Quantified Electroencephalographic Changes in Depressed Patients with and without Dementia

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We carried out quantified electroencephalograms (qEEG) in 17 patients with probable Alzheimer's disease (AD), who also met the DSM-III-R criteria for either dysthymia or major depression, and 18 AD patients with comparable intellectual impairment but no depression, 13 patients with depression but no AD, and 10 age-matched normal controls. There was a significant effect for depression in alpha relative power: depressed patients (with or without AD) showed a significantly lower alpha relative power in the right posterior region as compared to nondepressed patients; however, this change was observed over the right hemisphere in depressed non-AD patients, and in left, medial, and right posterior regions in depressed-AD patients. Depressed patients without AD showed a significant global decrease in delta power, whereas depressed patients with AD showed significant increments in delta power in posterior brain areas. In conclusion, AD patients with depression showed qEEG changes that were significantly different from qEEG changes in depressed non-AD patients.

Key Words: Depression, dementia, lateralization, quantified electroencephalography, delta power

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Introduction

While the presence of progressing cognitive deficits constitutes the hallmark of Alzheimer's disease (AD), psychiatric disturbances are also frequent. Depression is one of the most prevalent psychiatric disorders in AD, and is present in about 30–40% of AD patients (Loreck and Folstein 1993). In a recent study we examined the quantified electroencephalographic (qEEG) correlates of depression in AD. Patients were divided into groups with either mild or moderate AD, and further subdivided into those with or without depression (Pozzi et al 1993). There were two main findings. First, patients with moderate/severe AD had a significantly lower alpha/theta ratio than patients with mild AD. Second, there also was a significant effect for depression, with depressed AD patients having a significantly higher relative theta power than nondepressed AD patients, regardless of the severity of dementia.

Studies of qEEG changes in depressed patients *without* AD produced somewhat contradictory findings. Visser et al (1985) examined qEEG in elderly depressed subjects without neurological disorders and a group of age-matched controls and found no significant between-group differences. On the other hand, Brenner et al (1986) found a decreased $beta_1$, $beta_2$, and delta relative power in depressed patients as compared to normal controls. Luthringer et al (1992) replicated the finding of significantly decreased beta activity in depressed patients, but they reported a significant increment

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in theta activity as well. Up to our knowledge, there are no studies in which the qEEG changes in depressed non-AD and depressed AD patients were directly compared.

Aims of this study were to determine the specificity of qEEG changes in non-AD elderly patients with depression, and to determine whether the qEEG changes in AD patients with depression are similar to the qEEG changes in depressed nonAD subjects. This study had a 2 × 2 design, and included a group of AD patients with depression, a group of AD patients without depression, a group of non-AD patients with depression, and a group of age-comparable nondepressed and non-AD normal controls.

Subjects and Methods

Subjects

A consecutive series of patients with AD (with or without depression), and patients with primary depression (i.e., depression in the absence of known brain disorder) who attended the Neurology and Psychiatry Clinics of our Institute for regular follow-up visits were screened for inclusion in this study. Four groups were examined:

NON-DEPRESSED AD GROUP. This group consisted of 18 patients who met the NINCDS-ADRDA criteria (McKhann et al 1984) for probable AD. None of them met the DSM-III-R criteria (APA 1987) for either dysthymia or major depression. Every patient underwent a standardized neurological examination, laboratory tests, and computed tomography (CT) scanning to exclude other causes of dementia. Patients with questionable or very mild dementia (Clinical Dementia Rating [CDR] score = 0.5) (Hughes 1982) or patients with severe dementia (CDR score = 3) were not included (patients with severe dementia were not able to sit still and produced qEEG studies with artifacts). Other exclusion criteria were a focal lesion on the CT scan, and a Hachinski Ischemic score > 4 (Hachinski et al 1975).

DEPRESSED NON-AD GROUP. This group consisted of 13 patients who met the DSM-III-R criteria for either dysthymia or major depression. None of the patients met the NINCDS-ADRDA criteria for probable AD, and all of them had a Mini-Mental State Exam (MMSE) score > 24.

