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Basal Forebrain Atrophy is a Presymptomatic Marker for Alzheimer's Disease

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Abstract

Background—Alzheimer's disease (AD) is the most common degenerative neurological disorder. The onset of symptoms is insidious and follows a long period of progression of an asymptomatic pathology that proceeds in a precise anatomical and temporal sequence (1–3). Recent studies using quantitative MRI techniques have shown the localization of the *in vivo* pathology of AD and its antecedent, Mild Cognitive Impairment (MCI) (4). The objective of the present study was to determine whether a sensitive and reliable marker for the presymptomatic phase of the disorder could be identified by longitudinal analysis of an initially asymptomatic, community-based population.

Methods—148 healthy, cognitively normal participants in the Cardiovascular Health Study – Cognition Study had detailed clinical examinations and MRI scans in 1998/99 and 2002/03. Modulated voxel-based morphometry was used to compare regional brain volumes in subjects who remained cognitively normal after 5–6 years follow-up (n=127) to those who developed Probable AD during the same period (n=21).

Results—Among normal subjects destined to develop AD, there was significant atrophy in the basal forebrain area as long as 4.5 years before the development of clinical symptoms. When the left hippocampus was also atrophic, the onset of dementia typically occurred earlier than in cases in which the atrophy was confined to basal forebrain.

Conclusion—Atrophy in the basal forebrain precedes the development of AD in subjects with cognition judged to be normal by neuropsychological testing. The time required to develop dementia appears to be shortened if hippocampal atrophy is also present. These data indicate that atrophy restricted to medial basal forebrain is a biomarker that predicts development of probable AD in asymptomatic elderly subjects.

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Introduction

Alzheimer's disease (AD) is a major cause of disability among the elderly and one for which there is no treatment that can significantly alter the course of the disease. It seems likely that effective neuroprotective therapy, or therapy directed to alter the fundamental pathophysiology of AD will become available in the near future. When such therapy becomes available, it will be important to have methods to predict the onset of the disease before symptoms appear. The pathology of AD is well known and its gradual clinical progression from a presymptomatic phase through one characterized by single domain symptoms (e.g., amnesic mild cognitive impairment; MCI) to a fully-developed dementia is well-recognized. In accord with this, the neuropathology of AD has a specific spatial and temporal sequence of changes that was established initially by conventional postmortem examination (1–3) and, more recently, by *in vivo* analysis using imaging (4, 5).

In this study, we provide evidence for a presymptomatic marker for early brain changes of AD using a whole brain voxel-level analysis of MRI identified atrophy. Our objective was to identify brain regions that were affected prior to the development of AD by analyzing cross-sectional structural MRI data in the context of longitudinal neurobehavioral assessments of participants in the Cardiovascular Health Study - Cognition Study (CHS-CS) (6, 7). All of the study participants used in this analysis had extensive neuropsychological testing, and were considered cognitively normal at the time of the MRI scan in 1997–1998 (8); they were studied again 5–6 years later in 2002–2003. Longitudinal cognitive and caregiver information were used to determine the earliest clinical manifestations of any dementia, and prior screening information was available from 1992 onward (demonstrating a period of consistent normal cognition prior to the MRI scan). We used modulated Voxel-Based Morphometry (mVBM) (9, 10) to identify brain regions that were atrophic at the time of the MRI in 1997/1998 as a function of diagnostic classification in 2002/2003.

Methods

Subjects

The CHS-CS is an extension of the CHS and the CHS Dementia Study (6, 7, 11). In 1992/94, all eligible participants underwent an MRI of the brain (924 in Pittsburgh), and in 1998/99 those who were still living were re-scanned and adjudicated for the presence of cognitive deficits based on detailed neurobehavioral evaluation. Between 1992/94 and 1998/99, 160 participants died, 398 were diagnosed with a dementia or with MCI, leaving a total of 366 cognitively normal participants – 218 of these participants were alive, had undergone MRI scans, and were available for follow-up. In 2002/03, 142 of the normal subjects remained cognitively normal, and 68 had developed dementia. We created three groups of subjects for this analysis from the participants who were alive, came to the clinic, and underwent an MRI scan: 1) cognitively normal in 1998/99 and 2002/03 (n=127); 2) cognitively normal in 1998/99 and Probable AD in 2002/03 (n=21) (i.e., incident cases); and 3) Probable AD in 1998/99 (n=26) (i.e., prevalent cases). Only MRI data that met local QC/QA standards were used in the analysis.

