Quantitative Analysis of PET and MRI Data in Normal Aging and Alzheimer's Disease: Atrophy Weighted Total Brain Metabolism and Absolute Whole Brain Metabolism as Reliable Discriminators

Abass Alavi, Andrew B. Newberg, Elaine Souder and Jesse A. Berlin

Division of Nuclear Medicine, Department of Radiology, and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania

Average whole brain metabolic rates, when corrected for brain atrophy, are similar between patients with Alzheimer's disease (AD) and age-matched controls. To elucidate the relationship between reduced cognitive function and cerebral metabolism in patients with AD, we hypothesized that the absolute amount of glucose used by the entire brain may prove to be a more reliable indicator of the disease than metabolic rates calculated for a unit of brain weight. Twenty patients with the probable diagnosis of AD and 17 similarly aged controls underwent ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies as well as magnetic resonance imaging (MRI) within a few days of each other. Average metabolic rates, when corrected for atrophy, were 3.91 ± 1.02 and 4.43 ± 0.87 (mg of glucose per 100 cc brain tissue per min ± s.d.) respectively for AD patients and controls. Two other indices were determined, atrophy weighted total brain metabolism (calculated by multiplying the brain volume, determined by MR analysis, by the average metabolic rate) and absolute whole brain metabolism (calculated by multiplying the brain volume by the average metabolic rate corrected for atrophy). The former showed a very significant difference between the two groups (29.96 ± 7.90 for AD patients compared to 39.1 ± 7.0 for controls, $p < 0.001$). Atrophy weighted total brain metabolism also correlated very well with mini mental status exam (MMSE) scores ($r = 0.59$, $p < 0.01$). Absolute whole brain metabolism was significantly different between AD and control groups and correlated well with MMSE. These data demonstrate that although the metabolic rate per unit weight of the brain is unchanged in AD compared to controls, atrophy weighted total brain metabolism and absolute whole brain metabolism are significantly affected. Both indices may prove to be a sensitive correlate for cognitive dysfunction in AD.

J Nucl Med 1993; 34:1681–1687

Magnetic resonance imaging (MRI) and positron emission tomography (PET) have been widely used to investigate changes that occur in the brain in normal aging and in patients with Alzheimer's disease. Specifically, MR images have shown diffuse atrophy of both cortical sulci and ventricular spaces (*1–4*). PET studies have shown widespread hypometabolism, with the parietal lobes being particularly affected bilaterally (*5–15*).

Use of quantitative MRI analysis to obtain actual brain and cerebrospinal fluid (CSF) volumes, in addition to PET, has further enhanced our understanding of structure-function relationship in AD (*2,16,17*). Particularly, we have used volumetric data to "correct" mean whole brain and regional metabolism for brain atrophy (*18–22*). Results show that mean whole-brain metabolic rates, especially after correcting for atrophy, cannot be used to distinguish AD patients from controls (*2,7,19*).

We propose that by combining MRI volumetric data and PET metabolic data, we can calculate atrophy weighted total-brain metabolism and absolute whole-brain metabolism. These values reflect the net metabolic activity for the entire brain and not for mean metabolism averaged over the entire brain.

METHODS AND MATERIALS

Patients

Patients were referred by participating neurologists who specialized in the diagnosis and treatment of dementia. Twenty patients with a presumptive diagnosis of AD were recruited as part of a study designed to determine the effects of aging and dementia on brain structure and function. The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group (*23*) criteria were used by the referring neurologists for the diagnosis of probable AD. Thus, AD was defined as a progressive decline in memory and cognitive function with impairment in at least two areas of cognition and an onset between the ages 40 and 90 yr. Patients were included if results of

Received Dec. 23, 1992; revision accepted May 25, 1993.
For correspondence or reprints contact: Abass Alavi, MD, Div. of Nuclear Medicine, 117 Donner Building, HUP, 3400 Spruce St., Philadelphia, PA 19104.

TABLE 1
Subject Characteristics

Subjects	Age (yr) Mean ± s.d.	Age (yr) Range	Sex Male	Sex Female	MMSE (ave) (mean ± s.d.)
AD patients (n = 20)	64 ± 7	54–79	10	10	22 ± 6
Controls (n = 17)	68 ± 8	52–83	6	11	29.6 ± 0.24

medical history, physical examination and laboratory studies were not indicative of an underlying disease process that could have caused or maintained the dementing illness. The studies involved included a battery of blood tests, an EEG, a carotid Doppler study, MRI and PET. Each subject underwent a mini-mental status exam (MMSE) with a maximum possible score of 30 (normal) and a minimum possible score of 0 (severely demented).

