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Authors
Valladares-Neto, Dirceu C
Buchsbaum, Monte S
Evans, James
et al.

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EEG Delta, Positron Emission Tomography, and Memory Deficit in Alzheimer's Disease

Dirceu C. Valladares-Neto[a]
Monte S. Buchsbaum[b]
W. James Evans[c]
Dorothy Nguyen[d]
Patricia Nguyen[d]
Benjamin V. Siegel[b, e]
Jill Stanley[d]
Arnold Starr[c]
Steven Guich[d]
Daniel Rice[f]

[a] Fundação Hospitalar do Estado de Minas Gerais, Brazil;
[b] Department of Psychiatry, Mt. Sinai School of Medicine, New York, N.Y.; Departments of
[c] Neurology and
[d] Psychiatry and Human Behavior, University of California at Irvine, Calif.;
[e] Psychiatry Service, Department of Veterans Affairs Medical Center, Bronx, N.Y.;
[f] Ethel Percy Andrus, Gerontology Center, University of Southern California, Los Angeles, Calif., USA

Key Words
Dementia
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Temporal lobe

Abstract
Quantitative scalp EEG from 32 channels and the cerebral glucose metabolic rate from the 32 underlying cortical positions as assessed by positron emission tomography (PET) with ^{18}F-2-deoxyglucose (FDG) were obtained on 36 patients with mild to moderate senile dementia of the Alzheimer type and 17 age- and sex-matched normal control subjects. Subjects performed a verbal memory task during uptake of FDG. There were significant correlations between both delta amplitude and metabolic rate and memory performance during FDG uptake. Patients with Alzheimer's disease had significantly greater left temporal delta amplitude and lower glucose metabolic rates. Both EEG delta in microvolts and metabolic rate had similar diagnostic sensitivity, but PET had fewer false positives among normals. The left amygdala had the highest sensitivity and percent correct diagnosis of any brain area. Temporal lobe EEG delta activity showed higher correlations with hippocampal metabolic rate than metabolic rate directly under the electrode.

Introduction

Neuropathological studies of patients with Alzheimer's disease have generally identified the characteristic lesions in the medial regions of the temporal lobe: the hippocampus and entorhinal cortex [1, 2]. It has been suggested that the disease may originate in the medial temporal regions [reviewed in 3] and spread transsynaptically to the lateral temporal lobe and subsequently to parietal and frontal areas. However, brain imaging studies with EEG and SPECT have generally focused on lateral temporal and parietal differences. The increased delta and theta activities are widespread across the cortex but tend to be greatest in the temporal leads [4]. Changes in the left lateral temporal lobe EEG slow activity may appear in nondemented elderly with verbal memory deficits [5] suggesting that quite early change may appear in the EEG. While single photon emission computed tomography and posi-

M.S. Buchsbaum
Department of Psychiatry, Mt. Sinai School of Medicine
1 Gustave Levy Place
Box 1505
New York, NY 10029–6574 (USA)

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tron emission tomography (PET) studies have greater spatial resolution and spatial certainty, these results have also shown widespread cortical metabolic decreases in frontal and parietal [6] and temporal regions. Even incipient patients with quite mild dementia showed lateral temporal and parietal metabolic decreases [7]. However, most studies had small sample sizes and failed to control cognitive activity during the tracer uptake. When subjects performed a verbal memory task [8], more localized decreases in the temporal lobe were observed; with an olfactory memory task, the region of the parahippocampal gyrus showed decreases [9]. However, lateral temporal differences also appeared in this study.

If Alzheimer's disease uniformly begins in small regions of the medial temporal lobe, PET with its spatial resolution should reveal the greatest sensitivity and specificity as a diagnostic tool. However, if multifocal or global cortical change appears early or at the same time as clinical symptoms, measures of the cortical surface such as EEG should be equally sensitive. Since EEG and PET studies are typically performed in different patients, no direct comparison of regional metabolism and EEG has yet been available to assess the regional specificity of the methods.

