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Abnormal EEG Slow Activity in Left Temporal Areas in Senile Dementia of the Alzheimer Type

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Resting 32-channel topographical measures of EEG slow activity were compared in 12 elderly controls and 12 patients with senile dementia of the Alzheimer type. The patients had higher amplitude delta and theta than controls, especially in the left temporal regions. This greater amount of low frequency EEG activity in the left temporal area is consistent with recent EEG, neuropsychological assessment, and positron emission tomography findings in SDAT patients. Five patients with mild-to-moderate dementia (as determined by the Folstein Mini-Mental State scale) primarily exhibited focal, abnormal slow activity in the left temporal regions. Seven patients with severe dementia exhibited increased slow activity across the head, which was still most abnormal in the left temporal regions.

ABNORMAL EEG slow activity associated with dementia in elderly patients was described in the aging literature in the 1950s (1–3). Other than the description of "diffuse slowing," there was no attempt to define the topographical properties of this abnormality in various subtypes of dementia. Since that time, EEG slow activity in Senile Dementia of the Alzheimer Type (SDAT) has been reported by a large number of studies (4–11). However, there has been little agreement in this literature on the topographical distribution. This might be related to the small number of electrodes and the lack of a standardized reference electrode across these studies.

Most recently, three independent studies have reported that abnormal EEG slow activity (delta and theta frequency bands) in SDAT is greatest in the left temporal areas (12–14). These recent EEG findings overlap with the older positron emission tomography (PET) findings of temporal and parietal hypometabolic activity (15, 16) and the more recent PET findings of predominantly left hemispheric hypometabolic activity in SDAT (17, 18).

The first purpose of this study was to replicate the previous EEG left temporal findings with an independent group of SDAT patients and controls. The second purpose was to relate the left temporal EEG slow activity measure to the severity of dementia. The third purpose was to assess this left temporal EEG slow activity measure as an objective diagnostic instrument for early SDAT patients.

METHOD

Subjects. — The patients were 12 right-handed individuals (6 male, 6 female, mean age 72.7, *SD* = 7.1) who had been diagnosed as having SDAT by a physician (A.S.) without knowledge of the EEG results. The diagnostic criteria were those recommended by the Work Group on the Diagnosis of Alzheimer's Disease (19). They included (a) a normal magnetic resonance image scan that showed no evidence of small vessel infarcts or other structurai abnormalities of the brain; (b) normal blood chemistries with particular attention to vitamin B^{12}, folic acid, BUN, and hemoglobin; (c) evidence or involvement of more than one cognitive deficit that would suggest the pathology to be more diffuse; and (d) a history of gradual progression of symptoms.

Seven of these patients (3 male, 4 female, mean age 71.0, *SD* = 8.9) were classified as "severely demented" on the basis of having a Folstein Mini-Mental State Score (MMSS) (20) of 7 or below. Five of these patients (3 male, 2 female, mean age 75.2, *SD* = 2.5) were classified as "mild-to-moderately demented" on the basis of having a MMSS in the range of 16–25. The duration of illness was estimated by asking the patient's caretaker about when the earliest symptoms appeared. The mean duration of illness was 7.8 years for the severely demented group and 5.6 years for the mild-to-moderately demented group. Twelve control subjects (6 male, 6 female, mean age 71.4, *SD* = 4.6) were selected to participate. Six of these controls were spouses of the patients and the other six were recruited from senior centers in Orange County, CA. The MMSS range for these control subjects was 25–30. All patients and subjects were screened to exclude those with psychiatric and other neurological disorders, and with clinically significant cardiovascular disorders. In addition, these individuals were screened to exclude those with recent drug or alcohol dependence or a history of head injury. All of the subjects had been free of CNS active medication for at least 7 days before testing. In addition, all of the subjects had abstained from the use of caffeinated beverages on the day of the testing.

Procedure. — All recordings were made in a sound-attenuated and darkened room with subjects reclining at a 45° angle and resting their heads so as to minimize neck muscle tension. They were instructed to keep their eyes closed throughout the session and remain as relaxed as possible. EEGs were recorded in three 38-second periods. If the record showed evidence of drowsiness or excessive movement, the recording period was interrupted and the

Table 1. A List of the Electrodes Used in the ANOVA

Longitudinality	Hemisphericity				
	1	2	3	4	5
1	F7	F3	FF	F4	F8
2	T3	C3	FC	C4	T4
3	TT1	TCP1	CZ	TCP2	TT2
4	T5	P3	PZ	P4	T6
5	O1	PO1	OZ	PO2	O2

subject was asked to maintain a relaxed state of wakefulness.

