Brain Mapping in Dementia

Michael S. Mega, *† 1  Paul M. Thompson, * Arthur W. Toga,* and Jeffrey L. Cummings† 2

*Laboratory of Neuro Imaging, Division of Brain Mapping, Department of Neurology,
†Alzheimer’s Disease Center, and
‡Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, California 90095

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The application of brain mapping techniques in elderly and demented populations presents unique challenges but offers exciting breakthroughs in early detection and the monitoring of treatment efficacy. Utilizing brain mapping techniques in combination with a profile of cognitive performance and risk factors is currently the most powerful predictor of incipient Alzheimer’s disease (AD) in elderly individuals with mild cognitive impairment (MCI). In the absence of a biochemical marker, functional and structural neuroimaging is now the best biological marker for AD. Longitudinal prospective studies of individuals presenting to memory disorder clinics who later develop AD, by clinical (Johnson et al., 1998) or pathologic criteria (Jobst et al., 1998), show that these individuals have greater functional defects in parietal and posterior cingulate cortices than those individuals who do not develop AD. Similarly, longitudinal studies of patients with isolated memory impairment reveal that within a 4-year period 80% who also have medial temporal atrophy at baseline develop AD (de Leon et al., 1989, 1993). The combination of medial temporal atrophy and functional defects in parietal or medial temporal/posterior cingulate cortices has a higher sensitivity and specificity of correctly identifying pathologically confirmed AD than a clinician’s application of National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria (Jobst et al., 1998).

Once a valid and reliable methodology is established to identify regional atrophy and functional defects predicting incipient AD, then modern brain mapping techniques will have significantly advanced health care delivery. This chapter reviews the advances in brain mapping techniques as applied to aging and dementia, covering both structural and functional neuroimaging. We focus on efforts to uncover the pattern of regional atrophy and functional defects specific for AD. An emphasis on the application of modern brain mapping techniques will be provided together with the challenges in their application in the elderly population, where cortical atrophy adds to the normal anatomic variability of one person’s brain with a population’s average brain.

1 To whom correspondence should be addressed.
I. Structural Imaging

Structural studies based on computerized tomography (CT) and magnetic resonance imaging (MRI) provided evidence that the cortex in AD was significantly reduced compared to that in age-matched controls. In the middle stage of AD, atrophy is most pronounced in the temporal lobes (Brun and Englund, 1981). The greatest regional loss in cortical volume is found in the medial temporal allocortex and heteromodal frontal and parietal association cortices. The degree of atrophy varies among patients (Miller et al., 1980), yet cortical neuronal loss is two to three times greater in AD than in age-matched normals (Shefer, 1972). The identification of regional gray matter (GM) loss in AD compared to normal aging indicated that generalized atrophy did not occur in AD but rather specific brain regions are targeted by the pathophysiologic process. A regional predilection of the atrophic process in AD agreed with the emerging microscopic pathologic pattern found for neurofibrillary tangle (NFT) deposition. Seminal work (Braak and Braak, 1991) showed that the pathologic severity in AD could be staged based upon regional NFT density, beginning in medial temporal transentorhinal cortex and then spreading through heteromodal association cortices in frontal and parietal lobes to eventually affect sensory and motor cortices in the late stages of the disease. Similar to the regional progression of NFT burden in postmortem cases, longitudinal imaging studies also showed a greater loss of GM volume with disease progression in medial temporal and frontal/parietal cortices. An agreement among the pathological and imaging data supported a specific pattern of atrophy in the AD brain.

A. Segmentation

Early studies evaluating brain tissue changes in aging were based on serially sectioned pathological specimens outlined to derive planimetric GM and white matter (WM) volumes throughout formalin-fixed specimens (Anton, 1903; Jaeger, 1914) and documented a GM:WM ratio change of 2.26-2.38 at the age of three to 1.05-1.4 in the fifth and sixth decades, later confirmed with more modern pathological assessment (Miller et al., 1980). These initial studies revealed volumetric loss throughout aging and in dementia but they were subject to error due to shrinkage and dehydration during the fixation process. The first in vivo imaging attempts delineating brain tissue volumes in aging and dementia were conducted with $^{133}$Xe carotid injection (Høedt-Rasmussen and Skinhoj, 1966) and noted a progressive loss of GM: 48.8% in normals, 40.2% in mild dementia, and 33.4% in moderate dementia. The first volumetric CT studies in aging and AD respectively were by Yamaura et al. (1980) and Gado et al. (1982). Because of the low slice frequency interval, approaching 5 mm to 1 cm, these studies lacked precision in documenting subtle regional changes due to dementia versus normal aging. With the advent of MRI, trinary segmentation was initiated (Seab et al., 1988; Filipek et al., 1989; Jernigan et al., 1990, 1991; Rusinek et al., 1991) utilizing the differential intensities of GM, WM, and cerebral spinal fluid (CSF).

The application of brain mapping techniques in segmentation analysis is challenged by the simultaneous assessment of disease-specific tissue change, compared to normals, while controlling for normal anatomical variation. After segmentation of MRIs into GM, WM, and CSF, automated regions of interest (ROIs) analyses with current brain mapping techniques can be applied. Techniques have used nonlinear registration of a segmented, single-subject atlas to individual structural scans, with a 6% error (Gee et al., 1993). By using nonlinear warping with a probabilistic atlas, which incorporates the spatial distribution of a population’s anatomy (Mazziotta et al., 1995; Evans et al., 1996), control over anatomic confounds with preservation of age-related effects can be accomplished in an unbiased manner. We hypothesized significant frontal GM loss in elderly nondemented normals compared to young normals. To assess the GM quantity in lobar ROIs, high-resolution 3D MRI scans of 24 persons (12 normal right-handed males, mean age 30.0, SD = 7.7 years; 12 normal older right-handed males, mean age 70.9, SD = 7.0 years), after inhomogeneity correction (Sled et al., 1998), were processed with a minimum-distance classification algorithm (Kollokian, 1996) to segment the MRI data into WM, GM, and CSF voxels (Fig. 1).