The present study addresses this problem by undertaking EEG and ^{18}F-2-deoxyglucose (FDG) PET studies in 36 patients and 17 controls who performed a verbal memory task during the uptake of FDG for positron emission tomography scanning. This makes a direct comparison of the diagnostic sensitivity and specificity of the two measures and allows correlations between the measures to be examined.

Subjects and Method

Subjects

Thirty-six right-handed patients with probable Alzheimer's disease (18 women, 18 men, mean age = 73 ± (SD) 9.4) and 17 normal controls (9 women, 8 men, mean age = 70 ± (SD) 6.8) participated in the study. All patients had a Mini-Mental State Examination score (MMSE) [10] of at least 12 (range 12–26, mean = 19.3 ± 4.5), a Global Deterioration Scale rating from 3 to 5 and met the NINCDS-ADRDA Work Group criteria [11] for Alzheimer's disease. The Hamilton Rating Scale for Depression [12] was also obtained (mean = 4.6 ± 4.3). The patients with Alzheimer's disease were divided into mild (MMSE >19) and severe (MMSE <20) subgroups by the median value (MMSE = 19) of the Folstein MMSE scores.

Controls were screened to include only those without neurological or psychiatric disorders, epilepsy and previous head injury; most were the spouses of the patients. The MMSE scores ranged from 23 to 29 (mean = 26.8 ± 2.0). All subjects had not received any psychoactive medication for a minimum of 30 days before the study.

Subjects received a semi-structured diagnostic psychiatric interview, neuropsychological tests, physical examination, MRI, and PET scans. Subjects were excluded if MRI showed evidence of cortical infarctions or subcortical lacunar lesions >4 mm diameter. We also screened for heavy metals (serum lead, magnesium, copper, mercury; urine lead, mercury), arsenic (serum, urine), antinuclear antibodies, bromide, serum folic acid, vitamin B_{12}, rheumatoid factor, syphilis (hemagglutinin, RPR screen), alpha, beta and gamma globulins, and thyroid function (T_3 uptake, T_4 and TSH).

EEG Recording

All recordings were made in the morning, in a sound attenuated, electrically shielded, and darkened room, with the patient reclining at a 45° angle, and resting his head so as to minimize neck muscle tension. Recordings were made 5–10 min before the injection of FDG. The patient was instructed to keep his eyes closed throughout the session and to remain as relaxed as possible. Three 38-second periods of EEG were recorded. The record was interrupted and the patient was asked to keep a relaxed state of wakefulness if he or she evidenced drowsiness or excessive movement. Electrodes were placed on 32 positions over the scalp surface, using the International 10–20 system plus 10 extra leads [13].

The 32 channels were computed as an average reference recording after analog-to-digital conversion. All analyses were performed on average reference data.

EEG Computer Analysis

Data were collected with an on-line computer system. EEG activity for spectral analysis was filtered through 0.5-Hz high-pass and 50-Hz low-pass filters with 3 dB/octave rolloffs, digitized for each channel at 118 Hz, and recorded in 1.75-second blocks (207 points/block). All 32 leads for each epoch were visually inspected for eye blinks, eye movements, and other movement artifacts as established by previous EEG topographical studies [14]. Any 1.75-second epoch containing artifacts was eliminated from analysis. At least 18 artifact-free epochs per subject were included in the appraisal. The amplifiers were calibrated by recording a 10-Hz standard signal through all channels and determining the calibration factor for each channel. Before analysis each channel was proportionally adjusted. Piecewise quadratic interpolation was performed on the original 207-point 1.75-second epochs to transform them into 256-point 1.75-second epochs by a cosine bell. A standard fast-Fourier transform was applied to each of the artifact-free 1.75-second epochs in a recording; and the power estimates were computed at 0.57-Hz steps. The transform yielded a value representing the average magnitude, expressed in microvolts (square root of power). This was calculated as the square root of the sums of squares across the 0.57-Hz steps and generated the sine wave equivalent in microvolts. The bandwidths for each frequency were: delta, 0.57–3.99 Hz; theta 4.57–7.41 and alpha, 7.98–13.11.