Electrodes were placed on 32 positions over the scalp surface, using the International 10–20 system plus five extra leads on each hemisphere and two extra midline positions with linked ears as reference (Figure 1). These 32 channels were converted to an average reference recording by computation after analog-to-digital conversion. All analyses were performed on average reference data.

Data were collected with an on-line computer system. EEG activity for spectral analysis was amplified with a 3dB bandpass of 0.5–50 Hz and digitized for each channel at 118 Hz and recorded in 1.75 sec. blocks (207 points). All 32 leads for each epoch were visually inspected for eye blinks, eye movements, and other movement artifacts as defined by previous EEG topographical analysis (21). Any 1.75-second epoch containing artifacts was eliminated from further analysis. Typically, 20–30 1.75 second epochs (mean = 27.41, SD = 10.40) were included in the analysis per subject. 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 thus 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 for compatibility with our spectral analysis program. A window function consisting of a 10% cosine taper was obtained by weighting the 12 points at either end of each 256-point, 1.75-second epoch 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 yields the sine wave equivalent in microvolts. The bandwidths for each frequency were: delta, 0.57–3.99 cps; theta, 4.57–7.41 cps; alpha, 7.98–13.11 cps; beta, 13.68–19.95 cps. Continuous surface density maps of the entire scalp surface were created from these values, using a 4-nearest neighbor interpolation algorithm (22).

Differences between the demented and control subjects were assessed for each frequency band separately using 3-way ANOVA (BMDP2V) with repeated measures (23). Diagnostic category was the grouping variable, and Hemisphericity and Longitudinality were repeated factors. These factors were obtained by sampling 25 electrodes (Table 1) out of the original 32 and forming a 5 (Longitudinality) × 5 (Hemisphericity) grid. A technical error had resulted in the loss of 16 channels of information from one of the mild-to-moderately demented subjects. Another technical error had resulted in the loss of one channel of information from another mild-to-moderately demented subject.

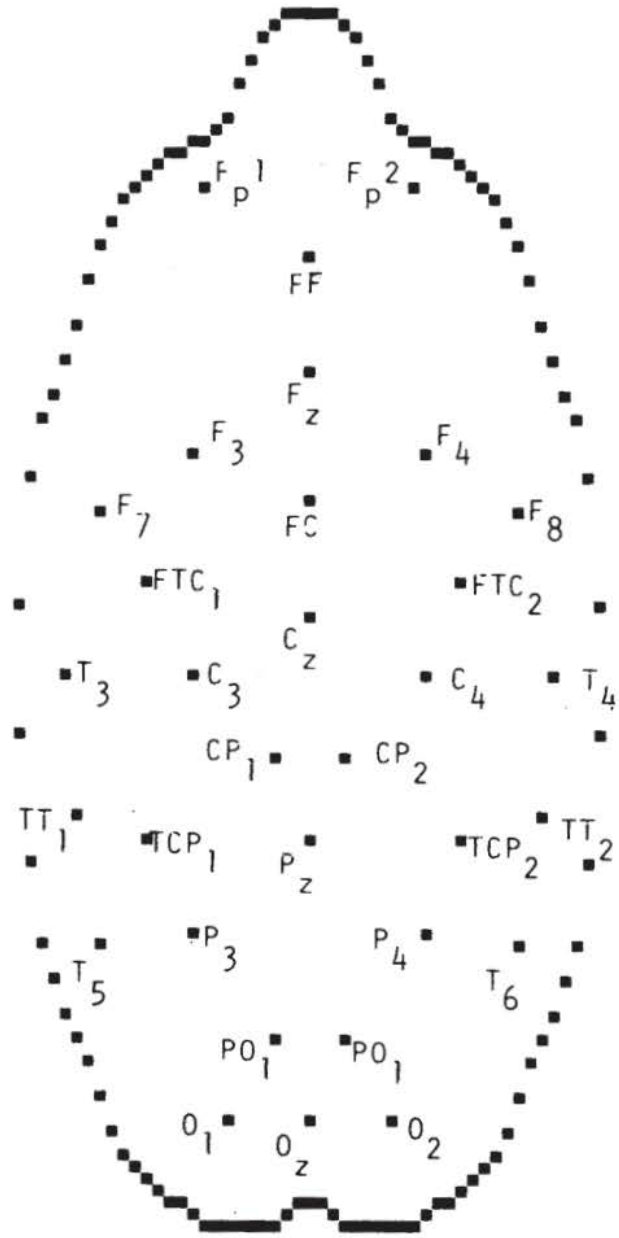

Figure 1. Placement of 32 electrodes at standard 10–20 system locations, midline and extra midline positions in centers of squares formed by the 10–20 system.