AD-DEPRESSED GROUP. This group consisted of 17 patients who met both the NINCDS-ADRDA criteria for probable AD and the DSM-III-R criteria for either major depression or dysthymia. None of these patients had a vascular lesion on the CT scan, and all of them had a Hachinski Ischemic score < 4. Twenty-five of the total group of 35 AD patients in this study were included in our previous report (Pozzi et al 1993).

NORMAL CONTROL GROUP. Normal controls were spouses of AD patients or healthy elderly volunteers from the community. None of them had a history of neurologic disease, psychiatric illness, severe head injury, drug abuse, cerebrovascular disease, or epilepsy.

Psychiatric and Neuropsychological Examination

After informed consent was obtained, patients and controls underwent a standardized psychiatric evaluation that included the following assessments:

STRUCTURED CLINICAL INTERVIEW FOR DSM-III-R (SCID). The SCID (Spitzer et al 1990) is a semistructured diagnostic interview for making the major Axis I DSM-III-R diagnoses. The SCID was administered by a psychiatrist blind to the remaining clinical and neurophysiological data, and the interview was carried out with the patient and at least one first-degree relative. Based on the SCID responses, DSM-III-R Axis I diagnoses of major depression and dysthymia were made.

HAMILTON DEPRESSION SCALE (HAM-D). The HAM-D (Hamilton 1967) is a 17-item interviewer-rated scale that measures psychological and autonomic symptoms of depression.

MINI-MENTAL STATE EXAM (MMSE). The MMSE (Folstein et al 1975) is an 11-item examination that has been found to be reliable and valid in assessing a limited range of cognitive functions.

EEG Recordings and Fourier Analysis

All EEG recordings were carried out using a 21-channel electroencephalographer as described in a previous publication (ATI-MP24) (Pozzi et al 1993). Gold-coated electrodes were applied to the scalp according to the International 10-20 system. The electrode positions were FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, OZ, and O2, with a linked-ears reference. After amplification, EEG data were passed through an antialiasing filter of 36 db per octave, and digitized at a sampling rate of 256 samples/sec per channel. The EEG samples were collected both with eyes closed and with eyes open. Artifacts due to eye movement, muscle tension, and drowsiness were excluded after a visual inspection of the recording, but orbital electrodes were not used. A minimum of 30 epochs of 1 second of artifact-free EEG data were selected in each modality. The EEG data were submitted to a Hanning window (Blackman and Tukey 1958), after which a Fast Fourier Transformation was performed. The total range of analysis was 2-32 Hz, and the EEG absolute power was calculated

for the delta (2.0–3.9 Hz), theta (4.0–7.9 Hz), alpha (8.0–12.9), $beta_1$ (13.0–19.9) and $beta_2$ (20.0–32.0) frequencies. Patients who were on psychoactive drugs that may potentially influence the EEG underwent a washout period of at least 2 days.

Data Analysis

The following measures were computed: 1) total power; and 2) proportion (percent) of total power per frequency band —i.e., (band power/T) × 100, where T equals the sum of the power in all frequency bands from 2–32 Hz (Gerson 1976). In order to fit the EEG data to a normal distribution, a log transformation of power values of every bandwidth in each derivation was calculated using log (x) for absolute power and log (x/(1-x)) for relative power where x is the fraction of total power in each bandwidth (John et al 1980; Gesser et al 1982). To facilitate analysis of the topological distribution of the total power, data were collapsed across electrodes into the following nine areas: A1 (F1-F3-F7); A2 (FZ-CZ); A3 (F2-F4-F8); A4 (T3-C3-T5); A5 (CZ-PZ); A6 (T4-C4-T6); A7 (P3-O1); A8 (PZ-OZ); and A9 (P4-02). Subsequently, percent band power was computed for each of these areas.

Statistical analysis involved multivariate and one-way analysis of variance (MANOVA). After significant main effects or interactions were found, post-hoc analysis were carried out using either the Tukey Honest significant difference (HSD) for equal samples or the Tukey test for unequal samples (Spojotvoll and Stoline test).

Results

Demographic Findings

No significant between-group differences were found in age (Table 1). Depressed and non-depressed AD patients had a similar duration of illness, but AD-depressed patients had significantly fewer years of education.