Neuropsychological Evaluation

Each of these subjects completed cognitive screening tests annually from 1992 to 1999, including the Digit Symbol Substitution Test (DSST) (12), Benton Visual Retention Test (BVRT) (13), and Modified Mini-Mental State Examination (3MSE) (14)). A neuropsychological test battery was administered in 1998–99 and 2002–03 to all the participants, and included the following tests (15): Premorbid intelligence: the American version of the National Reading test (AMNART) (16), Raven's Colored Progressive Matrices

(modified) (17), Memory: California Verbal Learning Test (CVLT) (18), modified Rey-Osterrieth figure (19), Language: Boston Naming test (20), Verbal fluency test (21), Visuoperceptual and visuoconstructional: Block design (modified from the Wechsler Adult Intelligence Scale-Revised) (12), modified Rey-Osterrieth figure (19), Psychomotor Speed: Trailmaking A, Baddeley & Papagno Divided Attention Task (Single Task) (22) Executive functions: Stroop Neuropsychological Screening Test (23), Trailmaking B and A/B (24), Digit Spans (12), Baddeley & Papagno Divided Attention Task (Dual Task) (22), and Fine Motor Control: Grooved Pegboard Test (25).

Neurological and psychiatric assessments

The neurological exam covered the entire nervous system, with particular emphasis placed on signs and symptoms relevant to age-associated neurological conditions. The examiner completed the Unified Parkinson's Disease Rating Scale (26) and the Hachinski Ischemic Scale (27). Symptoms of depression were measured with a modified version of the Center for Epidemiology Studies Depression Scale (28) and historical data were available from 1992 onward. Other psychiatric symptoms were measured using the Neuropsychiatric Inventory (29).

Diagnostic criteria

Dementia was diagnosed based on deficits in performance in two or more cognitive domains that were of sufficient severity to affect the subjects' activities of daily living, with normal intellectual function before the onset of cognitive abnormalities. An abnormal domain was present when at least two tests of the same domain were abnormal (7). For the purposes of this study, we analyzed only the data from the subjects who met criteria for Probable AD (30). That is, there were no other medical, neurological, or psychiatric comorbid conditions that could, in and of themselves account for the change in cognitive functions. The MRI scans were not reviewed until after the primary diagnostic adjudication, and thus did not affect the clarification of dementia.

Onset of dementia symptoms—In 2002–03, the Adjudication Committee examined the longitudinal changes in the cognitive screening tests from 1992 to 1999, and the proxy reports from the Dementia Questionnaire (31) and the Informant Questionnaire of Cognitive Decline in the Elderly (32) in order to determine the earliest onset of cognitive changes. Subjects who developed AD between 1998 and 2003, and whose initial symptoms of dementia were reported to have begun prior to 1998–99 were not included in this analysis.

We divided the individuals who went on to develop AD into two groups based on this information – one group with symptom onset prior to the year 2000 (n=9), and one with symptom onset beginning in 2000 or thereafter (n=12). When the first symptoms of cognitive dysfunction occurred prior to 2000 (i.e., within 2–3 years of the first exam) we refer to these subjects as being in the pre-2000 group. When the first symptoms of dementia did not occur until 2000 or later, we refer to these subjects as being in the post-2000 group.

MRI Scanning and mVBM Analysis

Each of the subjects had a high resolution anatomical T1-weighted spoiled gradient recalled image MRI scan on a GE 1.5T scanner (TR = 25, TE = 5, slices = 1.5 mm thick, 0 mm gap, 40° angle, FOV = 24×18). The scans were initially reoriented into the axial plane and resized to 1×1×1 mm voxels. They were normalized to a custom “older brain” template (33) based on 416 healthy elderly subjects, and the normalized images were segmented using a mixed model cluster analysis (9) which assigns each voxel a value reflective of a tissue type based on prior probabilities from the custom template. The segmented images were modulated by multiplying these files by the Jacobian determinant of their spatial transformation matrix, and the resulting

images were smoothed using a 10 mm isotropic Gaussian filter which rendered the data more normally distributed for use in the parametric statistical analysis of SPM2. For a more complete discussion of the modulated VBM approach, see the discussions by Good, Ashburner and colleagues (9, 10). The initial processing of the scans was run as a semi-automated script in SPM2 (<http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2>).