Thus, only 10 patients could be included in the ANOVA. However, for 15 of the channels there were 12 patients, and for 17 of the channels there were 11 patients who could be included in the t-tests described below. Huynh-Feldt reduced degrees of freedom were used to avoid Type I errors caused by falsely inflated d.f. in repeated measures ANOVA.

Where significant ($p < .05$) Group × Topographical lo-

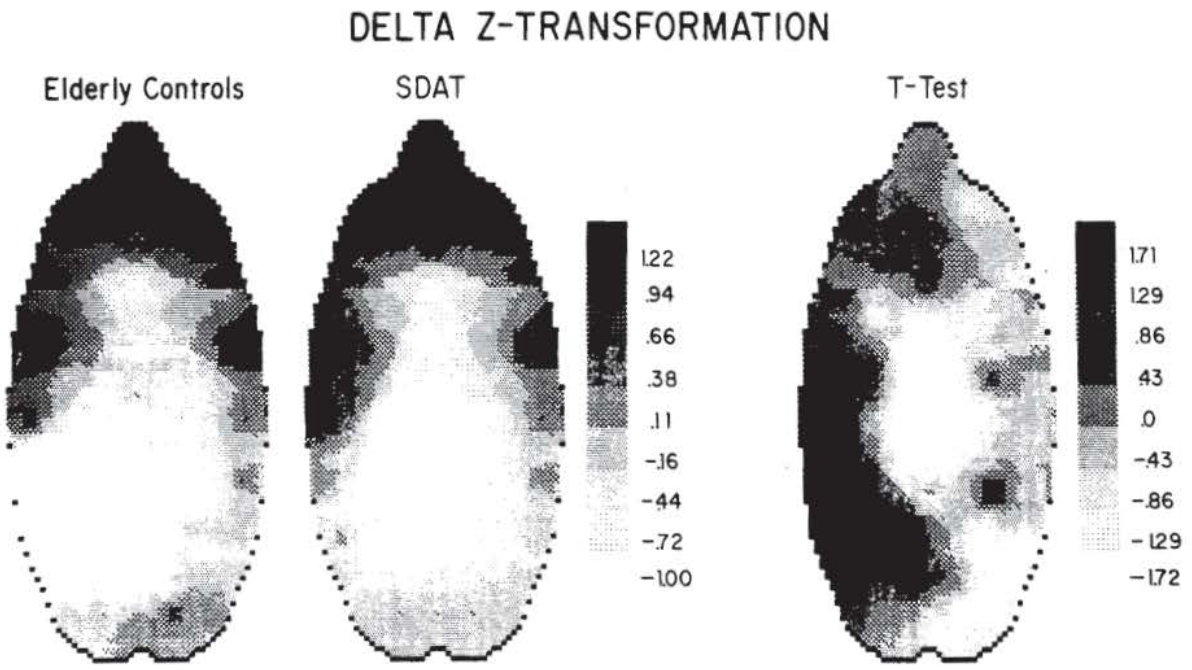

Figure 2. Left: mean normalized topographic maps of delta activity in elderly controls and SDAT patients; scale is in standard deviation units. Right: map of 32 t values for elderly/SDAT contrast done on each lead as post hoc tests following significant topographical direction × group interaction using ANOVA with appropriate reduction in degrees of freedom (see text). Numbers next to scale give lower limit for the gray scale box. Thus t values between −1.72 and −1.29 appear white, and t values greater than 1.71 appear black. Black is $p < .05$, 1-tailed; SDAT higher than controls.

cation ANOVA interactions were found, the ANOVA was repeated using values normalized with a z-transformation to correct for a possible multiplicative effect produced by differences in source strength (24) and to eliminate differences due to overall reduction in EEG power. This was done by calculating the mean and *SD* across the values for the 32 leads and then reexpressing each lead as (lead value-mean)/standard deviation. The z-transformed frequency bands yielding significant Hemisphericity × Group or Longitudinality × Group interactions were selected for calculation of group means and t-tests at each of the 32 leads.