Patients with evidence of any pathologic process that could maintain the dementia (i.e., multi-infarct dementia, Parkinson's disease, markedly abnormal laboratory values, head trauma) were excluded. Patients with mild medical conditions such as asthma, controlled hypertension, osteoporosis, arthritis and cataracts were included in the study. Patients were excluded if they had used any medications recently that could have a meaningful effect on the central nervous system function.

Controls

Control subjects in the same age range as the AD patients were recruited by placing newspaper advertisements in community newspapers. Those that qualified after a telephone screening were invited to present for a detailed history and physical examination. They were excluded if they had a history of any pathophysiological process that could potentially affect cerebral structure or function other than well controlled hypertension and controlled thyroid disease. Controls underwent the same extensive laboratory, neurologic and neuropsychologic testing as did patients. Those controls with mild laboratory abnormalities were included in the study. Controls were excluded if they had any history of neuropsychiatric disease, including head injury, cerebrovascular disease and depression, or a meaningful abnormality on their laboratory exams. The patient and control demographic data are presented in Table 1.

Image Acquisition

MR images were acquired with a 1.5-T unit with a head coil (Signa; GE Medical Systems, Milwaukee, WI). Transaxial slices, 5.0 mm thick, were obtained with a field of view of 20 cm and a pixel size of 0.781 mm. Images were displayed with a 256 × 128 matrix. T2-weighted images (TR/TE = 2,500–3,000/80) and proton density images (TR/TE = 2,500–3,000/20–30) were acquired for each patient. No compensation was made for pulsatile cerebrospinal fluid flow in these studies.

PET imaging was done according to previously used methods (*2*). Briefly, intravenous and intra-arterial catheters were inserted under local anesthesia. The patient's eyes were open, ears were unoccluded and ambient noise was kept to a minimum during the study. Fluorine-18-fluorodeoxyglucose (8 mCi/70 kg) was then injected. Arterial blood samples were initially drawn at short intervals followed by longer intervals after 10–15 min. PET imaging was initiated 40 min after the administration of FDG. Images were obtained with the PET V or Penn PET scanners.

Image Analysis

The MR images were analyzed on a Sun Microsystems workstation (Mountain View, CA). The studies were analyzed using a thresholding/segmentation technique that previously has been reported (*16*). Briefly, thresholds were set for both the proton density and the T2-weighted images. A two-dimensional histogram was obtained that compared each pixel's proton density and T2-weighted intensity. The investigator assigned regions on the histogram to indicate CSF and brain so they could be accurately segmented by the program. Regions were drawn around the total brain and ventricular spaces and divided into left and right sides. Volumes determined were then normalized by dividing by the volume obtained for the total intracranial volume, thus accounting for normal variations in head size. Structures in the posterior fossa were excluded in this analysis. All MR studies were analyzed blindly by an experimenter who was tested for reliability on a standardized set of 10 MR studies. The final values were statistically compared between the control and patient groups.

PET studies were also analyzed on a Sun Microsystems workstation using the PETVIEW program. For Penn PET studies, whole brain regions were hand drawn on the 50% threshold (as determined by the maximum counts in the cortex) on all available slices. For PET V studies, atlas overlays were used to determine both regional and whole brain counts. Whole brain counts were determined by the weighted mean average of the regional values for all available slices. CMRGlc values were determined using arterial glucose concentration curves and were calculated using established techniques (*19*). Recovered whole brain CMRGlc was calculated using all of the counts recovered from the brain during the study and placing them with the whole brain regions as determined by the 50% threshold line.

The uncorrected CMRGlc values were atrophy corrected using the following equation:

$$\text{atrophy corrected CMRGlc} = \frac{\text{mean CMRGlc}}{\text{percentage of brain tissue in the intracranial volume}}.$$

We decided to use two methods to calculate total brain metabolism. In one method, termed atrophy-weighted total brain metabolism, the effect of cerebral atrophy on cerebral metabolism was not corrected for and was calculated using the following equation:

$$\text{atrophy weighted total brain metabolism} = \text{mean CMRGlc} \times \text{brain volume},$$

and is expressed in milligrams of glucose per whole brain per min. Absolute whole brain metabolism, which was corrected for atrophy, was calculated using the following equation:

$$\text{absolute whole brain metabolism} = \text{atrophy corrected mean CMRGlc} \times \text{brain volume},$$

and is expressed in milligrams of glucose per whole brain per min. The final uncorrected, atrophy corrected, atrophy weighted total brain, and absolute whole brain metabolic values were then statistically compared between control and patient groups.