The modulated gray matter images were analyzed in SPM2 using subject group, age and total brain volume as subject-specific covariates. Following the identification of the specific areas of regional atrophy, volumes were extracted from within SPM2 at the cluster level within the regions identified for the comparison of the normal subjects and the patients with AD in 1998/99. The regions of significant differences were projected onto the average of the custom elderly template brain.

Results

Table 1 shows the demographic, clinical and neuropsychological characteristics of the study subjects as a function of their group classifications in 1998/99 and 2002/03. The participants who remained normal were younger than those who progressed to AD, and had higher 3MSE scores than the other groups. There were no differences between groups in terms of education, sex, race, APOE4 genotypes, vascular disease, or depression.

Grey Matter Abnormalities in AD Patients

AD results in a characteristic pattern of cerebral degeneration that can be easily distinguished on MRI scans, even early in the course of the dementia (34–38). Figure 1 (a, b, c) shows this typical pattern in 26 prevalent cases of probable AD patients who were identified in the CHS-CS cohort in 1998/99 ($p < .05$ (corrected), 30 voxels). There is significant volume loss in a contiguous bilateral band of cortical and subcortical structures including the mesial temporal lobes (entorhinal cortex, hippocampal formation, and amygdaloid complex), basal forebrain area (nucleus basalis), ventral striatum, and hypothalamus (the coordinates of the peak differences in these regions are shown in Table 2).

Grey Matter Abnormalities in Cognitively Normal Subjects

We compared the grey matter volumes of the subjects who remained cognitively normal during follow-up to those of the subjects who converted from normal cognition to probable AD (i.e., incident cases) during the same time period. Atrophic changes found in the MRIs of cognitively normal individuals who developed AD were: 1) bilaterally in the basal forebrain; and, 2) in the left amygdala and hippocampal formation (Figure 1d, e, f). The basal forebrain atrophy extended from the level of the isocortical-allocortical transition rostrally through the medial ventral striatum and medial nucleus basalis and diagonal band, and caudally into the lateral chiasmal hypothalamus. The atrophy in the left mesial temporal lobe was centered in the posterior and medial portions of the amygdala, with extension into the anterior hippocampus. There is also a very small area of atrophy in the midbrain in the presymptomatic MRI (Fig. 1e).

Prediction of Dementia

We measured the volumes of the hippocampi (left and right) and the basal forebrain within the regions identified by the contrast of the cognitively normal subjects to the subjects with probable AD at baseline (i.e., 1998/99 prevalent cases) (See Table 3).

We established a cut-off of the lower limit of normal for each region at the 10th percentile of the distribution of the subjects who remained normal throughout follow-up. We first analyzed the risk of developing dementia using these binary variables (i.e., normal/abnormal) and the

subject's age as risk factors; all of the variables were entered into the model simultaneously to assess their independent effects on risk.

For those individuals who were cognitively normal at the time of the baseline assessment, the relative risk of developing AD during follow-up increased by a factor of 8.93 (95% CI = 1.84 – 43.5, $p=.006$) when the volume of their basal forebrain fell below the 10th percentile of normal. Left hippocampal atrophy was also independently associated with an increased risk of conversion (Relative Risk=8.84, 95% CI = 1.33 – 58.8, $p=.024$), but atrophy in other regions did not confer additional risk of conversion from normal to AD.

Figure 2 shows the regional volumes in the basal forebrain area and the hippocampus (bilaterally) for the subjects who were: 1) normal in 1998/99 and 2002/03, 2) the cognitively normal subjects who converted to AD and who were in the post-2000 group, 3) the normal subjects who converted to AD and who were in the pre-2000 group, and 4) probable AD patients diagnosed in 1998/99. The volumes of the basal forebrain ($F(4, 185)=34.7$, $p<.001$) and the left hippocampus ($F(4,185)=10.9$, $p<.001$) were compared with One-Way ANOVAs followed by a Least Significant Difference test. Atrophy in the basal forebrain was present in normal subjects destined to have AD even when the subjects were in the post-2000 group (LSD Test, Normals vs. converters, $p's < .03$), and it was as severe as that seen in AD (LSD Test, $p's > .30$). By contrast, the volume of the left hippocampus showed a progression of pathological change. It was significantly atrophic in the pre-2000 group ($p<.001$) (i.e., first symptoms prior to 2000), and in those participants with prevalent AD ($p<.001$).