RESULTS

Control vs SDAT effects. — The SDAT patients had a larger amount of delta activity than the controls all over the head, with the differences being largest in the left temporal areas. In addition, the SDAT patients had a larger amount of theta activity than the controls all over the head, but the differences were only slightly larger in the left temporal area.

The ANOVA tests of the absolute amplitude in the four frequency bands for the main effect of diagnosis confirm that patients had significantly more delta ($F = 30.16$, df = 1,20, $p < .00001$) and theta ($F = 34.92$, df = 1,20, $p < .00001$) than controls, while there were no significant differences for alpha and beta. The patients had more delta than the controls in the left hemisphere relative to the right (Hemisphere × Diagnosis interaction, $F = 9.71$, df = 4,80, $p < .0001$), and the largest effect was in the left temporal region (Hemisphere × Longitudinal × Diagnosis interaction, $F = 3.15$, df = 16,320, $p < .01$) at the T3 electrode ($t = 7.45$, df = 21, $p < .00001$). Likewise, in the theta band, there were significant Hemisphere × Diagnosis ($F = 4.91$, df = 4,80, $p < .01$) and Hemisphere × Longitudinal × Diagnosis ($F = 2.79$, df = 16,320, $p < .01$) interactions and the largest effect was also at the T3 electrode ($t = 7.18$, df = 21, $p < .00001$). In the alpha band, there were no significant Topography × Diagnosis effects. Finally, in the beta band, there were significant Longitudinal × Diagnosis ($F = 4.16$, df = 4,80, $p < .05$) and Hemisphere × Diagnosis ($F = 3.47$, df = 4,80, $p < .05$) effects, but none of the t-tests on the individual leads were significant.

The greater abnormal left temporal slow activity in the SDAT patients was further supported by the ANOVA in the topographically normalized data. Significant Hemisphere × Diagnosis × Longitudinal interactions for both the normalized delta ($F = 2.76$, df = 16,320, $p < .01$) and normalized theta ($F = 1.06$, df = 16,320, $p < .01$) were found. Figure 2 demonstrates the topographically normalized amplitude and t-test maps for the delta frequency band. It shows that the largest effects were entirely concentrated in the left temporal regions. Figure 3 shows the topographically normalized amplitude and t-test maps for the theta frequency band. It shows that the effects were only slightly larger in the left temporal area.

To estimate the most important frequency range, we performed t-tests on the normalized EEG values at the four left temporal leads across all the individual 0.57 Hz steps in frequency within the delta and theta range. The strongest effect occurs around 1.14 Hz (Table 2).

Also, there was a significant negative correlation with MMSS at all leads for absolute delta. These correlations