PET Scanning

Before PET scanning, an individually molded, thermostatic plastic head holder was made for each subject, to minimize head movement. For the PET procedure, subjects were seated in a darkened isolation room. An intravenous line of 0.9% saline drip was inserted into the subject's left arm for blood sampling and another into the right arm for injection of the labeled glucose. The left arm was wrapped in a hot pack for arterialization of venous blood. All subjects used the right hand, whose movements were unrestricted, to perform

the task. All subjects were instructed on the memory task before injection time and were given practice trials to ensure their comprehension of the task. Two to three minutes before the FDG injection (4–5 mCi), room lights were extinguished and visual stimuli began; the stimuli continued for 30–35 min after the injection of the radionuclide. Subjects were continuously observed to ensure adherence to the instructions. Brief verbal encouragement was given and their hands were replaced on the keyboard in some cases. After 30–35 min of FDG uptake, the subject was transferred to the adjacent scanning room. Nine planes (CTI NeuroECAT) at 10-mm increments and parallel to the canthomeatal line were done between 45 and 100 min after FDG injection.

Scans were performed with both septa and shadow shields in, a configuration with measured in-plane resolution of 7.6 and 10.9 mm resolution in the z-dimension (axial). A calculated attenuation correction and smoothing filter were used. The scanner was calibrated each scan day, with a cylindrical phantom, and compared with well-counter data.

PET Task

Words from a 150-item word list were presented on a CRT monitor for 300 ms at 3-second intervals. Each word was presented a first time and subsequently repeated within a 6- to 18-second delay. All words were thus presented as novel (initial presentation) and familiar (second presentation) items. The subject's task was to distinguish novel and familiar stimuli and press one key with the index finger for 'novel' and another key with the ring finger for 'familiar' stimuli. Response times longer than 2 s were counted as errors.

Scan Slice Selection and Processing

Scans were transformed to glucose metabolic rate as described elsewhere [15]. Thirty-two cortical regions of interest corresponding to each electrode position were measured using a stereotaxic method based on patient MRI with electrodes described elsewhere [16], and 126 subcortical structures were assessed using stereotaxic coordinates [17] derived from a standard neuroanatomical atlas [18]. The validity of cortical peel techniques used here has been supported in recent reviews [19]. Regional glucose use was expressed in two ways, as absolute glucose metabolic rate (GMR) in μmol/100 g/min, and as relative GMR (ratio of regional GMR to whole brain mean GMR for surface cortical structures and to whole scan slice mean GMR for subcortical structures).

Statistical Analysis

We compared the EEG amplitudes at each electrode and PET metabolic rate in the cortex underlying each electrode in patients, mild and severe, and controls with multivariate analysis of variance (MANOVA) followed by t tests [20]. The group comparison MANOVA had one independent group factor (controls, patients) and three repeated measures factors, hemisphere (left, right), anteroposterior electrode position and lateral/medial electrode position. The disease severity contrast (MMSE mild vs. severe) MANOVA had one independent group factor (severity) and three repeated measures factors, hemisphere (left, right), anteroposterior electrode position and lateral/medial electrode position. These values were obtained by sampling 20 electrodes out of the original 32 and forming a 5 by 4 grid, as seen in table 1 [21].

We computed the product-moment correlation coefficients between regional metabolic rate or EEG and neuropsychological task performance as an exploratory analysis. Diagnostic sensitivity obtained with EEG and PET measures was compared using the method of Kalter et al. [23].

Table 1. Grid of electrodes used in the MANOVA

Anterior/Posterior	Hemisphere			
	left		right	
	lateral	medial	medial	lateral
1	F7	F3	F4	F8
2	T3	C3	C4	T4
3	TT1	TCP1	TCP2	TT2
4	T5	P3	P4	T6
5	O1	PO1	PO2	O2

As a further analysis more sensitive to focal topographical effects, the MANOVA was repeated for all the frequencies using values normalized with a Z-transformation to correct for a possible multiplicative effect produced by differences in source strength [22] and to eliminate differences due to overall reduction in EEG power. This was done by reexpressing the values of each one of the 32 leads as (lead value – mean of 32 leads)/standard deviation of 32 leads. The same transformation was applied to glucose metabolic rate values.