To localize the segmented anatomy from the probabilistically partitioned atlas, a fifth-order intensity-based polynomial warp (Woods et al., 1993) drove the partitioned atlas space into the subject’s native data, with subsequent correction of tissue counts for head size (Fig. 2). As hypothesized, there was a significant decrease in frontal GM ($p < 0.02$) and an increase in frontal CSF ($p < 0.001$) in elderly compared to young normals. Figure 3 graphically illustrates the decline in GM and increase in CSF with respect to age. In addition, we also found a significant decrease in occipital GM ($p < 0.05$) and a significant increase in CSF for the aged subjects in the occipital ($p < 0.02$), parietal ($p < 0.001$), and temporal lobes ($p < 0.02$).

This brain mapping technique demonstrates how high-resolution volumetric tissue analysis can be corrected for anatomic differences across subjects. While still preserving group differences using nonlinear warp-
Figure 1  Segmentation of young (left) and old (right) normal brains into gray matter (green), white matter (blue), and cerebral spinal fluid (red) using a minimum-distance classification algorithm (Kollokian, 1996) after inhomogeneity correction (Sled et al., 1998). Once segmented, a template, with probabilistically defined anatomic regions (Mazziotta et al., 1995; Evans et al., 1996), can be registered to each subject’s brain scan for subvolume analysis.

ing algorithms within a probabilistic atlas, an unbiased automated analysis is possible. Our findings support previous findings that as we age, we lose GM in frontal lobes and other regions.

B. Volumetrics

From earlier segmentation studies using both pathological data and in vivo imaging analysis, a pattern of atrophy associated with AD has emerged. The concentration of the atrophic process early in the course of the disease begins in medial temporal structures. Given the mediation of declarative memory by medial temporal structures, as well as the pathologic concentration of markers in hippocampal and entorhinal cortices, the search for early imaging changes in this region began in the early 1980s. Volumetric assessment of the hippocampus has produced the clearest distinction between AD and normal aging compared to any other region studied. Attempts also have been made to evaluate amygdalar volume; however, a clear distinction of anatomic landmarks demarcating the amygdala is difficult to achieve with in vivo imaging.

Given the wealth of evidence accumulated across studies and institutions showing significant hippocampal loss in AD compared to elderly controls, there is now no longer a need for any future studies to confirm that the hippocampus in AD is reduced in volume compared to normal aged individuals. The present challenge for hippocampal volumetry is to identify the earliest point at which the hippocampus becomes atrophic in patients with MCI and at what rate this change occurs over time. Identifying the first manifestation of hippocampal atrophy, or its rate of decline, makes the early diagnosis of AD possible and the same assessment may serve as a biological marker to evaluate disease-modifying pharmacological treatments.
1. Hippocampus and Amygdala

Hippocampal structures in AD exhibit a mean volume loss of between 20 and 52% compared with age-matched controls (Table I). The challenge presented to neuroimaging in aging and dementia is centered on patients with MCI, those at risk for AD. Qualitative (de Leon et al., 1989) and quantitative (Convit et al., 1993, 1995; de Leon et al., 1993; Soininen et al., 1994; Parnetti et al., 1996) studies of persons with age-associated memory impairment (AAMI) (Blackford and La Rue, 1989; Cook et al., 1992), or those who eventually develop AD but did not meet criteria for the disease at the time of initial evaluation (Kaye et al., 1997), have demonstrated significant hippocampal atrophy compared to normal age-related losses. Hippocampal volume loss due to normal aging may approach 46 mm$^3$ per year over the age of 65, with a near-linear decline (Jack et al., 1997). The hippocampus of the AD patient in the earliest stage of the disease is already 1.75 standard deviations beyond the normal age expected loss (Jack et al., 1997) and is correlated with a patient’s memory impairment (Scheltens et al., 1992; Golomb et al., 1994, 1996; Deweer et al., 1995; Laakso et al., 1995; Cahn et al., 1998; Kohler et al., 1998). The entorhinal cortex may be the focus of the atrophic process in early AD, with a volume loss of 40% in patients compared to controls (Juottonen et al., 1998).

A normal asymmetry of medial temporal volumes, right larger than left, has been confirmed in morphological studies based on in vivo imaging analysis (Table I); this normal asymmetry averages 6.7% across all studies. Longitudinal analysis reveals a trend for the reversal of this normal, right-larger-than-left hippocampal asymmetry as an early morphologic change in persons who later go on to develop AD (Kaye et al., 1997). Although only one study explicitly tested this reversal of normal asymmetry in persons with AAMI (Soininen et al.,
all studies of these mildly impaired persons reflect a reversal of the normal hippocampal asymmetry when bilateral volumes were reported (Soininen et al., 1994; Parnetti et al., 1996; Kaye et al., 1997). Persons with AAMI who are homozygous for the apolipoprotein E (ApoE) allele may have a greater reversal of the normal hippocampal asymmetry than those without the ApoE-4 allele (Soininen et al., 1995); yet the ApoE-4 allele is not associated with global atrophy in AD (Yasuda et al., 1998). As the disease advances, the ApoE-4 allele may be associated with imaging markers of medial temporal atrophy, compared to AD patients without the ApoE-4 allele (Tanaka et al., 1998), but hippocampal volume might not be the cause of this general temporal atrophy (Jack et al., 1998).