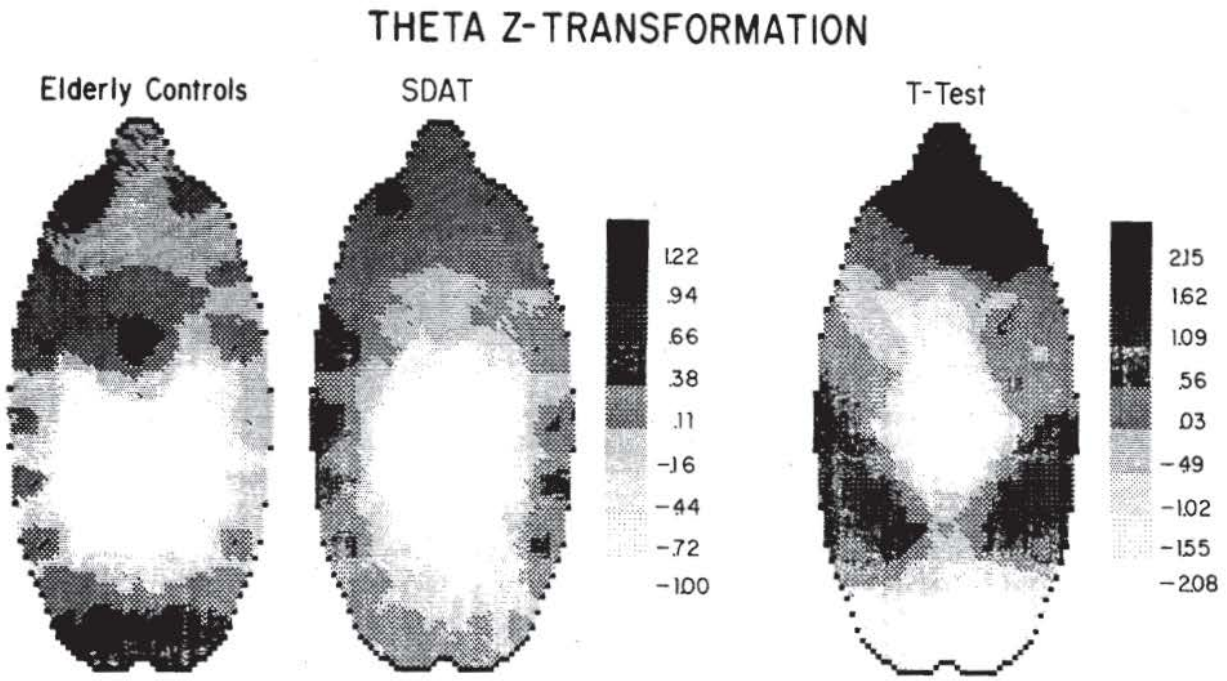

Figure 3. Left: mean normalized topographic maps of theta in elderly controls and SDAT patients. Scale is in standard deviation units. Right: maps of 32 exploratory t-test comparisons between elderly controls and SDAT patients done post hoc following a significant topography × group ANOVA. Black is $p < .05$, 2-tailed, SDAT patients higher than controls. Only TCP1 reached significance.

ranged from ($r = -.59$, $p = .05$) at TCP1 to ($r = -.85$, $p < .01$) at F3. However, there were no significant correlations between the normalized delta band EEG leads and the MMSS measures. In the theta band, the absolute theta at the EEG leads FP2 ($r = -.61$, $p < .05$) and C4 ($r = -.58$, $p < .05$) were significantly correlated with the MMSS measure. When the normalized theta measure was correlated with the MMSS, there were significant positive correlations at Cz ($r = .63$, $p < .05$), T3 ($r = .76$, $p < .01$), T5 ($r = .64$, $p < .05$), and TT1 ($r = .84$, $p < .01$).

A relationship of EEG delta to the severity of dementia was also illustrated by a comparison of the number of abnormal EEG leads in the moderately demented group vs the severely demented group. An abnormal lead was defined as one where the value at a lead is greater than two standard deviations above the mean value at that lead for the control group distribution. For this absolute delta measure of abnormality, all five of the moderately demented patients had six or fewer abnormal leads, whereas all seven of the severely demented patients had 16 or more abnormal leads ($\chi^2 = 12.99$, df = 1, $p < .01$). In fact, all of the severely demented patients had 30 or more abnormal leads, but 16 was chosen for the upper cutoff because of the 16 missing channels in the one of the moderately demented patients. In all five of the moderately demented patients, at least one anterior left temporal lead (T3 or TT1) was included as an abnormal lead. As a group, the mean activity for the moderately demented patients was only abnormal in four (T3, TT1, T5, FF) of the 32 leads, and three of these were left temporal leads. As a group, the mean activity for the severely demented patients was abnormal in 31 of the 32 leads; FC was the only normal lead.

For the absolute theta measure, the chi-square test of the number of patients in each group which had 6 or fewer abnormal leads vs 16 or more abnormal leads was not significant ($\chi^2 = 3.33$, df = 1, $p > .05$). As a group, the mean activity for the moderately demented patients was abnormal in a total of 9 leads, and 3 of these (T3, TCP1, and TT1) were left temporal. As a group, the mean activity for the severely demented group was abnormal in 24 leads. These results suggest that the theta abnormalities showed much less

Table 2. T-values Representing SDAT/Control Differences in Topographically Normalized EEG Power as a Function of Frequency (A Positive Value Represents a Larger SDAT Value)