Statistical Analysis

Analysis of variance (ANOVA) was performed on the whole brain CMRGlc values and showed no significant difference between PET V and Penn PET data for the control group. Further,

the difference between patients and controls did not depend on the machine and analysis method. Thus, the combined data are shown for whole brain CMRGlc values.

Mean volumetric and metabolic values from the two groups were compared using the independent sample Student's t-test. To ensure that possible violations of the assumptions of the ANOVA models (e.g., variables that were not normally distributed) did not influence results, the nonparametric equivalent to the t-test, the Wilcoxon rank-sum test, was also performed. The analysis of covariance (ANCOVA) was used to compare means across groups while adjusting for minor imbalances in the age and sex composition of the groups. Spearman's rho, a nonparametric correlation coefficient, was computed to examine the association between the CMRGlc values and brain volumes, and the MMSE.

All p-values presented are two-sided. Differences and correlations with p-values < 0.05 were considered statistically significant.

RESULTS

Results from the Wilcoxon test and the ANCOVA models agreed closely with the t-test results, so that only the t-test findings are reported. Whole brain ventricular, sulcal and total CSF volumes were significantly increased ($p < 0.01$) in AD patients compared to controls (see Fig. 1 and Table 2). Compared to control subjects, in AD patients the total CSF was increased 43.4%, ventricular volume was increased 62.5% and sulcal CSF volume was increased 39.3%.

In AD patients, CMRGlc values, when uncorrected for brain atrophy (Table 3), were significantly decreased compared to controls (values of 3.15 and 3.83 respectively, $p = 0.01$). However, corrected CMRGlc values in AD patients were not significantly decreased compared to controls (values of 3.91 and 4.43 respectively, $p = 0.11$). In contrast, AD patients showed a highly significant decline in atrophy weighted total brain metabolism compared to controls (with values of 29.96 and 39.09 respectively, $p = 0.0008$). AD patients also had significantly different absolute whole brain metabolic values compared to controls (with values of 37.24 and 45.09 respectively, $p = 0.014$).

Recovered CMRGlc values, but uncorrected for brain atrophy (Table 4), were not significantly decreased when AD patients were compared to controls (values of 4.89 and 5.38 respectively, $p = 0.17$). This differed from unrecovered (ROI-based) values which did show a significant difference in whole brain CMRGlc values. Recovered atrophy corrected CMRGlc values were also not significantly decreased in AD patients compared to controls (values of 6.06 and 6.22 respectively, $p = 0.78$). Again, AD patients did have a significant decrease in recovered atrophy weighted total brain metabolism compared to controls (with values of 46.61 and 55.23 respectively, $p = 0.026$). Interestingly, recovered absolute whole brain metabolism was not statistically different when compared to controls (with values of 57.86 and 63.73 respectively, $p = 0.18$).

All CSF volumes and metabolic values were compared to MMSE in patients with AD. The results of these comparisons are shown in Table 5. No volumetric data correlated significantly with MMSE in our study. Although the small negative correlations suggested slight trends of decreasing MMSE with increasing CSF volumes, significant correlations were only noted for metabolic values for both recovered and unrecovered. Moreover, atrophy weighted total brain metabolism significantly correlated with MMSE in both recovered and unrecovered values (Spearman rho of 0.49 and 0.59 respectively). Absolute whole brain metabolism also correlated similarly with MMSE. Unrecovered metabolic values had a higher correlation with MMSE than recovered values for all indices.