The current challenge in applying brain mapping techniques to hippocampal volumetry is to detect subtle early changes in persons with preclinical AD using a standardized technique that controls for normal anatomic variability and allows easy application across centers. Because high-resolution imaging is able to detect subtle early morphological changes, we used high-resolution imaging to test the hypothesis that patients with MCI have a significant reversal of the normal right-larger-than-left hippocampal asymmetry compared to elderly individuals with normal memory function. We also sought to determine which subregions of the hippocampus demonstrate significant atrophy in MCI since a previous study has implicated the hippocampal head as being the most severely affected in AD (Jack et al., 1997). In this example, we applied 1-mm contiguous volumetry within the Talairach coordinate space to evaluate the subtle early changes hypothesized to occur in the hippocampus of patients with MCI. The use of a common brain space for hippocampal analysis fulfills the brain mapping objective of standardization in methodology and ease of application across centers. All hippocampal volumes were lower in the MCI group compared to the cognitively intact elderly, with the right hippocampal head and total volume showing a significant loss ($p = 0.02$). The mean hippocampal volume results for the two groups are shown in Table II.

Although both hippocampi were reduced, we found a significant ($p = 0.02$) volume loss in the right anterior half of the hippocampus in patients with mild memory impairment. This finding agrees with the location of hippocampal atrophy seen in early AD patients (Jack et al., 1997) and suggests that the pathologic process responsible for this volume loss predates the clinical manifestations by several years.

The cause of the greater right hippocampal volume loss during the preclinical stage of AD, or in MCI, is unclear. The early reversal of the normal medial temporal asymmetry may reflect an asymmetry in the pathophysiology of early AD. There may be greater synaptic pruning, or neuronal loss, in the right hippocampus in patients with MCI or incipient AD that could contribute to volume loss first in this region. Conversely, individuals with developmental or acquired reductions in the neuronal reserve of the right hippocampus, reflected by smaller volumes, may simply be at an increased risk for mild cognitive decline. The cause for the early asymmetric change in MCI is unknown. All of our patients were right-handed; thus the influence of handedness could not be assessed. A trend for reversal of the normal hippocampal asymmetry has been documented to occur in normal elderly subjects nearly 4 years prior to their development of AD (Kaye et al., 1997), with equal rates of change for both hippocampi ($-14$ to $-46$ mm$^3$/year) (Jack et al., 1997; Kaye et al., 1997). These prior data suggest that the right-greater-than-left atrophic process predates the development of AD by more than 4 years. Long-term prospective studies that employ high-resolution imaging, or 3D mapping, will be needed to determine at what point prior to dementia onset hippocampal atrophy occurs.

A further objective in brain mapping is the development of automated techniques. With a semiautomated 3D mapping approach (Haller et al., 1996, 1997; Csernansky et al., 1998a), utilizing a hippocampal MRI template of a healthy control, nonlinear intensity-based warping of the template onto each subject’s MRI scan extracts the hippocampal boundaries from new subjects. Digital extraction occurs in two steps. The template is first coarsely aligned to each target scan by landmarks manually placed on the template and target scans. Next the target’s local anatomy is determined by a high-dimensional, au-
### Table I  Morphologic Studies of Hippocampus (Hippo) and Amygdala (Amyg) in Patients with Age-Related Cognitive Decline (ARCD), Alzheimer’s Disease (AD), and Elderly Controls

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<tr>
<th>Reference</th>
<th>Study modality</th>
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<th>Slice spacing</th>
<th>ARCD</th>
<th>AD</th>
<th>Controls</th>
<th>Percentage R &gt; L</th>
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<td>14</td>
<td>86% accuracy</td>
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<td>10</td>
<td>7</td>
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<td>CT</td>
<td>No qualitative</td>
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<td>–</td>
<td>9</td>
<td>8</td>
<td>100% accuracy</td>
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<td>30f</td>
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<td>126</td>
<td>(CDR 0.5) decrease of 1.75 SD</td>
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<td>Pucci et al., 1998</td>
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<td>5.0 mm</td>
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<td>26% develop AD in 3 years with a volume in 0–0.6 percentile of controls</td>
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<tr>
<td></td>
<td>Autopsy</td>
<td></td>
<td>3.0 mm</td>
<td>80</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

†Planimetric, an area assessment; linear, a line length. †Percentage with qualitative atrophy present: ARCD/AD/control. A/H = amygdala and hippocampus. ‡Medial temporal thickness. †Subjects with ARCD compared to controls. Subgroup analysis only. §A/H age-related volume loss. †The lateral nucleus shows the greatest asymmetry. ‡Volume of parahippocampal fissure (after 4 years, 2 controls and 23 of the ARCD subjects developed AD). ‡Reversal of normal R > L asymmetry. Sensitivity; specificity; pAD, possible AD; CDR, Clinical Dementia Rating. §Same data used in Soininen (1994).

tomated, continuum-mechanical fluid transformation (Miller et al., 1993, 1997). To determine hippocampal shape as well as volume characteristics, a triangulated graph of points is superimposed onto the surface of the hippocampus in the template and then carried along the warp as the template is transformed onto the target scans. Computing the transformation vector fields from this graphical surface generates a 3D model of each subject’s hippocampus. A pooled, within-group covariance matrix computed from the transformation vector fields can be used to compare the shape characteristics of the hippocampus in the two subject groups. This covariance matrix is reduced in its dimensionality by computing a complete orthonormal set of eigenvectors specific to the shape of the hippocampus. The first 15 eigenvectors, in decreasing order of power, are chosen a priori as adequately representing structural shapes, and a linear discriminant function is computed by sequentially using an optimal combination of eigenvectors selected through a stepwise procedure. Logarithms of the likelihood ratios are then calculated as shape metric values for each subject according to these optimal solutions, and the statistical significance of the group difference in shape is tested using Wilk’s Lambda. Displacement maps of the hippocampal surface that discriminated 18 very mild AD subjects’, Clinical Dementia Rating (Hughes et al., 1982; Berg, 1988) of 0.5, and 18 controls matched for age and gender are shown in Fig. 4 (Csernansky et al., 1998b).