Psychiatric Findings

As expected, depressed patients showed significantly higher HAM-D scores than nondepressed patients ($F(3,54) = 32.06$, $p < .0001$), and AD-depressed patients showed similar HAM-D scores than non-AD depressed patients, demonstrating that the severity of depression was similar for the AD and non-AD depressed groups. Patients with AD had significantly lower MMSE scores than non-AD patients ($F(3,54) = 12.4$, $p < .0001$). AD-depressed and AD nondepressed patients showed similar MMSE scores (Table 1). Nine of 17 depressed patients with AD had major depression and eight had dysthymia, while in the primary depression group 10 patients had major depression and three had dysthymia ($X^2 = 3.3$, $df = 3$, p = NS).

Three nondepressed AD, four depressed AD, and two depressed non-AD patients were on small doses of benzodiazepines, and one non-depressed AD patient was taking 25 mg of amitriptyline as an hypnotic. All of them were withdrawn from these medications at least 48 hours before the study.

Neurophysiological Findings

DEMENTIA EFFECT. Data for the eyes-closed condition was analyzed using a four-way ANOVA (*Depression* (depressed vs. nondepressed) × *Dementia* (AD vs. non-AD), and two repeated measures: *Side*: (left vs. medial vs. right) and *Site* (anterior vs. central vs. posterior)), and the dependent variable was each qEEG band. Patients with AD had significantly more delta ($F(1,54) = 21.70$, $p < .00001$) and theta ($F(1,54) = 30.34$, $p < .000001$) and significantly less alpha ($F(1,54) = 20.80$, $p < .00001$) and $beta_1$ relative power ($F(1,54) = 3.60$, $p < .05$) than patients without AD. There also was a significant Dementia × Site interaction: while both delta and theta were significantly increased in posterior areas ($p < .00001$ and $p < .0001$, respectively), alpha significantly decreased in posterior areas ($p < .001$), and $beta_1$ significantly decreased in anterior areas ($p < .05$) of AD patients.

DEPRESSION EFFECT. A four-way ANOVA showed no significant main effect for depression for any of the five bands, but there were several significant interactions. A significant Depression × Dementia interaction for delta band ($F(1,54) = 9.50$, $p < .005$) resulted from a decrease in delta relative power in depressed non-AD patients as compared to the other three groups (Figure 1). There also was a significant Dementia × Depression × Side interaction for the alpha band ($F(2,108) = 8.10$, $p < .001$), which resulted from a significant decrease in alpha activity in the right side in non-AD depressed patients vs. controls (Figure 2). Finally, there also was a significant Depression × Site × Side interaction ($F(4,216) = 4.31$, $p < .005$), which resulted from a significant decrease in alpha activity in depressed patients (AD and non-AD) in the right posterior region as compared to nondepressed patients.

DEPRESSION × DEMENTIA EFFECT. When comparisons were restricted to depressed and nondepressed patients with AD, a three-way ANOVA (Group × Side × Site) for each band showed several significant interactions. There was a significant Group × Site interaction in the delta band ($F(6,108) = 5.81$, $p < .00005$) which resulted from a significant increase in delta relative power in the posterior area in the AD-depressed group as compared to the nondepressed AD group. There also was a significant Group × Site interaction for theta band ($F(6,108) = 4.83$, $p < .0005$), which

Table 1. Demographics and Neuropsychiatric Findings[a]

	AD-Dep (n = 17)	Alzheimer (n = 18)	Depression (n = 13)	Control (n = 10)
Age (mean yr)	71.7 (7.2)	73.0 (7.8)	66.1 (8.2)	68.5 (8.6)
Sex (% male)	24	56	46	50
Education (mean yr)[b]	8.2 (5.7)	13.8 (5.2)	12.3 (6.5)	13.6 (3.2)
Duration of illness (yr)	3.7 (3.1)	5.2 (3.5)	4.3 (4.3)	—
MMSE score[c]	17.1 (7.2)	19.5 (6.3)	26.0 (2.1)	28.4 (1.8)
HAM-D score[d]	15.2 (6.6)	3.8 (3.2)	20.4 (8.5)	2.2 (1.8)

