the present study was to examine the volume of selective brain regions in a group of mildly impaired AD patients. Five regions were selected for analysis, all of which have been reported to show substantial change in the majority of AD patients at some time in the course of disease. Three of the volumetric measures were significantly different between AD patients and controls: the hippocampus, the temporal horn of the lateral ventricles and the temporal lobe. Two of the measures did not significantly differentiate AD patients and controls: the amygdala and the basal forebrain. A discriminant function analysis demonstrated that a linear combination of the volumes of the hippocampus and the temporal horn of the lateral ventricles differentiated 100% of the patients and controls from one another. These results have implications for both the early diagnosis and treatment of AD.

Introduction

A small number of magnetic resonance imaging (MRI) studies have compared regional measures of brain structures between patients with Alzheimer's disease (AD) and controls. They have included mildly to severely impaired patients and have measured a variety of brain structures, demonstrating significant differences between patients and controls in most, though not all, of the regions measured.

Seab et al [1] measured five brain regions, using a light pen, in 7 controls and 10 AD patients (4 of the 10 AD patients were mildly impaired). The regions included the hippocampus, the lenticular nucleus, ventricular spaces, subarachnoid spaces and total
brain area. They found that all of the measures differentiated the groups but only the hippocampal measure showed no overlap between patients and controls. Kesslak et al [2] measured the hippocampus, the parahippocampal gyrus and the striatum in 7 controls and 8 mildly and moderately impaired AD patients and found a significant difference in the hippocampal and parahippocampal measures, with no overlap between the groups. A volumetric measure of the striatum did not differentiate the groups. Charness and DeLaPaz [3] failed to find a difference between AD patients and controls in the volume of the mammillary bodies.

These results are consistent with computerized tomography (CT) and MRI studies demonstrating that regional measures of atrophy in the medial temporal lobe differentiate AD patients and controls better than measures of atrophy elsewhere in the brain [4-6]. They are also consistent with neuropathological studies demonstrating that medial temporal lobe structures are severely affected in AD [7-8].

The MRI studies conducted to date do not, however, provide information about selective brain changes in the early stages of AD, when patients are only mildly impaired. This is important because treatments for AD, to be optimally effective, must alter the course of disease when it is beginning. Non-invasive, ante-mortem markers of disease are also needed for mildly impaired patients so that when effective treatments are found they can be applied to patients who have experienced the smallest degree of cognitive loss [9]. The following study was therefore conducted in order to examine the volume of selective brain regions in a group of mildly impaired AD patients. Five regions were selected for analysis, all of which have been reported to show substantial change in the majority of AD patients some time in the course of disease.

**Methods**

**Subjects**

Fifteen subjects were included in the study, eight (6 female, 2 male) patients with dementia of the Alzheimer type and seven (5 female, 2 male) normal control subjects. They ranged in age from 63 to 80 years of age. The AD patients had a mean age of 72 years of age while the controls, with a mean age of 70 years, did not differ significantly from the AD group in terms of age.

The diagnosis of probable AD was made in concordance with NINCDS/ADRDA criteria [10]. It was based on the judgment of a neurologist, with independent agreement from both a psychiatrist and a neuropsychologist. Several tests (e.g., CT, EEG, SMA-20, VDRL, urinalysis, thyroxine and folate levels) were administered in order to exclude patients with medical etiology known to produce dementia. These tests ruled out various hydrocephalic, metabolic, neoplastic, infectious, and traumatic causes of dementia. Patients with a record of severe head trauma, alcoholism, serious psychiatric illness, learning disabilities, epilepsy, lung disease, kidney disease, or cancer were excluded. All AD patients received an ischemic score of 4 or less on the ischemic scale for estimating the likelihood of multi-infarct dementia [11]. All patients had a history of a gradually
progressive decline in cognition, demonstrated by difficulty in social or occupational function and impairments in memory and at least one other area of mental ability. The level of impairment of the AD patients was operationally determined by the administration of the Mini-Mental State Examination (MMSE), a widely used general test of cognitive function in demented patients [12]. The total score on the MMSE is 30; scores of 20 to 26 are considered to reflect mild impairment. Seven of the eight AD patients had MMSE scores of 21 or greater. The group of AD patients had a mean MMSE score of 23.9 with a range of 17 to 29.