Another 3D mapping technique produces group-average 3D hippocampal surface maps from manual outlines. Understanding the average hippocampal shape for a population, within a common coordinate space, fulfills the brain mapping objective of incorporating normal anatomic variability in the assessment.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study modality</th>
<th>Contiguous volumetry†</th>
<th>Slice spacing</th>
<th>n</th>
<th>Percentage R &gt; L</th>
<th>Percentage decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuff et al., 1997</td>
<td>MRI</td>
<td>Yes</td>
<td>1.4 mm</td>
<td>ARCD 12</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Mauri et al., 1998</td>
<td>MRI</td>
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<td>1.5 mm</td>
<td>AD 17</td>
<td>22</td>
<td>1.5</td>
</tr>
<tr>
<td>Pucci et al., 1998</td>
<td>MRI</td>
<td>No, linear</td>
<td>NA</td>
<td>Controls 7</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>Krasuski et al., 1998</td>
<td>MRI</td>
<td>Yes</td>
<td>5.0 mm</td>
<td>Hippo 5</td>
<td>19</td>
<td>26% develop AD in 3 years with a volume in 0–0.6 percentile of controls</td>
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<tr>
<td>Smith et al., 1999</td>
<td>MRI</td>
<td>Yes</td>
<td></td>
<td>Amyg 7</td>
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<td></td>
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<tr>
<td>Jack et al., 1999</td>
<td>MRI</td>
<td>Yes</td>
<td>1.5 mm</td>
<td>20</td>
<td>20</td>
<td></td>
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<tr>
<td></td>
<td>Autopsy</td>
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<td>3.0 mm</td>
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Another 3D mapping technique produces group-average 3D hippocampal surface maps from manual outlines. Understanding the average hippocampal shape for a population, within a common coordinate space, fulfills the brain mapping objective of incorporating normal anatomic variability in the assessment.

Table II  Mean Hippocampal Volumes (SEM) for Normal Cognitively Intact Elderly and Subjects with Mild Cognitive Impairment (MCI) Registered to the Talairach Coordinate Space via a Seven-Parameter Transformation

<table>
<thead>
<tr>
<th>Total hippocampal volume (mm3)</th>
<th>Anterior hippocampal volume (mm3)</th>
<th>Posterior hippocampal volume (mm3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Normal</td>
<td>2087 (114)</td>
<td>756 (74)</td>
</tr>
<tr>
<td>MCI</td>
<td>1887 (96)</td>
<td>599 (61)</td>
</tr>
</tbody>
</table>

a  p = 0.02 compared to right side in normals.
method. Creation of these surface maps is based on a parametric mesh construction (Thompson et al., 1996). Hippocampal contours are traced using a track ball on each relevant slice. The points making up a traced contour, after smoothing the effects of irregular hand movements, are connected across slices to create regularly ordered 3D meshes warping the hippocampal surface. To quantify a population's anatomic variability, the shape of the average hippocampus is first resolved. This allows the computation of 3D displacement vectors—the movement needed from each point on an individual's hippocampal surface to that corresponding point on the average hippocampus. Hippocampal variability, expressed as a 3D distance in the Talairach coordinate space, is then computed by taking the square of the mean of the square roots of the vector displacements necessary to align each node of the population's hippocampi onto the average hippocampus. This computation of the root mean square (rms) allows the production of a population variability map shown in Fig. 5 for elderly controls. Understanding the normal anatomic variability in a population is crucial for the application of modern brain mapping techniques in disease states.

C. Cortical Morphometry

Controlling cortical morphology within a population presents one of the greatest challenges to modern brain mapping (Vannier et al., 1991; Christensen et al., 1997). The importance of mapping gyral morphology within a population is relevant not only to structural imaging in dementia, for the pursuit of a global pattern of atrophic change specific to AD, but also in functional imaging assessments when functional data are averaged across a group of individuals, each having unique gyral morphology. Attempts to control the variability of cortical anatomy have relied mainly on (1) the transformation of structural and functional imaging data into a common coordinate space (typically the Talairach space) and (2) the blurring of functional imaging data with a Gaussian smoothing kernel of varying size (ranging from 8 to 12 mm). Sulcal variability within the Talairach coordinate space for a population of elderly normal individuals can reach 14 mm about mean locations for temporal or parietal sulci. Using a Gaussian smoothing kernel to equalize such extreme cortical variability within a population blurs the functional imaging signal and thereby decreases the sensitivity of localizing subtle functional changes.

As demonstrated in the hippocampal mapping above, the first step in controlling for cortical morphologic variability is to measure it. The starting point for mapping variability in cortical patterns is to pick a common coordinate space in which the expression of variability can be documented. Once again, the Talairach space serves as a convenient initial reference.
space for the representation of variability. After high-resolution 3D MRI scans of 19 AD patients (mean age 75.8, SD = 8.7 years) and 20 controls (mean age 72.7, SD = 6.1 years) of similar gender, educational level, and handedness were edited to eliminate nonbrain tissue, a 3D surface model was constructed. Major and minor sulci on both the cortical surface and midline regions are manually outlined and resolved into 3D sulcal meshes. Sulcal averaging (Thompson et al., 1996, 1997) across the individuals within the two populations enabled the mean location of each sulcus to be computed for a population as described above. The mean location of major and minor sulci, and their variability about that mean, were mapped to provide 3D information on cortical morphology within the populations (Thompson et al., 1998). The anatomic variability within the AD population is tightly correlated with neuropsychological test performance for regions traditionally associated with both visual spatial and frontal-executive performance (Mega et al., 1998). Two factors contribute to variability within a population: normal individual gyriﬁcation and, in a disease population such as AD, the atrophic process.