[a] SDs are shown in parentheses.
[b] $F(3,54) = 3.62$; $p < .05$ (AD-Dep vs. remaining groups, $p < .05$).
[c] $F(3,54) = 12.42$; $p < .00001$ (AD vs. non-AD, $p < .001$).
[d] $F(3,54) = 32.06$; $p < .00001$ (depressed vs. nondepressed, $p < .0001$).
AD-Dep = Alzheimer's disease and depression; MMSE = Mini-Mental State Exam; HAM-D = Hamilton Depression Scale.

resulted from a significant increment in theta relative power in the posterior area of the AD-depressed group as compared to the AD nondepressed group (Figure 3). Finally, a significant Group × Site interaction was also found for the alpha band ($F(6,108) = 4.80$, $p < .0005$) which resulted from a significant decrease in alpha relative power in the posterior areas of the AD-depressed group as compared to the non-depressed AD group (Figure 4).

ALPHA REACTIVITY. A similar ANOVA with repeated measures using alpha reactivity ratio as the repeated measure was also performed. Patients with AD showed a significantly higher alpha reactivity ratio than non-AD patients ($F(1,60) = 21.79$, $p < .0001$). No significant effects were found for either Depression ($F(1,60) = 6.1$, p = NS) or Depression × Dementia interaction ($F(1,60) = 5.5$, p = NS).

TOTAL POWER. A four-way ANOVA with repeated measures showed a significant higher total absolute power in the non-AD group as compared to the AD patients ($F(1,54) = 4.8$, $p < .05$). No significant Depression ($F(1,54) = 2.52$, p = NS), or Depression × Dementia interaction were found ($F(1,54) = 0.8$, p = NS).

GENDER EFFECTS. Since there was a between-group difference (albeit not significant) in gender distribution, statistical analyses were carried out using gender as a between-factor. No significant Sex × Band interaction was found ($F(4,224) = 0.97$, p = NS).

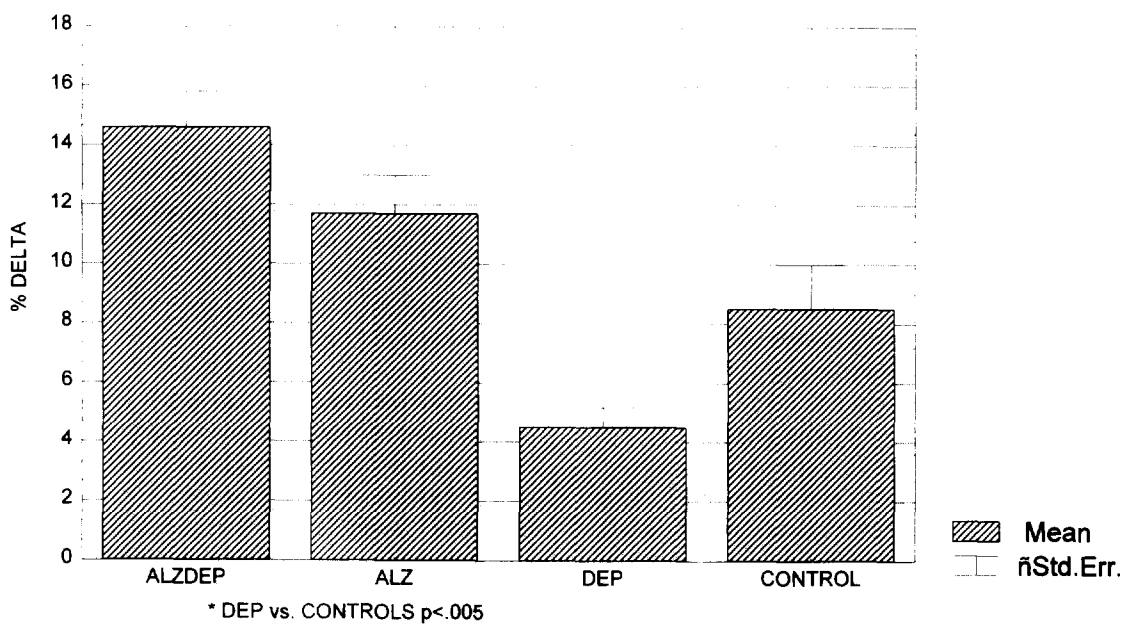

Figure 1. A significant decrease in delta relative power is shown in all brain areas of depressed non-AD patients ($F(1,54) = 9.50$, $p < .005$); (Dep vs. AD $p < .005$, Dep vs. AD-Dep $p < .0005$, Dep vs. controls $p < .05$).