Topographic Mapping

Surface density maps of the entire scalp were created from all the statistically significant values using a 4-nearest neighbor interpolation algorithm described eleswhere [13].

Results

Electroencephalography

The Alzheimer group showed greater normalized delta activity than controls, in both the left lateral area and in the right medial area. There was a reduction of normalized delta activity in the lateral right areas which decreased even more with the severity of the disease. In the mildly affected group, the normalized delta had its values slightly reduced in the left midline areas while the severe group displayed the same values as the control group (table 2). The order of p values for significant post-hoc t tests ($p < 0.05$), for normalized delta waves between patient group and controls, was T6 ($p < 0.05$), PO2 ($p < 0.03$), TT1 ($p < 0.02$) and P4 ($p < 0.01$) as seen in figure 1. The severe patient group showed higher delta than the mild patient group at TT1 ($p < 0.02$) and O2 ($p < 0.04$) while reduced at T6 ($p < 0.01$).

Delta amplitude in microvolts (table 3) was higher across all leads in the patients (mean = 62.4 ± 26.4) than in the controls (mean = 47.0 ± 9.9) by MANOVA ($F = 6.86$, d.f. = 1,50, $p = 0.01$). Also, the severe Alzheimer

Table 2. Normalized delta activity in Alzheimer's disease (mean ± SD)

	Normal controls		Mild Alzheimer's		Severe Alzheimer's	
	lateral	medial	lateral	medial	lateral	medial
Left	0.37±0.87	−0.54±0.90	0.44±0.97	−0.59±0.71	0.56±0.84	−0.50±0.95
Right	0.53±1.03	−0.71±0.84	0.32±0.84	−0.62±0.63	0.04±0.84	−0.44±0.94

MANOVA, diagnostic group × hemisphere × lateral/medial, F = 7.91, d.f. = 2, 46; p = 0.001.

Table 3. EEG delta activity in Alzheimer's disease (mean ± SD)

	Controls		Mild Alzheimer's		Severe Alzheimer's	
	Lat	Med	Lat	Med	Lat	Med
S1	59.4±11.8	45.3±9.2	75.2±25.0	55.2±20.5	83.1±27.7	69.5±29.3
S2	48.0±8.0	37.4±4.5	60.0±21.9	47.5±19.6	70.9±24.1	55.6±20.7
S3	44.8±7.5	41.7±14.4	56.4±23.0	52.6±23.3	68.0±22.8	63.6±25.4
S4	48.7±9.8	40.6±5.8	60.5±25.6	51.3±20.0	68.2±23.8	64.4±27.5
S5	52.4±10.0	45.7±5.5	65.1±28.8	59.1±23.1	73.2±28.5	72.1±30.8

MANOVA, anteroposterior × lateral/medial × severity F = 2.20, d.f. = 8, 86.00, p = 0.04, severity F = 5.67, d.f. = 2, 46, p = 0.0063, hemisphere × lateral/medial × severity F = 5.50, d.f. = 2, 46, p = 0.07.

Table 4. Normalized glucose in Alzheimer's disease (mean ± SD)

	Normal controls		Mild Alzheimer's		Severe Alzheimer's	
	Lat	Med	Lat	Med	Lat	Med
S1	0.73±0.08	1.18±0.12	0.64±0.15	1.17±0.17	0.75±0.25	1.00±0.23
S2	1.08±0.09	1.25±0.13	1.05±0.14	1.35±0.17	1.04±0.17	1.28±0.21
S3	1.14±0.08	1.15±0.09	1.12±0.09	1.18±0.14	1.16±0.17	1.13±0.22
S4	1.12±0.07	1.08±0.16	1.10±0.12	1.10±0.16	1.05±0.20	1.17±0.29
S5	1.15±0.08	1.13±0.13	1.17±0.15	1.10±0.17	1.09±0.16	1.07±0.22

MANOVA, anteroposterior position × lateral/medial × severity, p = 0.003 F = 3.58, d.f. = 5.6, 132.