The normal controls were participants in a study of normal aging being conducted by the investigators. Subjects with a history of alcoholism, psychiatric illness, epilepsy, chronic lung disease, kidney disease, or cancer were excluded from the study. In addition to an MRI, the normal control subjects received a series of laboratory tests to rule out serious systemic illness and were administered neuropsychological testing to eliminate the potential of including persons with cognitive symptoms of a dementing illness.

All subjects provided informed consent for study participation.

*Magnetic Resonance Image Acquisition*

The MRI images were acquired by a GE Signa imager of 1.5 Tesla. Spoiled Grass (SPGR) echo sequences were used with a 3-D T1 weighted gradient, echo time of TE = 5 msec and a repetition time of TR = 35 msec. The slice thickness was 1.5 mm, the field of view = 220 mm, flip angle = 45 degrees and the matrix size = 256 x 256. Coronal images were taken from the occipital poles to the frontal poles with a total of approximately 124 images obtained per subject.

The digital data were stored on magnetic tape from which they were transferred to a SUN computer (Sparcstation 1). A special program developed by the investigators displayed several images simultaneously and permitted the operator to interact with the images. The operator (RJK) identified and outlined the regions of interest by visual inspection, blinded to the status of the subjects.

All regions were outlined on coronal sections. Each scan was initially viewed from the slice displaying the junction of the calcarine and parieto-occipital sulci to a slice rostral to the temporal poles. Outlining of structures was then conducted in a rostral to caudal fashion. With the exception of the basal forebrain, all measures were taken separately for the structures in the left and right hemispheres. Five brain regions were outlined and a computer program [13] calculated the volumes of the regions, scaled to the supraventricular reference volume of the subject, using the Sparcstation 1. This automated procedure segments the brain in a hierarchical, "knowledge-based" manner. Thus, the brain regions are segmented in a specific order, based upon the nature of the segmentation problems presented by each structure. The segmentation algorithm also uses a priori information about the approximate location of the anatomic regions. Details of the program have been published previously [13]. The landmarks used to delineate the regions of interest are described below and they are visually portrayed in *Figures 1 - 5*.
Amygdala: The rostral border of the amygdala was defined as the level at which the grey matter of the temporal lobe became continuous with the grey matter of the orbital frontal cortex. The medial border and portions of the superior border were defined by the surface of the temporal lobe. The remaining portion of the superior border was formed by drawing a straight line parallel to the inferior surface of the brain from the junction of the amygdala and basal forebrain to the white matter. Laterally and inferiorly the white matter of the inferior longitudinal fasciculus and temporal stem separated the amygdala from the rest of the temporal lobe. Caudally, outlining of the amygdala stopped when it was no longer visible in the temporal lobe of the section. The borders of the amygdala are not as clearly defined on MRI as adjacent structures, such as the hippocampal formation. However, with close examination, the landmarks were identified that yielded reliable measures.

Basal Forebrain: The basal forebrain comprises a discontinuous diffuse region of telencephalic grey matter beginning rostrally at the level of the amygdala and extending caudally to the level of the lateral geniculate nucleus. In order to define a region that could be assessed in a consistent manner across cases, it was decided to take measurements through three levels of the basal forebrain at the level of the anterior commissure comprising the nucleus basalis of Meynert, the area of the basal forebrain that has been implicated in AD [14]. This was accomplished by first identifying the coronal slice that contains the anterior commissure as it crosses the midline. The basal forebrain was then demarcated by outlining from the junction of the basal forebrain and amygdala along the inferior surface of the brain medially excluding the optic chiasm and tracts to the third ventricle. The interhemispheric surface of the ventricle was then followed to the inferior surface of the anterior commissure and then an arch was drawn along this surface back to the junction of the basal forebrain and amygdala. This method outlines an area that includes most of the nucleus basalis but also includes parts of the globus pallidus (subcommissural), preoptic and/or anterior hypothalamic areas and perhaps the most posterior part of the olfactory tubercle. This procedure was repeated on one slice rostral and one slice caudal to the slice containing the anterior commissure crossing the midline each of which contained enough information to allow for extrapolating the extent of the inferior surface of the commissure.