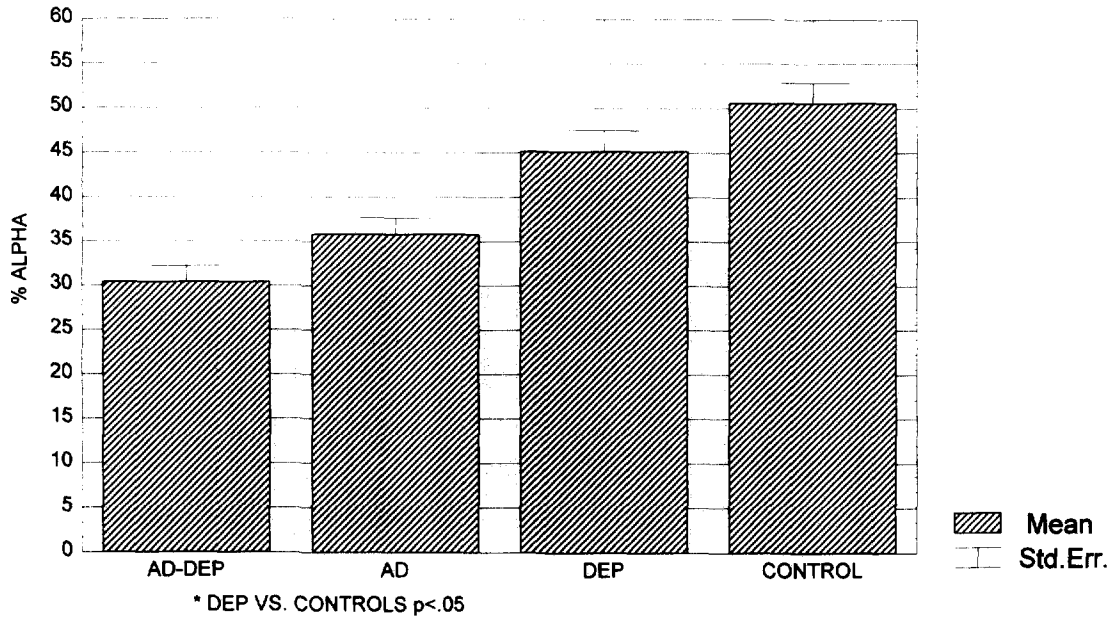

Figure 2. A decreased alpha relative power is shown in the right hemisphere of depressed patients as compared to controls ($p < .05$).

Finally, when patients on psychoactive medications were excluded from the statistical analysis, significant between-group differences were not changed.

Discussion

This is, to our knowledge, the first study to compare qEEG correlates of depression in both non-AD and AD depressed patients, and showed several important findings. Compared to normal controls, non-AD depressed patients showed a significant global reduction in delta relative power, as well as a significant reduction in alpha relative power to the right hemisphere. In contrast, depression in AD subjects produced significantly different qEEG changes. As compared to non-depressed AD patients, depressed AD patients showed significant increments in both delta and theta relative power,