Frequency in Hz	Electrode Location			
	T3	FTC1	TCP1	TT1
.57	1.45	2.88*	2.84*	3.74*
1.14	3.95*†	3.45*	2.79*	4.33*†
1.71	1.34	1.81*	4.07*†	3.49*
2.28	1.47	1.19	3.11*	2.46*
2.85	1.45	.93	3.19*	2.66*
3.42	.85	.81	1.50	.58
3.99	.96	1.16	2.62*	1.09
4.56	1.51	.91	1.21	1.28
5.13	2.22*	1.08	1.77*	1.59
5.70	2.16*	.06	2.30*	.83
6.27	3.48*	1.55	2.94*	1.93*
6.84	.70	.48	1.56	1.09
7.41	.95	.67	1.68	.51
7.98	.19	.41	1.20	−.31

* indicates two-tailed significance at the .05 level.
† indicates two-tailed Bonferroni significance at the .05 level.

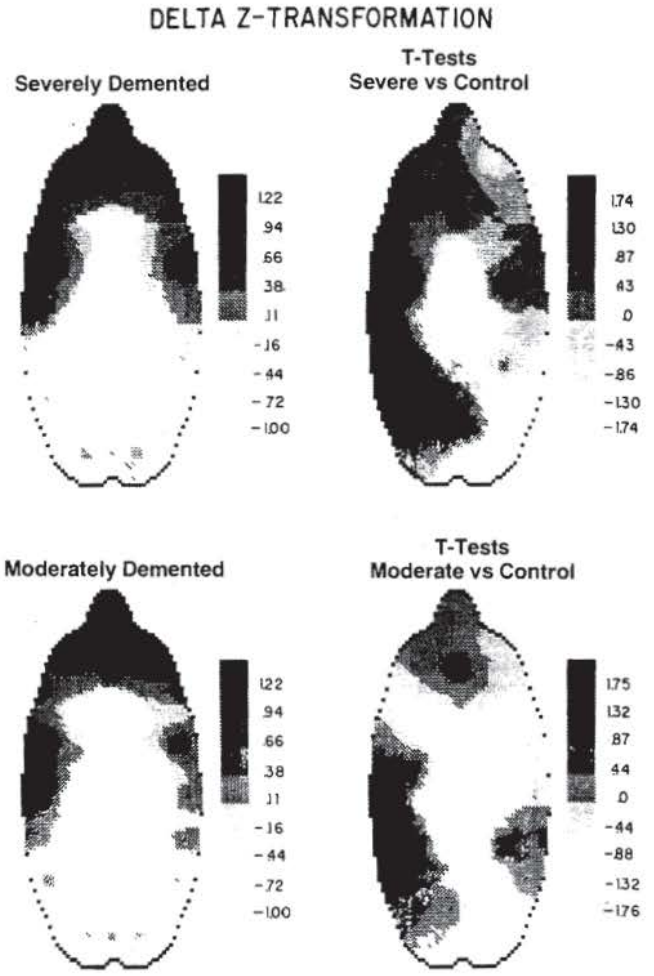

Figure 4. Left: mean normalized topographic maps of delta in severely demented and mild-to-moderately demented sub-groups (see text). The scale is in standard deviation units. Black indicates a lead which is on the average 1.22 standard deviation units above the mean. Right: maps of 32 *t*-test comparisons between severely demented patients and controls (above) and mild-to-moderately demented patients (below). Black is $p < .05$, 1-tailed, patients higher than elderly controls.