Hippocampus: Rostrally, outlining of the hippocampus began when the white matter of the alveus became discernible. Laterally and superiorly, the borders of the hippocampus were defined by the inferior horn of the lateral ventricle, medially by the angular bundle and inferiorly by the white matter joining the parahippocampal gyrus. Caudally, outlining of the hippocampus stopped at the level where the fornix appearing as a solid white line through the collateral trigone.

Temporal Horn of Lateral Ventricles: Measurement of the temporal horn of the lateral ventricles began with its first appearance beneath the amygdala. Measurement continued caudally until the inferior horn of the ventricle joined the lateral horn of the ventricle to form the collateral trigone (atrium).
Temporal Lobe: Measurement of the remainder of the temporal lobe (i.e. neocortex, entorhinal cortex and white matter) began with its first appearance at the temporal pole and consisted of outlining the cortical surface into the sulci. In slices where the temporal lobe is continuous with the rest of the brain, a line was drawn from the inferior and medial most portion of the Sylvian fissure to the superior surface of the superior most subcortical structure present (i.e. amygdala, hippocampus, or ventricle). The line then followed along the inferior surface of the subcortical structures to the medial surface of the temporal lobe. The outlining of the temporal lobe stopped when the temporal horn of the lateral ventricle formed the collateral trigone.

Reliability

Two methods were employed to determine the reliability of the procedures used to define the regions of interest. First, the operator (RJK) re-measured a subset of the cases (3 patients and 3 controls), blinded to the status of the subjects. Second, another operator (MBM) independently measured a subset of the cases (3 patients and 3 controls), also blinded to the status of the subjects. The reliability of the algorithm used to calculate the volumes has been previously established to be high [6].

Results

Student's t-test was used to compare the difference in total volume between each of the selected structures for the AD patients and controls. The results of these analyses are shown in Table. Of the five structures compared, the temporal lobe, the temporal horn of the lateral ventricles and the hippocampus were significantly different at the .004 level or greater. The amygdala measure, while not reaching the level of a significant difference, showed a trend towards significance. Only the basal forebrain measure failed to even show a trend towards significance.

In order to determine which variables were most useful in differentiating the groups a discriminant function analysis was performed. First, all variables were entered in the analysis to determine the overall probability of a group difference between AD patients and controls. This discriminant function significantly differentiated the groups (chi square = 25.48; p < .0001). Next, a forward stepwise discriminant function analysis was performed in order to determine which variables best discriminated the groups. Only variables that met the criterion of a .05 level of significance were entered into the equation. The classification accuracy was determined when all of the variables had been selected. The first variable that was selected was the volume of the temporal horn of the lateral ventricle. The second variable selected was the volume of the hippocampus. With these two variables included, 100% of the subjects were correctly identified (chi square = 28.27; p < .0001). No other variable exceeded the .05 significance level for selection.

Pearson product moment correlations were used to evaluate the reliability with which the regions were measured. Mean intra-rater reliability was 0.91, and mean inter-rater reliability was 0.92. The correlations were significant at less than the 0.05 level.
Discussion

The results of the present study indicate that mildly impaired AD patients have measurable and highly significant changes in the size of the hippocampal formation and the temporal horn of the lateral ventricles. Moreover, discriminant function analysis demonstrated that a linear combination of these two measures significantly differentiated 100% of the patients and controls. The measure of the temporal lobe, as a whole, also was significantly different between patients and controls, however this measure was not selected by the discriminant function analysis as optimally differentiating the two groups of subjects.

These findings are consistent with the fact that significant pathology can be found in the temporal lobe of patients with only mild symptoms of AD [15]. The evidence of temporal lobe involvement early in the course of the disease is consistent with the hypothesis that damage to the hippocampal formation is the likely cause of the severe memory impairment in AD. Impairments of memory have been reported to follow damage to the hippocampus in human patients and ablations of the hippocampus in non-human primates [16-21]. Numerous recent studies have demonstrated that tests of delayed recall are most effective at differentiating mildly impaired AD patients from normals and other patient groups [22-24]. AD patients have also been shown to have an abnormally rapid rate of forgetting at delay intervals under 10 minutes [25].