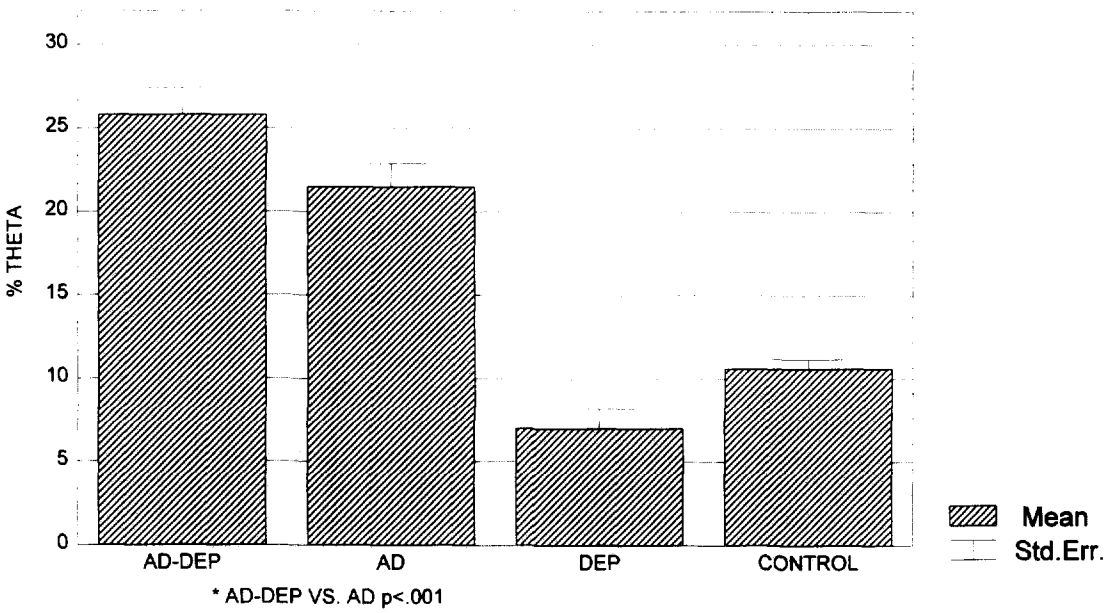

Figure 3. A significant increment of theta relative power is shown in posterior brain areas in AD patients with depression as compared to nondepressed AD patients ($p < .001$).

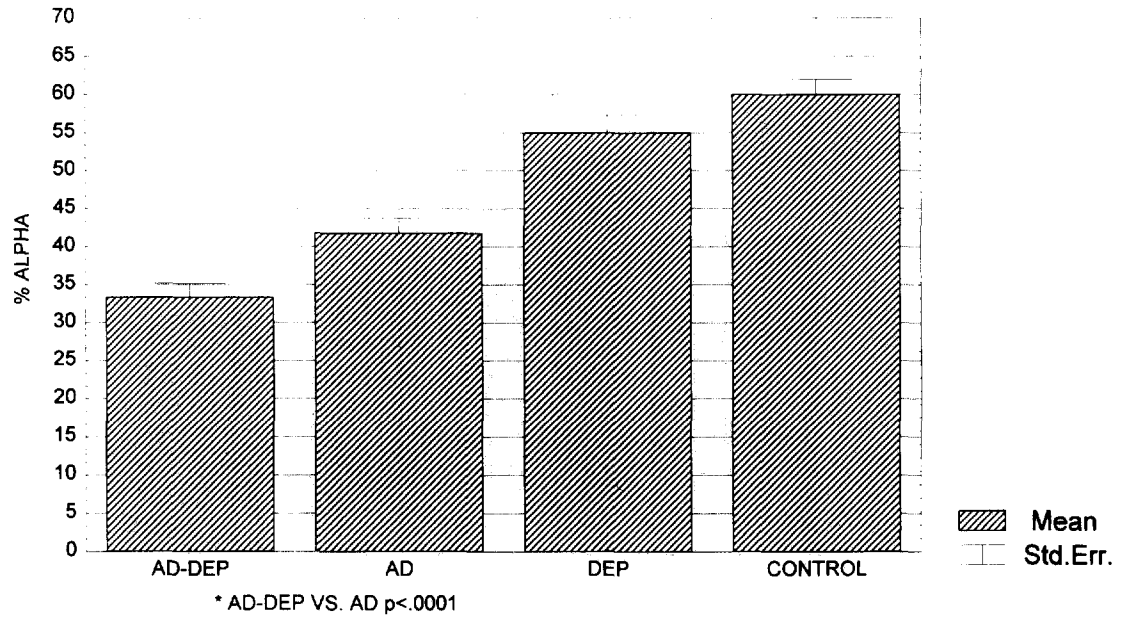

Figure 4. A significant decrease in alpha relative power is shown in posterior brain areas in AD patients with depression as compared to nondepressed AD patients ($p < .0001$).

as well as a significant reduction of alpha relative power which was restricted to posterior brain regions.