Finally, we regressed conversion to AD on the structural variables and dichotomous classifications (impaired/unimpaired) for each cognitive domain for the normal subjects. The composite neuropsychological domain variables were created by combining standardized scores from individual neuropsychological tests, and then converting these to T-scores (see (15) for details); a T-score of 35 or less was considered abnormal. The basal forebrain volume was a significant predictor of conversion, but in addition, impairments in language ($p=.037$) and memory ($p=.013$) were also significantly associated with risk of conversion from normal to AD.

Discussion

The data presented here add to our understanding of the sequence of neuropathological changes that occur during the progression from normal cognition to a state of clinical dementia. These data were acquired from a community-based cohort of cognitively normal, aging individuals who had neurological and neuropsychological testing and brain MRI performed at the beginning and end of a 4 year interval. The cognitive data were then correlated with the results of voxel-based morphometric analysis of volumetric MRI data. The analyses show for the first time in cognitively normal subjects that atrophy of the medial basal forebrain can precede the development of a clinical syndrome of dementia meeting criteria for Probable AD by as much as 4–5 years. This regionally specific tissue loss appears to represent the first component of what becomes widespread atrophy involving a contiguous region of related limbic and basal forebrain structures. The combination of basal forebrain and hippocampal atrophy signaled a rapid progression to clinical AD.

The loss of cholinergic neurons in the basal forebrain is a cardinal feature of AD (39), as is atrophy of the ventral striatum (40). An enlarged third ventricle, adjacent to the striatum-basal forebrain complex, was the most consistent finding in CT-scan studies of patients with mild/moderate AD (41), and patients with mild AD have volume loss in the structures that surround the third ventricle (42, 43). *In vivo* studies of activation of microglia (44), and of amyloid deposition (45–47) also find that the ventral striatum is affected early in AD. There is an

association between loss of neurons in the lateral and anterior medial nucleus basalis and the volume of the third ventricle, as well as between loss of neurons of the anterior nucleus basalis and grey matter volume in the prefrontal, temporoparietal, and posterior cingulate cortices (48).

The most widely-accepted view of the progression of the pathology of AD is expressed in the protocol of Braak staging (1, 3). The first areas with neurofibrillar changes occur in the mesial temporal lobe and spread in an orderly sequence to other brain areas. However, other subcortical nuclei, including those of the basal forebrain can show early AD pathology even in the absence of cortical involvement (49). From our data, we propose that one typical pathological progression in AD includes neuronal degeneration and atrophy first appearing in the basal forebrain followed by mesial temporal lobe and, finally, association cortex. If this is correct, basal forebrain atrophy is a crucial marker for the presymptomatic phase of AD. However, at this stage of our analyses, we do not know whether the early basal forebrain atrophy itself is associated with altered cognition or behavior; the atrophy found in our study is a presymptomatic change not associated with functional impairment as shown by our behavioral testing (all of the subjects were classified as normal in 1998/99). There were no significant correlations between basal forebrain volumes and measures of memory and learning in the subjects who remained normal during follow-up. However, we did note modest associations (r 's $\approx .20 - .25$) between atrophy and memory in the subjects who developed AD. We presume, therefore, that further extension of the AD pathology, beyond what we observed here, would result in the patterns of association demonstrated by Mesulam and colleagues (50).

Most research on the prodromal phase of AD has focused on alterations in the hippocampus and related structures (36, 51–57), and prospective studies have found that hippocampal atrophy in presymptomatic individuals was highly predictive of AD (5, 58, 59). Individuals with MCI, an early manifestation of AD (60), have alterations in multiple cortical and subcortical areas, including the parietotemporal and prefrontal cortices, posterior cingulate gyrus (61–64), insula, mammillary bodies, and thalamus (43, 65). Alteration of the temporoparietal cortex and posterior cingulate gyrus are strong predictors of incident AD in subjects with MCI (62, 63, 66). The time of follow-up in the majority of the studies ranged from 1 to 3 years meaning that these individuals are more like our converters who were “late” in the process (i.e., pre-2000 AD group). Our findings suggest that basal forebrain atrophy may be the first detectable morphological alteration in at least some individuals who will develop AD, and that it can precede symptomatic dementia by several years.