After the variability in a normal elderly population is mapped, sulcal displacement from normal locations can be determined for an AD population. Displacement values in the x, y, and z axes of AD patients from the average control location suggest a speciﬁc pattern of 3D atrophy within AD (Zoumalan et al., 1999). Sulcal displacement across all individuals, referenced to the normal location, shows a signiﬁcant correlation between the right midline frontal region and the Ruff ﬁgural ﬂuency test ($r = 0.48, p < 0.01$). The left temporal region and naming ability showed a signiﬁcant correlation (the left superior temporal sulcus with verbal fluency $r = 0.41, p < 0.05$). The temporal-occipital region and visuospatial ability also were linked as revealed by displacement of the right inferior temporal sulcus that signiﬁcantly correlated to the Benton visual retention test ($r = 0.40$ and $-0.45$ for correct and errors, respectively; $p < 0.05$). The left collateral sulcus and verbal memory were linked as reﬂected in the Buschke-Fuld recall, storage, and retrieval scores ($r = -0.53, -0.63$, and $-0.59$; $< 0.01$). Thus, sulcal displacements in the Talairach space are related to cognitive performance and implicate a speciﬁc cortical pattern associated with AD. Once a speciﬁc cortical pattern is established for the AD population, brain mapping techniques will discern, from high-resolution 3D MRIs, whether individuals with cognitive complaints have incipient AD.

Another technique for determining brain changes in disease states from normal individuals (Fox et al., 1996a) or within a disease population across time (Fox et al., 1999) is the brain boundary shift integral (BBSI) (Fox and Freeborough, 1997; Freeborough and Fox, 1998). The basis for BBSI determining morphological changes is to average the structural imaging studies of a group and then create a subtraction of that average compared to a control or baseline average. This subtraction produces areas of brain that are dissimilar between the two groups, thus revealing the location of volumetric loss throughout the 3D volume. Rates of total brain volume loss in AD compared to controls are signiﬁcant (5-20 vs <-2 ml/year) (Fox et al., 1996b; Rossor et al., 1997) and are related to cognitive decline in AD (Fox et al., 1999). The averaging of individuals in the two groups is conducted using linear registration. Once the average volume for the two groups is determined, simple subtraction can provide a difference image that
is thought to reflect atrophy. This technique is demonstrated in GM maps of young and old normals (Fig. 6). Linear registration techniques do not control for anatomic variability and thus subtractions of averages based on linear registration will be confounded by registration error and normal morphologic variability that occurs from differences in group anatomy rather than entirely from disease-specific changes. Nonlinear intensity-based registration algorithms are superior in controlling the anatomic variability within a population.

Normal anatomic variability can be controlled with warping algorithms of increasing degrees of freedom from linear to nonlinear. Perfect correspondence between an individual and template, or a group of subjects, can be achieved by using surface-based high-dimensional continuum-mechanical warping. Warping of structural data to their average anatomy according to the constraints of fluid or elastic mechanics has been accomplished for an AD population as demonstrated in Fig. 7. The warping field that governs the transformation of any given subject to the template contains information that is specific to both the individual’s anatomy and the atrophic changes imparted by disease. Evaluating the warping field and resolving it into tensors that define the 3D vectors displacing any given point in a reference volume to the corresponding target volume will enable the production of tensor maps. Tensor mapping can then be used to reflect the 3D displacements that result from both the atrophic process and normal anatomic variability. Using principal component analysis to determine which eigenvectors associated with a tensor field are more responsible for normal anatomic variability and which may be most responsible for disease-specific, atrophic morphologic change is the goal of modern research in morphologic brain mapping within dementia and aging.

II. Functional Imaging

The earliest functional imaging studies in aged and demented individuals (Freyham et al., 1951; Kety, 1956; Lassen et al., 1957) were conducted using the nitrous oxide method of Kety and Schmidt (1948). These studies showed significant declines of cerebral perfusion in demented subjects compared to controls but were not capable of regional subhemispheric analysis. Nonetheless, a specific pattern of functional defects in dementia was tentatively suggested in an early review: “From these studies emerges the somewhat surprising suggestion that perhaps even dementia is to some extent a regional cerebral disease, namely, a disease of the dominant hemisphere.” [p. 66] (Lassen and Ingvar, 1963). With the advent of [$^{18}$F]fluorodeoxyglucose positron emission tomography (FDG-PET) to measure in vivo metabolism, regional cerebral metabolic defects were established in dementia (Benson, 1982, 1983; Foster et al., 1983), stroke patients (Benson et al., 1983; Metter et al., 1983; Benson, 1984), and subcortical degenerative disorders (Mazziotta et al., 1987; Grafton et al., 1992). In the mid-1980s, the patterns of functional defects involving structurally intact brain tissue emerged across dementing disorders. Functional deactivation of brain regions disconnected from subcortical activating projections was found in patients with thalamic or striatal lesions; this remote deactivation is termed diachisis (Meyer et al., 1993). Thus, stroke patients who present with isolated subcortical lesions but demonstrate classical cortical language abnormalities were found to have functional defects in structurally intact cortical language regions. Similarly, in degenerative extrapyramidal disorders such as progressive supranuclear palsy, or Parkinson's disease, individuals who were clinically demented showed functional imaging abnormalities in frontal cor-
tical regions that were relatively spared from pathological changes. Consequently, any functional imaging assessment in dementia must consider the distributed neuroanatomy of a deactivated region and search for a disconnection of cortical or subcortical projections. In AD deafferentation may result from NFT burden in the entorhinal region, thereby disconnecting projections to frontal, parietal, and temporal association cortices. Such deafferentation of ascending cholinergic input due to cell loss in the nucleus Basalis of Meynert has been suggested. However, studies with lesions in baboons of the nucleus Basalis of Meynert have failed to replicate (Le Mestric et al., 1998) the earlier finding of hypometabolism in frontotemporal cortex (Kiyosawa et al., 1989).

A. Methodological Considerations

1. Partial Volume Correction

In additio to deafferentation, partial volume error also contributes to the loss of signal in functional imaging studies in aging and dementia. Given the resolution of most current PET (3.5-mm full width at half-maximum) or SPECT (6-mm full width at half-maximum) scanners, partial volume error will occur when the tissues of GM, WM, or CSF are averaged in the relatively large functional imaging voxel (Mazzotta et al., 1981). In the elderly and demented brain, this averaging of the three tissue compartments is particularly severe given the degree of atrophy occurring in normal aging and dementia. Atrophy is the strongest correlate to focal hy-
pometabolism (Jamieson et al., 1987; Fazekas et al., 1989). Thus, the interpretation of functional imaging studies in aging and dementia must take into account the partial volume error in assessing the functional viability of brain regions. Conversely, partial volume error may assist the researcher in identifying individuals with AD compared to normal controls in that the effects of atrophy will result in greater hypoperfusion, or hypometabolism, in AD compared to a control cohort. However, if the research question centers on the actual functional nature, or ligand concentration, within brain regions, then partial volume correction (PVC) must be performed.