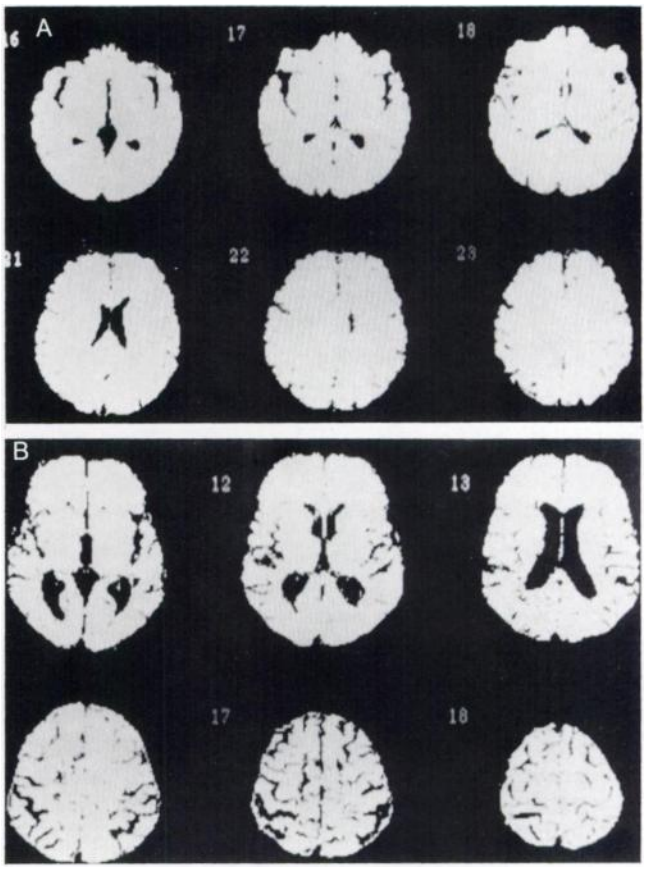

FIGURE 1. Control subject MRI pixel representation of brain tissue (A), generated by the segmentation program slightly below, at, and slightly above the lateral ventricles. Note the large ventricular and sulcal sizes (shown in black) in the AD patient MRI pixel representation of brain tissue (B) in comparison to those in the control subject.

TABLE 2
AD and Controls Total, Ventricular and Sulcal Volume*

	Total CSF (mean ± s.d.)	Ventricular CSF (mean ± s.d.)	Sulcal CSF (mean ± s.d.)
AD patients	19.5 ± 3.2†	3.9 ± 1.9†	15.6 ± 3.0†
Controls	13.6 ± 2.8	2.4 ± 1.0	11.2 ± 2.9

*Expressed as a percentage of total intracranial volume.
†Significantly different than controls, $p < 0.01$

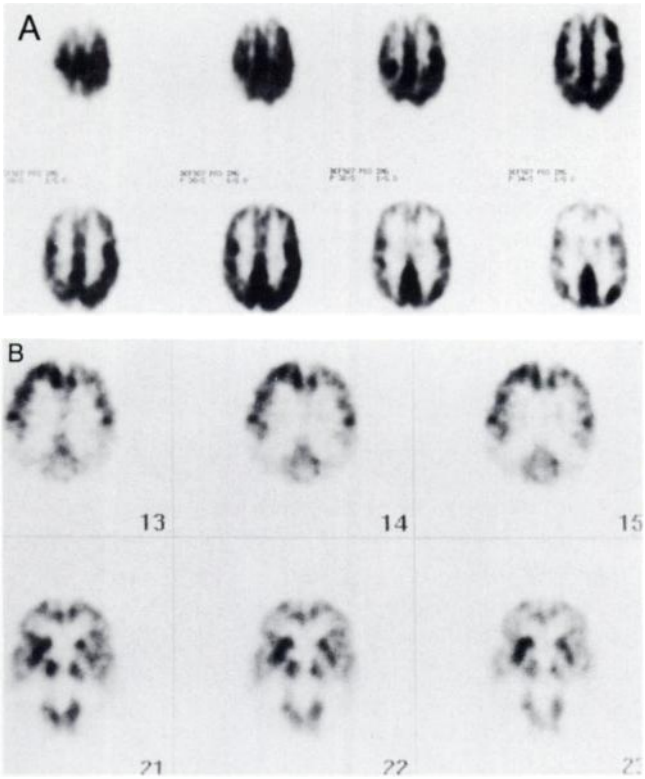

FIGURE 2. Control subject PET image (A) showing normal metabolism that is relatively evenly distributed throughout all brain regions. There is, however, minimal reduction in frontal lobe metabolism, which is consistent with normal aging. This is in comparison to the marked hypometabolism seen in the AD patient PET image (B), particularly in the parietal region.

DISCUSSION

We compared the MR volumetric analysis, PET metabolic values and a combination of MRI and PET data to determine which of these approaches might best distinguish AD patients from controls.