Table 5. Absolute glucose under the electrodes in Alzheimer's disease (mean ± SD)

	Normal controls		Mild Alzheimer's		Severe Alzheimer's	
	Lat	Med	Lat	Med	Lat	Med
S1	14.2±2.8	23.2±3.7	10.6±3.2	18.2±5.3	8.9±4.9	11.2±5.7
S2	21.2±4.2	24.5±3.8	16.7±4.0	21.4±5.3	11.9±4.8	14.4±6.7
S3	22.5±4.1	22.7±4.2	17.9±3.9	18.4±5.1	13.2±5.3	12.9±5.0
S4	22.1±4.0	21.2±4.0	16.8±4.0	17.9±5.4	12.0±5.1	13.7±6.9
S5	22.7±4.1	22.1±3.9	17.5±4.6	17.4±3.9	12.6±4.9	11.5±4.7

MANOVA, anteroposterior position × lateral/medial position × severity F = 6.5, d.f. = 5.8, 135, p < 0.001.

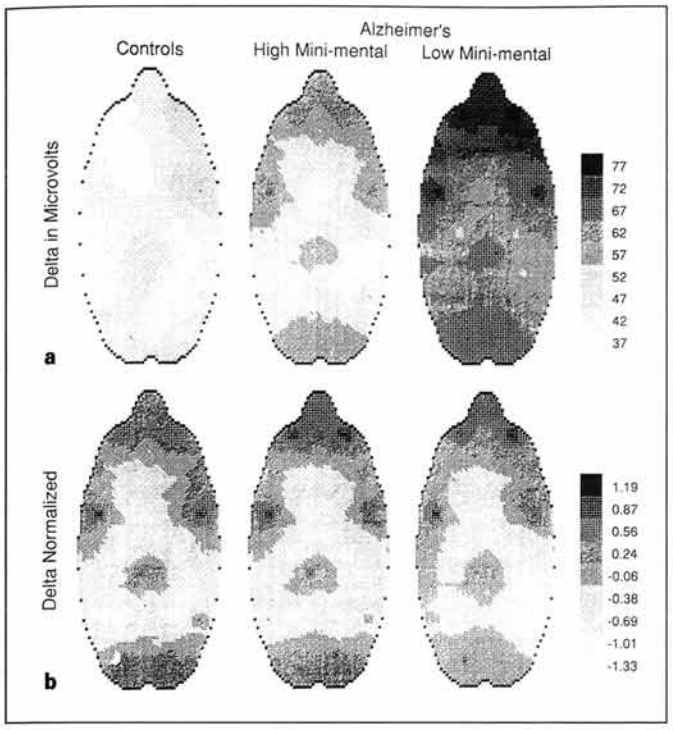

Fig. 1. EEG delta activity in controls and patients with Alzheimer's disease. EEG activity shown in microvolts (**a**) and normalized (**b**to a mean of zero and standard deviation of 1.0 across the scalp. Microvolt maps show general increase in delta activity with severity of illness. Normalized maps indicate relatively increased left temporal delta and decreased occipital activity.