The individuals in this study who progressed from normal cognition to clinical AD appeared to do so at a relatively rapid rate. This raises the question as to whether our subjects are representative of the process of conversion from normal cognition to dementia. There are few data to inform this question because studies of aging and cognition are not typically longitudinal, and the combination of imaging with neuropsychological testing over time is unusual. Our sample of subjects converting from normal to AD is relatively small and it is likely that there is considerable variability in the process in a large population. The continuing analysis of longer term follow-up data from the CHS should be informative in this regard.

Indeed, the CHS-CS cohort is particularly useful for examining the factors associated with progression from normalcy to dementia because the participants had confirmed normal mental status for 6–8 years before the onset of the symptoms of dementia. Cross-sectional studies, and longitudinal studies of short duration have the risk of including nominally “normal” subjects in whom clinical decline has already started, but that cannot be detected because of the lack of an adequate baseline measure. These individuals are more likely to resemble subjects with early AD (at least in terms of MRI scans), and thus may bias study results. A community-based study has the further advantage that it avoids some of the recruiting bias which confounds the interpretation of the results of studies from referral clinics or research centers. Less than 10%

of the demented participants in CHS had been identified by the family or physician (6) suggesting that we captured these cases in their earliest phase.

Our data complement and extend those reported recently on CNS structural changes that predict the development of AD in subjects with MCI (4, 5). In those studies, atrophy in the medial and inferior temporal lobe was observed as long as 3 years prior to the development of AD from MCI. We also found progressive hippocampal atrophy as individuals were temporally closer to the clinical dementia. Among the subjects who first developed symptoms within two years following the MRI scan, there was greater loss of hippocampal volume relative to those subjects who did not develop their symptoms for more than 2 years after the scan. However, the extent of basal forebrain atrophy in these two groups of subjects was the same as that found in the prevalent AD subjects. Thus, while hippocampal atrophy may be necessary for the development of clinical dementia, it is basal forebrain atrophy that signals the onset of the AD pathological process.

mVBM has the advantage that it is machine driven and not subject to operator intervention. This makes the technique amenable to the analysis of large datasets, and there is good correspondence between mVBM-derived results and those from more classic region of interest analyses (67). However, VBM can be confounded if there is a systematic bias in the data being examined. In the present case, the expansion of the lateral ventricles have made the segmentation step of the preprocessing more susceptible to edge effects at the GM/CSF border (for example). If the ventricles have to be reduced during the process of spatial normalization (which would be a bigger concern in the AD group than in the cognitively normal subjects) then the grey matter nearby also needs to be reduced (see (68)). Thus a structural difference due to differences in the size of the ventricles may appear as GM atrophy in VBM, although the modulation step of our processing should minimize this effect. Thus, our findings need to be confirmed using other techniques that are less susceptible to such artefacts of processing (e.g., (48)). We do not believe, however, that this concern obviates our findings. First, as noted above, there is an increasing body of evidence that the basal ganglia and related structures are affected in AD, and there are obvious neuropathological abnormalities in the basal forebrain area; so, our findings fit with the known pattern of neuropathological changes. Second, given the more extensive atrophy in the AD subjects, we might have expected to find more widespread periventricular abnormalities, given the data from this sample showing such expansion (69, 70). The fact that this pattern of atrophy *only* occurs in the ventral regions of the ventricles makes us more confident in the current findings. Finally, in spite of the fact that systematic bias “*may* produce differences that are detectable by VBM. They are all real differences among the data...”((68), pg. 1241; italics added), given that these findings are reproducible and are in accord with the neuropathology, we feel that for the moment they deserve careful attention.

With the potential availability of neuroprotective agents for degenerative brain disorders, it is increasingly important that disease be identified in the presymptomatic state with methods that are generally available, safe, non-invasive, reliable and relatively inexpensive. MRI potentially meets all of these criteria. The major issues to be resolved with respect to using structural MRI for a presymptomatic diagnosis of AD are establishing the criteria for selecting an at risk population, developing a set of normative data for comparison, and implementing rapid, automated techniques for volumetric measurements (e.g., (71–75)). Data from community based samples such as the one used here should contribute importantly to that process. On the basis of the data presented here, we conclude that basal forebrain atrophy represents a candidate biomarker for presymptomatic brain changes in the evolution of AD.

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Figure 1.

Figure 1 shows the brain regional atrophy among Probable AD patients compared with normal subjects in coronal (a), mid-sagittal (b), and axial (c) views. The images are corrected for multiple comparisons using a False Discovery Rate of $p < .05$, and an extent threshold of 30 voxels. The results of the modulated VBM analysis are projected onto the standard T1-weighted MRI image (from SPM2) aligned to the Montreal Neurological Institute template.