The increasing power of brain imaging and the development of novel techniques for brain modeling allow incorporating high-resolution structural data into PET analysis. A variety of methods for PVC of PET data, using the kinetic properties of specific tissue components, have been proposed. Metabolic rates of GM are 3-4 times that of WM, while CSF is presumed to have no metabolic activity. Binary segmented MRI scans (total brain tissue separated from CSF) convolved, or reduced in resolution, to the in-plane resolution of the PET images have been done (Meltzer et al., 1990). A limitation of binary correction is that it does not address partial volume averaging of GM with WM. This is crucial in AD, which has a significant reduction in GM volume compared to normal controls (Høedt-Rasmussen and Skinhøj, 1966; Creasey et al., 1986; Prohovnik et al., 1989; Rusinek et al., 1991). Atrophy-corrected PET, using a binary segmentation method, in AD patients and elderly controls eliminated apparent significant reductions of metabolism in many cortical regions within the AD group's uncorrected PET data (Meltzer and Frost, 1994; Meltzer et al., 1996). A trinary correction method has been applied to PET (Müller-Gärnert et al., 1992; Ibanez et al., 1998). Trinary correction (separating GM, WM, and CSF) will eliminate partial volume error and allow more accurate measurement of the metabolic activity from the remaining synapses present in AD patients.

We employed a pixel-based PVC approach to a group of normal elderly control and AD individuals to test the hypothesis that temporal lobe hypometabolism in AD, relative to controls, will be reduced in PVC-PET compared to uncorrected statistical difference maps. The accuracy of PVC depends upon accuracy of the segmentation of the MRI scan, accuracy of the registration of the segmented MRI scans with the PET data to be corrected, and the inhomogeneity of the PET point spread function. Previous PVC methods either have registered a binary segmented MRI image to the PET data set, after convolution to the resolution of the PET, for correction of the GM/WM, and CSF signal or have used automated MRI image segmentation based on the probability maps within the International Consortium of Human Brain Mapping (ICBM) probabilistic atlas (Evans et al., 1996) to reduce any thresholding bias. We evaluated PVC and uncorrected FDG-PET studies from five AD patients and five healthy controls within the ICBM 305 probabilistic atlas. The two groups were matched for age, gender, and level of education. A semi-automated minimum-distance classification algorithm (Kollokian, 1996) was used to segment the individual native MRI data into WM, GM, CSF, and background voxels after inhomogeneity correction was accomplished (Sled et al., 1998). Native MRIs and tissue maps were registered via point-based affine transforms with the FDG-PET data; these transforms were then concatenated with intensity-based affine registrations (Woods et al., 1993) of the MRIs into the ICBM 305 space. A ratio of 4/10 (GM/WM/CSF) was used to recompute native PET voxel values, based upon the segmented high-resolution MRI data; both corrected and uncorrected PET data sets were then normalized to each group's global mean. In this rest-state subtraction paradigm, a subvolume thresholding (SVT) was applied (Dinov et al., 2000) to the uncorrected and corrected PET data to assess change in differences among normals and the AD group. The SVT approach uses the anatomic probabilistic maps associated with the ICBM 305 atlas (Collins and Evans, 1997) to evaluate the ROI between-group variance and estimate both the regional and voxel statistical group differences. PVC was performed prior to SVT.

Figure 8 shows the total brain voxel difference between the partial volume corrected and uncorrected tissue maps. Figure 9 illustrates individual slices in the statistical maps, comparing the PVC technique with uncorrected data. Substantial reduction in the volume of significant voxels was seen in the perisylvian and medial temporal regions with PVC. Regardless of the correction technique, all studies show a similar underestimation of functional signal within AD brains due to partial volume error. Our preliminary findings demonstrate the effect of atrophy correction within a probabilistic brain atlas and suggest that atrophy accounts for a large percentage of the measured hypometabolism in AD FDG-PET data. PVC should not be done when high sensitivity is desired in discriminating between demented and normal elderly.

2. ROI vs. Group Analysis

Evaluating functional imaging data beyond qualitative assessment can be done either with ROIs drawn on functional imaging slices, with ROIs drawn on the same subject’s MRI registered to that subject’s functional imaging study, or from averaging groups of functional
imaging data sets into a common space for statistical analysis on a voxel-by-voxel basis. There are difficulties with each technique. The ROI drawn on a functional imaging slice is prone to error because of the poor anatomic delineation of the low-resolution functional data set. ROIs drawn on MRI and then coregistered to functional data are time-consuming and limited in the amount of information that can be gained. Any ROI analysis will collapse the pattern of functional signal within an ROI into a single number that is then analyzed for statistical significance. This single value may not adequately reflect the subtle disease-specific variability within the subregions of an ROI. Group analysis of functional mapping on a voxel-by-voxel basis avoids the drawbacks of ROI analysis by permitting all data within a functional scan to participate in a statistical analysis. The advantage of voxel-by-voxel assessments is constrained by the difficulty in controlling for anatomic variability of individuals within a population and avoiding Type I errors occurring from multiple voxelwise testing. There are solutions to solving these drawbacks.

To control for anatomic variability many statistical mapping approaches apply a Gaussian smoothing kernel to the functional data as described previously; however, this decreases the resolution of the functional data set. Another approach employs a probabilistic atlas to control for anatomic variability within a population by weighting functional imaging voxels with more or less emphasis, depending upon where they fall within an anatomical probability cloud. This type of analysis has been performed on functional imaging data shown in the example using SVT above. The voxel-by-voxel analysis of functional imaging data can be performed without the use of a Gaussian smoothing kernel, thus better localizing functional differences.