The MR volumetric data in this study corroborated those from an earlier study conducted by our group (*2*). In both studies, AD patients had significantly increased CSF volumes in the sulci, the ventricles and the combination of the sulci and ventricles (the increases observed in this current study were 39.3%, 62.5% and 43.4% respectively, $p < 0.01$). However, there has been some controversy in the literature, in studies using MRI or CT, regarding the extent of CSF expansion in AD patients compared to controls as well as the correlation between CSF changes and the neuropsychiatric findings (*24–33*), specifically with the MMSE scores. We found no significant correlations between CSF volumes and MMSE scores. Thus, while quantitative volumetric analysis may distinguish AD patients from controls, it fails to explain the extent and severity of the disease. Further, the fact that there was significant expansion of the ventricles, (increased 62.5% compared to controls) suggests that brain atrophy is the result of a longstanding process with significant loss of white matter, even in mildly demented patients (as in this study).

When whole brain CMRGlc values (as determined by PET) were used, several interesting findings were noted comparing AD patients and controls. Whole brain CMRGlc values (uncorrected for atrophy and unrecovered) were found to be significantly decreased compared to controls (3.15 and 3.83 respectively, $p = 0.01$). This contrasts somewhat with the results reported earlier by our group (*2*) in which no significant difference was found (e.g., AD patient values were 3.11 and controls 3.61). Similar conflicting data have also been noted in differing results by other groups (*8,9,34,35*).

When recovered whole brain CMRGlc values (uncorrected for atrophy) were compared, there was no significant difference between the values for AD patients and controls (4.89 and 5.38 respectively, $p = 0.17$). Despite the fact that the recovered whole brain CMRGlc value incorporates the entire metabolic activity in the brain (in contrast to the unrecovered values which are measured using the ROIs), the results indicate that recovered whole brain CMRGlc might not represent a good marker for distinguishing AD patients from controls.

When CMRGlc values are corrected for brain atrophy, it also fails to distinguish AD patients from controls. In this study, we found no significant difference between AD patients and controls when comparing the atrophy corrected CMRGlc values. Further, this inability to distinguish the

TABLE 3
Whole Brain PET Data for AD and Controls

	CMRGlc (uncorrected) (mean ± s.d.)	CMRGlc (corrected) (mean ± s.d.)	Atrophy weighted total brain metab (mean ± s.d.)	Absolute whole brain metab (mean ± s.d.)
AD patients	3.15 ± 0.83*	3.91 ± 1.02†	29.96 ± 7.90‡	37.24 ± 9.65§
Controls	3.83 ± 0.70	4.43 ± 0.87	39.09 ± 7.02	45.09 ± 8.52

*Significantly different from controls, $p = 0.01$.
†Not significantly different from controls, $p = 0.11$.
‡Significantly different from controls, $p = 0.0008$.
§Significantly different from controls, $p = 0.014$.
CMRGlc values in mg glucose/100 cc/brain tissue/min; atrophy weighted total brain metabolism values in mg glucose/brain/min; and absolute whole brain metabolism values in mg glucose/brain/min.

TABLE 4
Recovered Whole Brain PET Data for AD and Controls

	Recovered CMRGlc (uncorrected) (mean ± s.d.)	Recovered CMRGlc (corrected) (mean ± s.d.)	Atrophy weighted total brain metab (mean ± s.d.)	Absolute whole brain metab (mean ± s.d.)
AD patients	4.89 ± 1.22*	6.06 ± 1.48†	46.61 ± 12.24‡	57.86 ± 14.89§
Controls	5.38 ± 0.88	6.22 ± 1.07	55.23 ± 9.82	63.73 ± 10.07

*Not significantly different from controls, p = 0.17.
†Not significantly different from controls, p = 0.72.
‡Significantly different from controls, p = 0.026.
§Not significantly different from controls, p = 0.18.
CMRGlc values in mg glucose/100 cc brain tissue/min; Atrophy weighted total brain metabolism values in mg glucose/brain/min; and absolute whole brain metabolism values in mg glucose/brain/min.

two groups was found in both recovered and unrecovered values. This is in agreement with earlier reports by our group in which there was no significant difference found in atrophy corrected CMRGlc values between AD patients and controls (*2*).

Findings from this and previous analyses clearly indicate that the brain volume is significantly decreased in patients with AD, even in the early stages of the disease. Similarly, there is a significant reduction in CMRGlc values regionally (parietotemporal lobes and, to some extent, the frontal lobe) and to a lesser extent in the whole brain. However, when corrected for brain atrophy, CMRGlc for the average substance of the brain is not significantly different between AD and control subjects. We, therefore, decided to measure the atrophy weighted total brain metabolism and absolute whole brain metabolism (rather than the mean whole brain metabolism) as a means of distinguishing the AD from control state. We hypothesized that metabolic abnormalities of the brain precede structural changes. However, by the time most patients are diagnosed as having AD, most will have developed a significant degree of brain atrophy. Therefore, by combining the anatomic data for the entire brain with the metabolic measures provided by PET, we may be able to determine the effects of the disease on the brain.