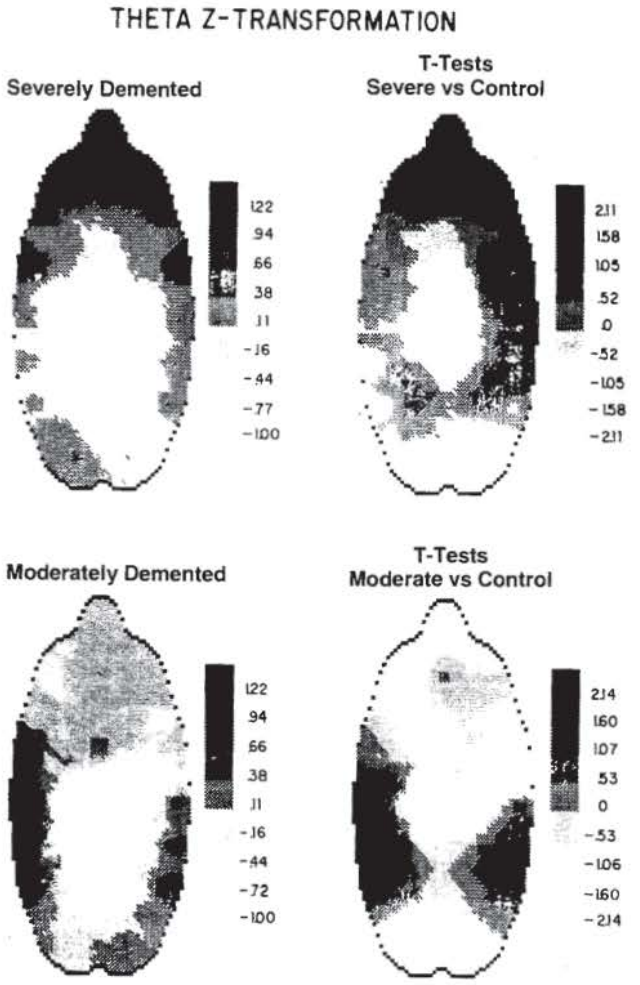

Figure 5. Left: mean normalized maps in severely demented and mild-to-moderately demented patients (see text). Scale is in standard deviation units. Right: exploratory *t*-test maps of severe vs control and mild-to-moderate vs control differences. Black is $p < .05$, 2-tailed, patients higher than elderly controls. Significant differences were only seen in the mild-to-moderate comparison and only in the left temporal areas.

of the trend which was observed for delta, where moderately demented patients had a predominantly focal left temporal abnormality pattern in comparison to severely demented patients.

In a further effort to get a view of where the *largest* abnormalities were for both the moderately demented and the severely demented groups, *t*-tests were performed on the topographically normalized delta and theta band data. Because of the SDAT vs Control delta effects in the previous literature, one-tailed *t*-tests were done on the delta band data, whereas only exploratory (two-tailed) *t*-tests were done on the theta band data. Both the severe and the mild-to-moderate groups showed the greatest concentration of topographically normalized delta effects in the left temporal areas (Figure 4). However, this normalized delta effect was much more restricted to the left temporal area in the mild-to-moderate group, where the left temporal leads TT1, FTC1, T3, and TCP1 and the right temporal lead TCP2 were all significant. The normalized delta effect was not as restricted to the left temporal area in the severely demented patients, where the left temporal leads TT1, FTC1, and TCP1 as well as P3, PO1, and FTC2 were significant. In the theta comparisons, only the mild-to-moderate group showed a predominantly left-temporal abnormality pattern (Figure 5).

As a final illustration of the greater left temporal effect for delta, Figure 6 presents a scatter plot of the absolute delta activity at electrodes T3 and Cz in the patients and the controls. There is no overlap between the patients and the controls at T3, while there is some overlap at Cz. All of the patients that overlapped with the controls at Cz were in the mild-to-moderately demented group.

Discussion

This is now the fourth recent study to suggest that abnormal EEG slow activity in SDAT patients is greatest in the left temporal areas (12–14). While this study is based upon a relatively small number of patients, it does suggest that this left temporal slow activity effect might be related to the

severity of the disease process. Patients with mild-to-moderate dementia primarily exhibited a focal abnormal left temporal slow activity pattern, whereas patients with severe dementia exhibited a more diffuse slow activity pattern that was most abnormal in the left temporal regions. These effects were particularly clear in the delta frequency band.

While the abnormal left temporal EEG slow activity effect is consistent with recent PET reports of greater left hemispheric dysfunction in SDAT patients, a relationship with the severity of SDAT was not found in the Loewenstein et al. PET study (18). One explanation for this discrepancy could be the different severity range of the patients in these studies. The Loewenstein et al. study had a much more restricted MMSS range without any patients in the severely demented group range (0–7) of this present study.

These data suggest that focal, left anterior temporal EEG slow activity might be a sensitive indicator of the milder stages of SDAT. At the T3 electrode, there was no overlap between the patients and the controls in the distribution of absolute delta activity (Figure 6), while there was overlap at Cz. All of the overlap at Cz was due to the mild-to-moderately demented patients. This could imply that patients in the milder stages of SDAT might have much more focal left temporal slow activity with a relative sparing of other areas. The diagnostic implications of these data are tempered presently by the small number of patients, along with the lack of confirmatory neuropathological information on these patients.