Another approach in controlling for anatomic variability utilizes surface-based, high-dimensional, continuum-mechanical registration of a selected ROI. Constrained warping of data, depending upon the hypothesis to be tested, is less processor dependent when high-dimensional warps are used. We apply this technique to the hippocampus, which has a great deal of variability in the Talairach space (Fig. 10), in AD, MCI, and controls. The variability of PET signal decreases when the hippocampal surfaces pull the PET data into perfect correspondence (Fig. 11). Here the variability of the PET signal in the subtraction of the MCI from the control group's FDG-PET is significantly reduced compared to the same cases subtracted with affine registration alone.

Figure 8 Volume difference in total brain z-scores from statistical maps of hypometabolism on FDG-PET between AD patients and elderly controls (CNT). Partial volume corrected FDG-PET identifies fewer significant voxels compared to uncorrected PET maps.

Figure 9 Statistical maps of hypometabolism as measured by FDG-PET in AD patients compared to elderly controls. Atrophy contributes to much of the hypometabolism seen in the AD FDG-PET data as revealed by the uncorrected data (right) compared to the partial volume corrected data (left).
Figure 10 The average 3D surface models of 10 control, 10 MCI, and 10 AD patients' hippocampi derived from manual outlines. Note the mismatch of these averages in the Talairach coordinate space.

B. Resting Studies

1. SPECT and PET

SPECT evaluation in AD compared to elderly controls consistently shows decreased perfusion in temporal and parietal association cortices. The sensitivity/specificity for identifying clinically diagnosed AD patients within a general dementia population by qualitative analysis using HMPAO-SPECT has a broad range, 76-88%/43-87% (Holman, 1991; Masterman et al., 1997), and is helped by qualitative medial temporal atrophy assessment, 77%/93% (Lavenu et al., 1997). Longitudinal evaluation of patients who present to memory disorder clinics but are not frankly demented has shown that the posterior cingulate, left thalamic, and left medial temporal regions are significantly hypoperfused in a group that later goes on to develop AD within 2 years of examination (Johnson et al., 1998), but replication of these results by visual analysis of individual patients may not be possible (McKelvey et al., 1999). Evaluation of a single, questionably demented patient's functional imaging data, with reference to known variability of a normal elderly group, is just beginning (Signorini et al., 1999).

FDG-PET in AD is a window on the metabolic activity of neurons not destroyed by the disease. The earliest abnormalities on PET are found in the posterior parieto-occipito-temporal areas before clinical symptoms emerge; as the disease progresses, the hypometabolism moves anteriorly to affect the temporal and finally frontal cortices (Benson, 1982, 1983; Benson et al., 1983; de Leon et al., 1983; Ferris et al., 1983; Foster et al., 1983; Friedland et al., 1983; Duara et al., 1986; Grady et al., 1986, 1987; Salmon and Franck, 1989; Haxby et al., 1990). These changes may be loosely correlated with data from cross-sectional, postmortem studies showing the progressive regional deposition of amyloid deposits and NFTs (Braak and Braak, 1991). Presumed preclinical AD patients evaluated with FDG-PET have also shown biparietal metabolic abnormalities before clinical criteria for probable AD are met. The use of genetic markers to identify a population at risk for the disease, in combination with functional imaging studies demonstrating the existence of brain pathology, may provide very early detection of AD (Small et al., 1995; Reiman et al., 1996). Functional imaging abnormalities may predate medial temporal volume loss in genetically at-risk persons (Reiman et al., 1998) and preclinical carriers of the Swedish Alzheimer amyloid protein mutation (Julin et al., 1998). Alzheimer's disease patients with the ApoE-4 allele (Lehtovirta et al., 1998) or the $\alpha$-antichymotrypsin type A allele (Higuchi et al., 1997) have greater regional defects on functional imaging than those without these genetic burdens.

In addition to partial volume error and deafferentation, described above, other possible causes for hypometabolism on FDG-PET include synapse loss and dysfunctional energy metabolism or glucose transport.
The activity observed on FDG-PET, assuming that blood flow and glucose utilization remain coupled, reflects the metabolism of active synapses as they restore their resting ionic gradients via Na/K-ATPase (Hand et al., 1979; Mata et al., 1980; Kadakaro et al., 1985; Ginsberg et al., 1987). Metabolism of glucose and the production of ATP from the electron transport chain in mitochondria of AD may be normal or dysfunctional. Synapse loss is the best cellular correlate with the degree of cognitive impairment in AD patients (Terry et al., 1991), with the greatest regional loss seen in frontal areas across pathological studies (Davies et al., 1987; Hamos et al., 1989; Samuel et al., 1993). Given their high metabolism, synapse dropout will result in a lower glucose metabolism on FDG-PET studies. Loss of synapses will also result in atrophy. In a pathological study conducted 16 months after an AD patient was evaluated with FDG-PET, regional hypometabolism correlated with cell loss, gliosis, and amyloid plaques (APs) (McGeer et al., 1986).

The remaining synapses in AD patients may have primary defects in energy metabolism. Five glucose transporters (Glut1-5) have been identified (Bell et al., 1990), and two are present in the brain: Glut1 and Glut3. Glut1 is present in the endothelial cells of the blood-brain barrier and is the glucose transporter in glial cells; Glut3 is found in neurons. Using quantitative immunohistochemistry, Harr et al. (1995) found a 49.5% decrease in Glut3 immunoreactivity in the outer portion of the molecular layer of the dentate gyrus in AD brains. This area is the termination zone of the perforant pathway whose cells of origin are the layer II pyramidal neurons of the entorhinal cortex; cells that suffer the earliest burden of NFT in AD. Since glucose uptake influences metabolism, deafferented cells might downregulate Glut3 in AD, contributing to the hy-
pometabolism seen on FDG-PET. An estimation of the kinetic parameters describing the forward and reverse FDG transport ($K_{1s}$ and $k_{2s}$, respectively) and the phosphorylation of FDG by the enzyme hexokinase ($k_1^*$) has been done in AD compared to controls (Friedland et al., 1989; Jagust et al., 1991). A significant decrease of $\sim20\%$ in $K_{1s}$ in the frontal and temporal cortices in AD compared to controls was found (Jagust et al., 1991). Transport of FDG across endothelial cells (Glut1 transporter) through the interstitial space and into neurons (Glut3 transporter) is reflected by $K_{1s}$. Abnormalities in Glut3 could be responsible for the reduction in $K_{1s}$. However, a $20\%$ reduction in glucose delivery to cells will not significantly reduce energy metabolism (Lund-Anderson, 1979)—some other metabolic defect must be present in AD.