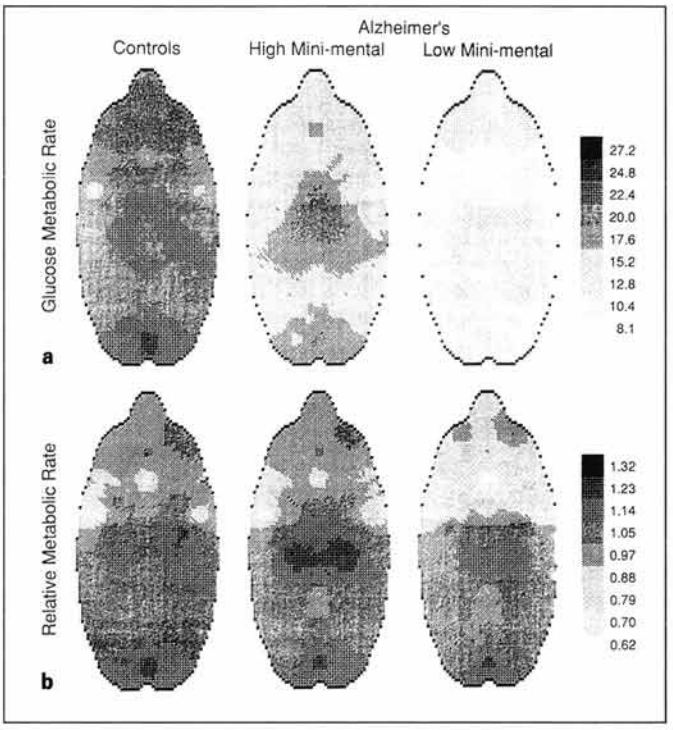

Fig. 2. Glucose metabolic rate at brain underlying scalp electrode points. Metabolic activity is shown as in figure 1 with absolute metabolic rate (**a**) and relative metabolic rate (**b**). Metabolic rate shows general decrease with severity of illness. Relative map shows frontal and temporal relative decrease. Apparent decreases of metabolic rate at right frontal lead locations (Fp2) in low mini-mental score group parallel increased relative delta at this location (fig. 1b left). This suggests that the delta change is not entirely attributable to incomplete removal of eye movement artifact since this lead location is not immediately under the frontal eye fields.

patients presented higher delta (mean = 68.9 ± 26.7) compared with the mild ones (mean = 58.3 ± 24.1).

The Alzheimer and the control groups did not show a different pattern of normalized theta activity. However, the theta amplitude in microvolts was higher for patients (mean = 82.2 ± 45.7) than for controls (mean = 44.7 ± 20.3; MANOVA, F = 12.28, d.f. = 1,50, p = 0.001), but no regional differences were confirmed.

Positron Emission Tomography

PET analysis was carried out exactly as in the EEG procedure with 32 cortical regions. Patients with Alzheimer's disease showed lower normalized lateral metabolic rates than controls especially for temporal and parietal regions (fig. 2, table 4). The Alzheimer group also displayed lower absolute metabolic rates (15.8 ± 6.4) as compared with controls (22.7 ± 5.4; F = 23.6, d.f. = 1,51, p = 0.00001, see table 5). GMR values were lower within the severe group (12.6 ± 5.8) than in the mild patient group (18.4 ± 5.9). Again this was most marked for lateral and posterior brain areas (table 5).

Comparison of Diagnosis Sensitivity and Specificity of EEG and PET

Absolute delta amplitude in microvolts and glucose metabolic rate in micromoles/100 g/min had similar sensitivity and specificity and followed the MANOVA in showing lateral regions superior to medial (table 6). Surprisingly, relative measures showed much lower sensitivity and specificity, indicating the greater diagnostic usefulness of global cortical measures for the disease. While it is of theoretical interest that absolute metabolic rate in the left amygdala had the greatest sensitivity (71%) of any area of the brain considering both EEG and PET, normalized and absolute, this value did not actually differ significantly from most other PET and EEG locations when tested statistically with the method of Kalter et al. [23]. This sensitivity was the same for the contrast of controls with the mild severity subgroup (sensitivity 72%). Both

Table 6. Percent diagnostic sensitivity and specificity

	Lateral				Medial			
	sensitivity		specificity		sensitivity		specificity	
	EEG	glucose	EEG	glucose	EEG	glucose	EEG	glucose
Absolute								
Left	66	69	76	94	71	69	76	88
Right	60	77	76	94	66	71	88	94
Relative								
Left	54	54	59	65	49	49	53	41
Right	43	54	35	65	60	51	65	53

EEG and PET detected about 70% of the patients correctly and identified only 6–20% of normals as having the disease. The best EEG leads were F3 and F7 (sensitivity = 69%). If there was any advantage of PET over EEG it was for specificity; few normals had as low absolute glucose as the patient group.

PET FDG Uptake Task

The Alzheimer group showed poorer verbal memory performance during glucose uptake than the control group, but no difference in reaction time (table 7). While performance was poorer, no significant difference in reaction time was observed, consistent with the cooperation and motivation observed in the subjects.