The diagnostic implications of these data are also complicated by the fact that EEG slow activity is not specific to SDAT. Asymmetric EEG slow activity has been reported to be prevalent in the elderly in qualitative EEG studies of cerebrovascular disease (6,25). However, the one qualitative study (25) which documented the locality of these abnormalities suggests that they are more right temporal and more diffuse than those of the mild-to-moderate SDAT patients of the present study. EEG slow activity in multi-infarct patients has also been reported by two recent quantitative EEG studies which looked at both multi-infarct and Alzheimer-type dementia patients (12,14). Both of these recent studies used far fewer electrodes than the present study and, therefore, might not have been sensitive to a more focal pattern of left temporal EEG slow activity which could be more specifically related to the milder forms of SDAT. In spite of this, both of these studies report that their multi-infarct patients had more diffuse slow activity all over the head than their Alzheimer patients.

While a number of qualitative EEG studies report that focal left temporal EEG slow activity is found in a significant number of normal elderly individuals (4,25,26,27), the present data indicate that there are definite quantitative differences between SDAT patients and normal elderly controls in the degree of focal left temporal slow activity. These present findings are consistent with the neuropathological observation of marked abnormalities of the temporal areas in Alzheimer's disease (28,29). It should be remembered that, along with increased numbers of senile plaques and tangles, temporal lobe atrophy was also first suggested to be a neuropathological marker for senile dementia of the Alzheimer type (29).

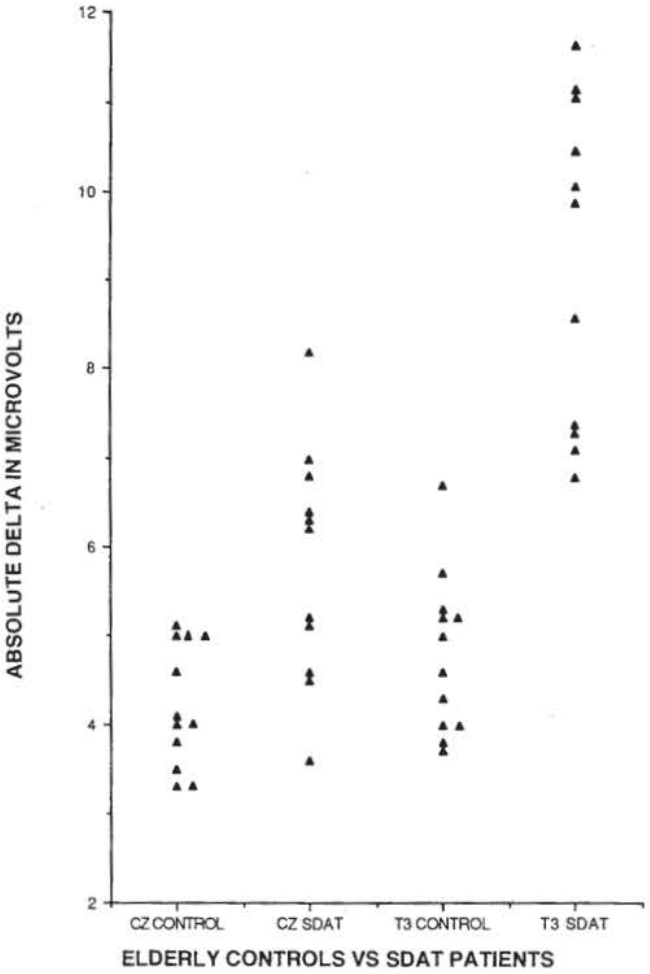

Figure 6. Scatter plot demonstrating differences between elderly controls and SDAT patients in absolute delta. There was no overlap between the distributions of these two groups at T3, but there was overlap at Cz. All of the overlap at Cz was due to patients who were mild-to-moderately demented.

These findings also raise the possibility that the focal left temporal slow EEG activity often reported to be prevalent in normal elderly individuals (4,25–27) could be an early manifestation of Alzheimer's disease. Word-naming deficits are prevalent in the milder forms of clinically diagnosed Alzheimer's disease (30–33) and word-naming deficits have also been related to severe left temporal slow EEG activity in normal elderly individuals (27). However, memory deficits have never been associated with left temporal slow EEG abnormalities in the normal elderly. Research is needed which addresses the possibility of Alzheimer-like cognitive deficits in the normal elderly with left temporal slow EEG abnormalities.

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