Amyloid is deposited in the posterior parietal lobe early in AD (Arnold et al., 1991), an area first affected on FDG-PET in at-risk patients (Small et al., 1995; Reiman et al., 1996). Hippocampal structures are also affected but are not well visualized by PET. The parietal abnormality supports amyloid as contributing to the hypometabolism on FDG-PET in AD. Although plaques do not correlate with the degree of cognitive loss, and presumably neuronal dysfunction, seen in AD (Terry et al., 1991), altered synaptic function is associated with the accumulation of amyloid $\beta$-protein (A$\beta$) (Terry et al., 1994). Accumulation of reactive oxygen species (ROS) may be the mechanism of A$\beta$ neurotoxicity. A$\beta$ induces lipid peroxidation in synaptosomes (Butterfield et al., 1994) and cultured cortical cells (Behl et al., 1994). Injury could result from free radical production in A$\beta$ itself (Hensley et al., 1994) or secondarily from calcium influx (Mark et al., 1995). If A$\beta$ contributes to the hypometabolism on FDG-PET in AD by initiating the production of ROS, oxidative damage is a likely destructive mechanism.

Modern brain mapping techniques allow the mapping of A$\beta$ and other markers such as NFTs with the metabolic changes in AD to provide a unique inquiry into pathologic relationships with functional imaging abnormalities in AD. Figure 12 provides an overview of this methodology in AD patients who undergo functional imaging with FDG-PET close to death, permitting functional-histological-biochemical integration within a common AD atlas (Mega et al., 1997; Mega et al., 1999). Future work is necessary to understand the pathological basis of the functional defects in the AD population.

C. Activation Studies

1. PET and fMRI

Activation protocols in aging and dementia are exploratory and methodologically difficult with cognitively impaired individuals who are easily distractible. Coupled with the methodological problems of activation protocols with demented persons is the challenge of controlling for spatial variability in an elderly and AD population when data are averaged in a common space. The first attempted activation study comparing AD to elderly controls used FDG-PET and a verbal memory task but failed to show any functional increase (Miller et al., 1987). Similar global metabolic increases were found with picture preference and reading memory tasks for both AD and controls (Duara et al., 1990a, b, 1992). Using a continuous visual recognition task with an ROI analysis of FDG-PET, Kessler et al. (1991) found a mean, task-related, global metabolic increase for elderly controls that was $15\%$ greater than the increase in the AD group. With the appropriate cognitive challenge, AD patients appeared to activate greater volumes of brain tissue than controls (Deutsch and Halsey, 1990; Grady et al., 1993). This compensatory recruitment of an increased volume of brain activated by cognitive tasks in AD, compared to normal elderly controls, has been found with varying paradigms (Becker et al., 1996; Woodard et al., 1998; Bäckman et al., 1999). Preliminary results suggest that an activation protocol may be a better predictor of clinical disease severity, and perhaps diagnosis, than resting studies (Pietrini et al., 1999). Combining high-resolution MRI with functional MRI in a hippocampal ROI analysis of elderly controls, elderly with isolated memory dysfunction, and AD patients using a face-encoding task, Small et al. (1999) observed a progressive reduction in hippocampal activation across the three groups, with the AD patients showing the least activation. Future studies should determine which task activates the most eloquent region in predicting incipient AD and what the variability of a given response is for normal and demented populations. With data on the distribution of possible responses in a given anatomical region, single subjects can then be compared to this distribution to determine their risk of ensuing dementia so that therapies may be initiated in the preclinical disease stage. Population data sets such as this will require control over the anatomic variability across the aged and demented brain that modern brain mapping techniques now offer.

III. Summary

The application of brain mapping techniques in dementia is challenged by the disease-related anatomic changes superimposed over the normal morphological variability of the human brain. The structural variability, both normal and disease related, impairs the ability of
Figure 12 Integration of functional imaging, morphology, histology, and biochemistry into a population-based AD Atlas. Nonlinear surfaced-based warping allows the registration of histological and biochemical samples into each patient's high-resolution cryosliced brain volume (Mega et al., 1997; Mega et al., 1999). MRIs acquired during life are the target for registration of the postmortem cryoimage data and are also used to create a continuum-mechanical brain atlas (see Chapter 6) that serves as the space to integrate the multimodal data.

Functional imaging studies that combine individual's data to discern the subtle changes of incipient AD form normal aging. Using nonlinear surface and intensity based warping techniques, combined with novel atlas ing strategies, control over this variability is possible. The future automation and dissemination of current brain mapping techniques promise preclinical detection of AD-specific structural and functional abnormalities on an individual basis. With these powerful population-derived tools, early treatment with disease-modifying agents will significantly decrease the prevalence of AD in the next century.
Acknowledgments

Support for this work was provided by an NIA career development award (K08AG100784) to M.S.M. and by an NIA Alzheimer's Disease Research Center grant (P50 AG16570), an Alzheimer's Disease Research Center of California grant, the Sidell-Kagan Foundation, and the Human Brain Project: NIMH/NIDA (P20MH/I4 52176). NSF (BIR9322434), and NCRR (RR05956, RR13642, and NS38753).

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