Correlations of EEG Activity and GMR with Neuropsychological Performance

Task performance on the recognition of new (previously unviewed) words during the FDG uptake was correlated with both EEG delta and metabolic rate. For absolute data (EEG in microvolts and metabolic rate in micromoles/100 g/min) this correlation was present widely across the scalp and cortical surface and reached $p < 0.05$ at nearly every location. Low delta and high metabolic rate were correlated with good performance. Hippocampal correlations were not significant. No significant correlations were seen for the Hamilton Rating of Depression, suggesting that depression symptomatology was not an important determinate of either EEG or PET change. Relative data showed a more focal distribution of significant correlations between metabolism and task performance with only the temporal (for T3, T5, T6, r = 0.04, 0.36, 0.45, respectively), frontal (Fz, F3, F4, FC, r = 0.47, 0.41, 0.51, 0.50) and right occipital (O2, r = 0.39) areas showing $p < 0.05$. Relative metabolic rate correlations for the right and left hippocampus (r = −0.52, −0.38) and amygdala (r = −0.37, −0.34) with task performance were all significant and negative. For relative delta, parietal (PO1, −0.42) and frontal (F4, −0.37) were $p < 0.05$; positive correlations were observed at T6 (r = 0.40) and O2 (r = 0.45).

Table 7. Verbal memory task performance during glucose uptake (% correct)

	Alzheimer's	Normal controls	p	t
Novel words	45.5 ± 19.7	90.6 ± 11.9	0.000	7.86
Familiar words	40.9 ± 15.7	81.4 ± 31.8	0.000	7.38
Latency, ms reaction time	937 ± 237	839 ± 126	0.13	1.56

Correlations between EEG Delta and Cortical Surface Metabolic Rate with Hippocampal Metabolic Rate

EEG delta was more highly correlated with hippocampal metabolic rate than with metabolic rate assessed directly under the EEG electrode position (table 8).

Discussion

Delta Amplitude and Metabolic Rate

Patients with Alzheimer's disease were found to have greater delta activity and lower metabolic rates across the entire cortex. Regional analysis showed that this effect is greatest in the left lateral part of the cortex and progressively greater in more severely ill patients. The results are more highly localized in the cortex by PET than EEG. The quantitative EEG findings of increased temporal delta are in agreement with many other authors [24–29] as well as with our previous studies on independent samples [4, 30].

Table 8. Correlations between hippocampus and EEG/glucose metabolic rate

	GMR hippocampus × delta	Under the electrode GMR × delta	GMR hippocampus × under the electrode GMR
Left			
P3	0.550	0.063	0.606
T3	0.330	−0.059	0.741
T5	0.282	0.022	0.654
FTC1	0.350	0.110	0.619
TCP1	0.352	0.250	0.669
TT1	0.285	0.026	0.716
Right			
P4	0.261	0.088	0.638
T4	0.415	0.001	0.689
T6	0.412	0.009	0.578
FTC2	0.420	0.091	0.595
TCP2	0.368	0.077	0.667
TT2	0.402	0.023	0.630

While Dierks et al. [31] found theta rather than delta effects, again the left temporoparietal region was the most highly discriminating between clinical groups. Some authors who did not record from the temporal lobe did not find increased delta, especially when the occipital lead was examined [32–35]. Recently Kwa et al. [36] have reported correlations similar to ours between temporal slow EEG activity and relative flow from HMPAO SPECT studies in a group of 20 patients with Alzheimer's disease. Thus EEG, flow and metabolic rate all seem to index the same lateral temporal cortex phenomena in Alzheimer's disease.