The negative findings in the present study are also of importance. Neither the amygdala nor the basal forebrain significantly differentiated the group of mildly impaired AD patients from controls. These results are not inconsistent with neuropathological data demonstrating loss of cells in these brain regions in AD; they suggest, however, that the damage to these regions are not likely to occur in the very earliest stages of disease.

The measurement of the amygdala showed a trend toward significance, suggesting that damage to this region may have begun but was not yet detectable by the MRI methods available. Moreover, the damage to the amygdala does not appear to be uniform. While the cortical nucleus has been reported to show a 38% loss in volume the medial basal nucleus only shows a 14% loss in volume [26]. The present measurement procedures cannot differentiate subnuclei with accuracy and therefore utilize a combined measure.

The measurement of the basal forebrain did not show even a trend toward significance. This suggests that significant damage to the basal forebrain may not exist at the time that AD patients are in the earliest stages of disease. This is consistent with the fact that therapeutic agents designed to increased cholinergic transmission have not, to date, demonstrated a highly significant clinical effect on the behavior of AD patients. It is also consistent with reports that damage to the basal forebrain in AD is quite variable. While it has been reported to be as high as 90% in some autopsy series [11], others have found less consistent damage to the basal forebrain [27]. It should, however, be pointed out that the basal forebrain presented the greatest challenge in terms of measurement, as the region is diffuse and compromises were necessary in order to measure it in a reliable
manner. The nucleus basalis portion of the basal forebrain implicated in previous studies of AD, was, however, included in the measurements performed here.

The results also suggest that the hippocampus and the temporal horn of the lateral ventricles may be useful as antemortem markers of AD in mildly impaired patients. It should, however, be pointed out that the small sample size makes it unlikely that the subjects were representative of the general population at large. It is also unlikely that the accuracy of identification of the subjects will remain at 100% in subsequent samples. It is easier to obtain an ideal fit of the data to a discriminant function when relatively few data points (i.e., subjects) are involved. Larger samples will invariably lead to a "shrinkage" in the identification accuracy due to increased variance. However, the results suggest that while the optimal set of variables for discriminating AD patients from controls may be larger than that used in the present study, the ultimate accuracy of discriminating AD patients from controls with MRI volumetric measures in a larger sample is likely to be good.

**Figure Legends**

**Figure 1:** Coronal spoiled grass (SPGR) 3D T1 weighted image of a healthy control subject showing the coronal level at which measurement of temporal lobe (T) begins.

**Figure 2:** Coronal spoiled grass (SPGR) 3D T1 weighted image of a healthy control subject showing the coronal level at which measurement of the amygdala (A) is begun on the right side of the figure. The amygdala is not present on the left side since the temporal
lobe has not yet become contiguous with the orbital surface of the frontal lobe at this coronal level. Continued measurement of the temporal lobe (T) also indicated.

**Figure 3:** Coronal spoiled grass (SPGR) 3D T1 weighted image of a healthy control subject showing the basal forebrain (B) measure. Arrows on the left side of the figure indicate the locations of the temporal stem and inferior longitudinal fasciculus, which serve as the lateral and inferior borders of the amygdala, as well as the appearance of the inferior horn of the lateral ventricle. Areas of amygdala (A) and temporal lobe (T) are also indicated on the right side of the figure.

**Figure 4:** Coronal spoiled grass (SPGR) 3D T1 weighted image of a healthy control subject. The figure indicates the outlines used to demarcate the regions of interest: amygdala (A), hippocampal formation (H), temporal lobe (T). On the left side of the figure an arrow indicates the separation between the amygdala (A) and the hippocampus (H).
Figure 5: Coronal spoiled grass (SPGR) 3D T1 weighted image of a healthy control subject. The right side of the figure illustrates more caudal coronal levels of the temporal horn of the lateral ventricle (V), hippocampal formation (H), temporal lobe (T).

Figure 6: Percentage of the intracranial volume occupied by each of the structures measured in both patients with Alzheimer's disease (AD) and normal healthy control subjects (N). Asterisk indicates a significant difference between the two groups (P<.004)

Table: Comparison of MRI Total Volume Measurements in Alzheimer Patients and Controls
Region of Interest MRI Measurements

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