Before further comments, some limitations of our study should be addressed. First, while patients on psychoactive drugs were withdrawn from the medications at least 2 days before the study, some influence of these drugs might have remained. While longer washout periods are certainly desirable, they are difficult to instrument in patients with a severe mood disorder; however, when patients on psychoactive medications were excluded from the statistical analysis, significant between-group differences were not changed. Second, both depressed groups (with our without AD) included patients with either dysthymia or major depression, and small sample sizes did not allow further examinations of differences in these two diagnostic groups. Whether these two types of depression have specific qEEG correlates should be further examined.

In the present study we demonstrated a significantly lower alpha relative power in the right hemisphere of elderly depressed non-AD patients. Several studies have assessed qEEG changes in depressed patients, and most of them have consistently shown an activation (i.e., decreased alpha relative power) in the anterior areas of the right hemisphere (Shaffer et al 1983). Moreover, a similar change in right hemisphere alpha activity was found in normal individuals after they were presented with negatively ladden emotional stimuli (i.e., films designed to elicit a negative affect) (Davidson and Fox 1982). Further support for the association between depression and changes in alpha activity over the right hemisphere was reported by Ulrich et al (1984), who found that antidepressants given to depressed patients produced an increase in alpha relative power over the right hemisphere.

The question that now arises is whether depressed patients with AD show similar changes in the alpha band as depressed patients without AD. A MANOVA showed a significant effect for depression (regardless of the presence of AD) and depressed patients had a significantly lower alpha relative power in the right posterior quadrant as compared to nondepressed patients; however, while both AD and non-AD patients with depression had a reduction of alpha relative power, the topography of this change was significantly different. While depressed non-AD patients showed a decreased alpha relative power over the right hemisphere, the depressed-AD patients showed this change over left, central, and right posterior areas. Thus, in depression without AD, the alpha power was decreased unilaterally (right < left), while in depression with AD the alpha changes were bilateral and followed an anterior-posterior pattern (posterior < anterior).

Relative delta band power has also been reported to change in depressed patients. Brenner et al (1986) examined a series of 35 patients with AD, 23 patients with major depression, and 61 elderly controls. They found a significant reduction in delta activity in their group of depressed patients, which is similar to our present finding. In both Brenner's et al and the present study, delta changes were found over anterior, central, and posterior regions of both left and right hemispheres. In our study, however, these

changes were only observed in depressed patients without AD, since depressed patients with AD showed a significant *increment* in the delta relative power restricted to posterior areas. Finally, AD patients with depression also showed a significant increment in theta relative power as compared to AD patients without depression. Similar changes were not found in depressed non-AD patients when compared to the normal control group.

Taken together, our findings demonstrate specific qEEG changes in patients with AD and depression, which are different from the qEEG changes in depressed patients without AD. Several hypotheses may explain this discrepancy. First, it may be that the mechanism of depression in AD is different from the mechanism of primary depression. Several independent investigators described a significant greater loss of neurons in the locus coeruleus in depressed as compared to nondepressed AD patients (Zubenko and Moosy 1988; Zweig et al 1988; Förstl et al 1992). A second possibility is that the qEEG changes in depressed patients with AD are influenced by the dementia itself. This is a likely possibility, since all three qEEG changes observed in depressed-AD patients (i.e., region-specific changes in alpha, delta, and theta bands) were also observed in nondepressed AD patients, albeit to a significantly lesser degree.

In conclusion, our study demonstrated specific qEEG changes in non-AD depressed patients, which involved the alpha band in the right hemisphere, and the delta band. Patients with AD and depression also showed significant qEEG changes which were different from changes in depressed non-AD subjects. Whether these qEEG changes predict a faster course of the illness, as suggested by recent reports (Kuskowski et al 1993), will have to be examined in future longitudinal studies.

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