Diagnostic Sensitivity of PET and EEG

PET and EEG delta had not dissimilar sensitivity and specificity for absolute values although PET had somewhat greater regional effects. Our best PET area out of 158 was the left amygdala, an area also identified as yielding the greatest sensitivity and specificity in a MRI volumetric study by Pearlson et al. [37] which explored 12 variables. Our overall sensitivity and specificity of 71% and 94% (79% correctly identified) is similar to the 67% sensitivity and 100% specificity (81% correctly identified) of Pearlson et al. using multivariate methods combining amygdala and entorhinal cortex. It is interesting that the comparison of normals and the subgroup of mild severity patients yielded a very similar sensitivity, suggesting that metabolic decreases in this area are present in mild as well as more severe cases equally. This is consistent with the concept reviewed by Morrison [3] that the illness has its origin in medial temporal regions. It also suggests that both MRI (5 mm thick in the sample of Pearlson et al.) and PET (7.6 mm resolution) can resolve areas sufficiently disease involved and demonstrates the advantages of replication for imaging techniques where large numbers of brain areas are explored.

While the current PET study and the MRI study by Pearlson et al. [36] both identified the left amygdala as the region yielding the most sensitive diagnostic indicator, our sensitivity values were not significantly different from values obtained from many cortical areas. Indeed, Smith et al. [7] found even higher sensitivity and specificity for lateral cortex metabolic values. It should also be noted that contributions from adjacent parahippocampal gyrus and associated structures could well contribute to both PET and MRI findings. Further, both studies compare normals and patients with well characterized Alzheimer's disease, rather than patients with cerebrovascular or other forms of dementia. While simple memory or dementia scales might show similar sensitivity and specificity in the Alzheimer/control contrast, PET and MRI might be much superior in distinguishing the localized deficits of Alzheimer's from multifocal or diffuse change in other dementing illness.

Task Performance

Good performance on the FDG uptake task was associated with higher metabolic rate and lower delta amplitude widely across the cortex but not subcortical structures. This could reflect a general chronic severity relationship rather than failure of task activation, since patients with Alzheimer's disease have low metabolic rates and high delta activity while at rest (see review above). Removing global metabolic rate with normalization limited correlations to frontal and temporal regions, and removing global delta limited correlations to frontal and parietal areas. Relative delta waves in the temporal areas did not show negative correlations with performance; in fact, a positive correlation at T6 and O2 were observed. Note, however, delta EEG correlated with the GMR at the hippocampus but not with the GMR under the electrodes (table 8). One might have expected higher cortical correlations because the cortical region of interest is larger than the hippocampal one and might be less influenced by noise and stereotactic error. However the hippocampal effect appeared sufficiently strong and/or other medical temporal structures contributed to allow the relationship to be statistically significant. It should also be noted that relative data

can reflect large changes elsewhere in the brain and hippocampal correlations can be influenced by widespread cortical change.

Cortical Atrophy

Lower metabolic rates in the higher delta and more impaired patients might be due to more cortical atrophy and dilution of medial temporal areas assessed for metabolic rate measures with cerebrospinal fluid. However, statistical correction for cerebrospinal fluid areas did not change normal/Alzheimer group metabolic rate differences [7], suggesting that atrophy does not exceed the degree of metabolic deficits observed. Direct comparisons of PET, MRI, and autopsy specimens also persuaded McGeer et al. [38] that reduced metabolic rate 'is a real reduction in tissue metabolic rate and not an artifact due to adventitious inclusion of metabolically inert CSF'.

Taken together, these findings suggest a greater association between cortical than hippocampal metabolic activation and individual differences in performance. Large cortical areas may need to function together to succeed at the maintenance of attention and motor components of the task and the integration of memory activity. Performance scores may not differentiate as well between neuroanatomical sources of processing failure. In this group of relatively mildly ill patients, the overactivation of the hippocampus under the pressure of the experimental task setting may be a marker for inefficiency as reported in other studies [39]. Note that all patients had poor performance in comparison to normal subjects but a far wider range of scores avoiding the range restriction of the normal group.

This study provides evidence that medial temporal metabolic changes may be slightly more common than lateral temporal or parietal changes. Medial temporal change may also be important in the shifts into slow EEG activity which can characterize early Alzheimer's disease as well as nondemented individuals with memory deficits. While the EEG and PET may have similar diagnostic sensitivity and specificity in a normal/Alzheimer contrast, PET may prove more specific when contrasts with cerebrovascular or other dementias are desired.

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