The atrophy in the basal forebrain and left temporal lobe in individuals who were destined to develop AD (compared to those who were not) (d, e, f) was similar in locus to that seen in the AD patients, but was less extensive. The statistical threshold was set at $p < .001$ (height) and 30 contiguous voxels (extent).

Brain Regional Volumes in 1998/99 as a Function of Classification in 2002/03

Figure 2.

Figure 2 shows the regional volumes in the basal forebrain and the left hippocampus among the subjects who remained normal (1998/99 through 2002/03), and those who developed AD during follow-up. These groups included the subjects who were cognitively normal in 1998/99, and who developed their first symptoms either Pre- or Post-2000.

Table 1
Characteristics of Study Subjects assessed in 1998/99 as a Function of their Diagnostic Classification in 1998/99 and 2002/2003

1998: 2002:	Normal Normal	Normal AD (Post-2000)	Normal AD (Pre-2000)	AD	Statistic F/ χ^2
N=	127	12	9	26	
Age (Years)	77.3 (3.5)	80.0 (3.2)	78.6 (4.9)	83.2 (5.0)	19.4 ⁵
Education (Years)	16.6 (4.1)	15.6 (4.7)	14.1 (3.7)	15.5 (5.1)	1.56
Sex (N (% Male))	58 (46)	4 (33)	2 (22)	10 (39)	2.8
Race (N (% White))	104 (82)	11 (91)	5 (56)	20 (76)	4.8
APOE* ⁴	26 (23)	4 (33)	3 (33)	9 (41)	3.2
Hypertension ²	56 (44)	4 (33)	4 (44)	14 (52)	3.6
Diabetes ²	14 (11)	1 (8)	2 (22)	2 (7)	3.0
Heart Disease ²	14 (11)	5 (42)	0 (0)	10 (37)	18.3 ⁵
CES-D ³	23 (18)	6 (50)	1 (11)	5 (19)	3.36
3MSE (1998)	96.9 (3.4)	94.8 (4.0)	94.9 (3.7)	76.7 (13.4)	88.8 ⁵
Neuropsychological Composite Scores ⁴					
Memory	50.5 (7.6)	49.5 (3.5)	44.3 (7.0)	23.7 (4.7)	71.1 ⁵
Language	51.2 (7.3)	46.8 (9.7)	45.5 (9.1)	29.4 (15.0)	31.4 ⁵
Construction	51.7 (7.6)	48.9 (9.6)	45.4 (8.8)	34.7 (13.2)	20.9 ⁵
Executive	49.9 (6.0)	49.7 (5.1)	49.1 (4.2)	47.1 (8.3)	1.56
Motor	52.5 (7.3)	47.4 (7.5)	45.9 (15.3)	36.5 (12.6)	15.6 ⁵

¹ Number (percent) with at least on E*4 allele

² Number (Percent) of participants in the group meeting CHS criteria for the condition

³ Number (percent) scoring 8 or higher on the Center for Epidemiological Studies Depression Scale (28)

⁴ Neuropsychological Composite Variables expressed as T-scores using age-and education-adjusted norms.

⁵ p < .001

Table 2
Coordinates (in MNI Space) of Peak Voxels in Regions Showing Significant Differences from Normal Control Subjects

Region	X	Y	Z	Peak Z
AD Patients				
Basal Forebrain	7	-9	-13	5.57
Left Hippocampus	-22	-7	-16	5.82
Normal to AD Converters				
Basal Forebrain	-1	-4	-9	4.47
Left Hippocampus	-26	3	-26	3.73

Table 3

Volume of Region of Interest Extracted using SPM2 as a Function of Diagnostic Group by Year of Study

1998: 2002:	Normal Normal	Normal AD (Post-2000)	Normal AD (Pre-2000)	AD
Basal Forebrain Volume	.40 (.05)	.30 (.06)	.29 (.05)	.30 (.04)
Left Hippocampus Volume	.52 (.07)	.52 (.10)	.43 (.12)	.44 (.06)
Right Hippocampus Volume	.53 (.07)	.55 (.07)	.44 (.12)	.45 (.07)

Note: The volume unit is the mean volume (mL) per voxel within the region of interest, adjusted for the total brain volume, and the Gaussian smoothing filter.