TABLE 5
Spearman Correlations Between MMSE and Other Variables

Variable	Spearman Rho	p-value
Total CSF volume	−0.23	0.35
Total ventricle volume	−0.30	0.22
Total sulcal volume	−0.17	0.50
Whole brain metabolism	0.60	0.01
Corrected whole brain metabolism	0.53	0.02
Rec. whole brain metabolism	0.51	0.03
Corr. Rec. whole brain metabolism	0.48	0.04
Atrophy weighted whole brain metabolism	0.59	0.01
Atrophy weighted whole brain metabolism	0.49	0.04
Absolute whole brain metabolism	0.59	0.01
Abs. Rec. Whole brain metabolism	0.51	0.03

Atrophy weighted total brain metabolism was calculated by multiplying the whole brain volume by the mean whole brain CMRGlc. This value was found to be highly significant in distinguishing AD patients from controls. Unrecovered atrophy weighted total brain metabolic values showed a much greater difference between AD patients and controls than the uncorrected or corrected, recovered or unrecovered mean CMRGlc values. The unrecovered atrophy weighted total brain metabolism for AD patients had a mean value of 29.96 compared to controls which had a mean of 39.09 (p = 0.0008). The recovered atrophy weighted total brain metabolism values also distinguished AD from controls (values of 46.61 and 55.23 respectively, p = 0.026), although there were no significant differences in the recovered (atrophy corrected or uncorrected) mean CMRGlc values. Unrecovered absolute whole brain metabolism showed a highly significant difference between AD and controls, recovered absolute whole brain metabolism did not show a significant difference between the groups. These results suggest that the combination of volumetric and metabolic data might yield a very sensitive marker for distinguishing AD from controls. Further, atrophy weighted total brain metabolism appears to be better than absolute whole brain metabolism (or mean CMRGlc values) at distinguishing AD from controls.

To determine if a correlation existed between volumetric or metabolic values and severity of disease in AD patients, we compared these quantitative measurements with the MMSE scores. The CSF volumes showed no significant correlations with MMSE. Reports from other groups have revealed inconclusive results with regard to this correlation (*28,32,33*). However, all metabolic values obtained in this study showed a significant correlation with MMSE. This has also been shown by other investigators, particularly in the relationship between regional CMRGlc values in the parietal and temporal lobes and neuropsychological deficits (*4,11,35,36–41*). Even the corrected, recovered CMRGlc, which failed to distinguish AD patients from controls, had a significant correlation with the MMSE scores. However, the strongest correlations were seen between unrecovered values and MMSE scores. Further, both the atrophy

weighted total brain metabolism and the absolute whole brain metabolism had significant, high correlations with MMSE suggesting that both of these indices might reflect cognitive dysfunction.

The results from this study indicated that CSF volumes can distinguish AD patients from controls, but do not correlate well with the severity of the disease. Mean whole brain metabolism rates (recovered or unrecovered) cannot distinguish AD patients from controls, but correlate well with severity of the disease. Absolute whole brain metabolism correlates well with MMSE, but is a suboptimal index for distinguishing AD from controls when recovered values are considered. However, atrophy weighted total brain metabolism, which combines both volumetric and metabolic data is not only a very strong marker for distinguishing AD patients from controls (for both recovered and unrecovered values), but also correlates highly with the severity of the disease.

We further suggest that atrophy weighted total brain metabolism might be the best marker for AD early in the course of the disease, before significant atrophy or hypometabolism occurs. Also, atrophy weighted total brain metabolism might correlate very well with more specific neuropsychiatric parameters other than MMSE. Finally, as it becomes possible to determine regional brain volumes, absolute and atrophy weighted regional metabolic activity may prove quite useful not only for distinguishing AD patients from controls (by examining, for example, the parietal lobes), but for helping determine severity of the disease, as well as correlating with specific neuropsychiatric deficits. The latter approach is currently being pursued in our laboratory.

ACKNOWLEDGMENTS

This work was supported by a National Institute of Health grant NIH AG 03934-10; a fellowship from the National Institute of Mental Health (5-T32-MH-18902); the Benjamin and Mary Siddons Measey Foundation to Andrew Newberg; and MRRC grant P30 HD26979 from the NICHD.

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