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Quantitative EEG and Statistical Mapping of Wakefulness and REM Sleep in the Evaluation of Mild to Moderate Alzheimer's Disease

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Key Words

Quantitative EEG
REM sleep
Wakefulness
Alzheimer's disease
Brain mapping

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Abstract

Statistical probability mapping was used to quantify and localize EEG differences between 27 patients with Alzheimer's disease (AD) and 25 age- and gender-matched controls. Differences in mean activity in four EEG frequency bands (delta, theta, alpha, beta) for wakefulness and for REM sleep were examined. t-statistic maps clearly highlighted common pattern anomalies in AD patients in the two states. More specifically, Alzheimer patients were more affected than control subjects in parieto-temporal and frontal regions. These differences were more prominent in REM sleep and consisted primarily in an increase in absolute delta and theta activities, and a decrease in absolute alpha and beta activities. Discriminant analysis, using a ratio of slow over fast frequencies, yielded a classification rate of 90.4% (sensitivity 81.5%, specificity 100%) for REM sleep. For wakefulness, the same measure allowed correct classification of 80.8% of the subjects (sensitivity 66.7%, specificity 96%).
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Dementia can be caused by more than 60 disorders. Alzheimer's disease (AD) is considered to be the most common and one of the most devastating dementing disorders, representing at least 50% of cases [1]. The probability that a person develops AD increases with age, with prevalence reaching 20% for people over 85 years [2]. The development of methods for detecting and diagnosing this disease in its earliest stages and for quantifying its progression is of crucial interest. Quantitative EEG analyses and brain-mapping methods have been proposed as promising tools in this endeavor [3-6].

Recently, Petit et al. [7-9] showed that EEG slowing during REM sleep is a more sensitive biological marker of AD than is EEG slowing during wakefulness. The REM sleep EEG measure allowed complete discrimination of

AD patients at mild to moderate stages from age-matched control subjects [8]. However, this study was conducted with a small number of subjects and used a limited bipolar recording.

The primary goal of this paper was to perform a topographical study with a new and larger sample of patients and a more complete EEG recording in order to identify brain regions presenting significant cortical slowing in AD. Two techniques were used to meet this goal. t-statistic mapping was used to highlight patterns of changes common to AD patients. Discriminant analyses were used to evaluate the power of REM sleep EEG measures when compared with wakefulness EEG measures for discriminating AD patients from controls.

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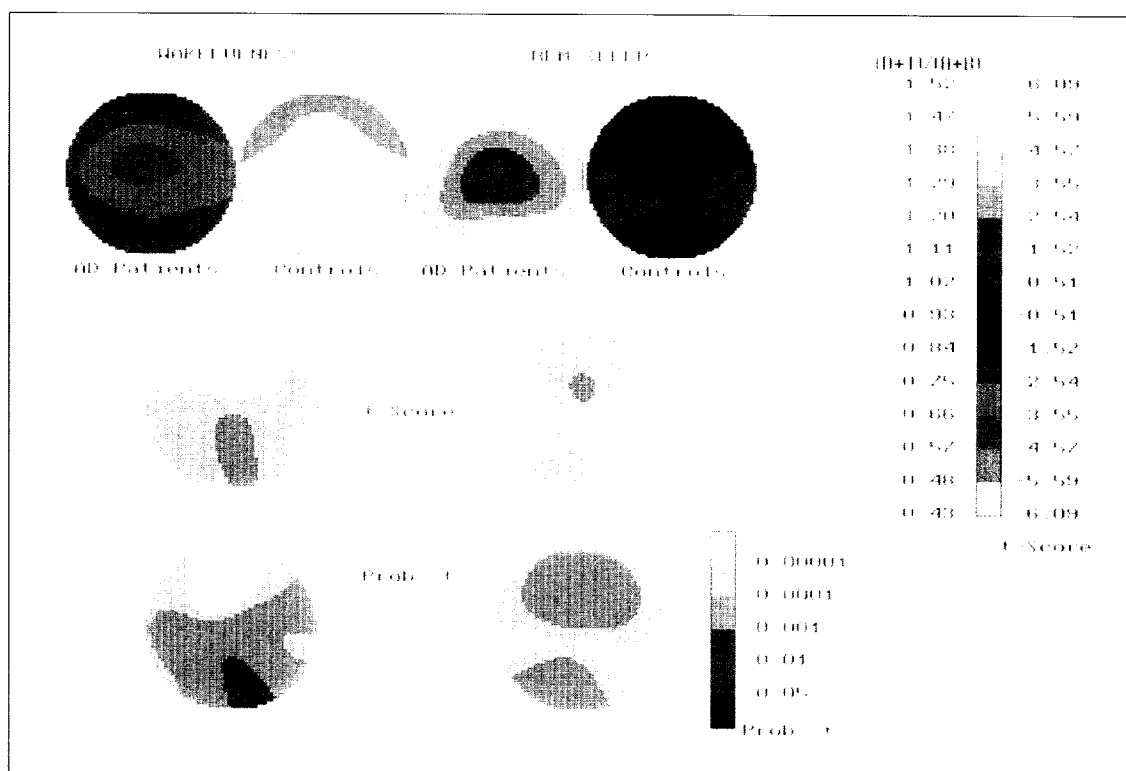


Fig. 1. Maps in the first row present mean ratio scores for the AD and control groups, for wakefulness and for REM sleep. Maps in the second row display corresponding t values for each state. Maps in the third row present significance probabilities associated with the t-value maps. The small scale displays the range of these probabilities: yellow represents the most significant between-group differences ($p < 0.00001$), while black represents non-significant differences below the 0.05 threshold. Ratio maps and t-value maps demonstrate much more slowing in the AD group than in the control group in the two states; it is observed for all regions in both states ($p < 0.05$). For wakefulness, the most significant ($p < 0.00001$) EEG slowing occurs in the frontal regions; for REM sleep, the most significant slowing occurs in the parieto-temporal regions of both hemispheres.

Methods

Subjects

The study included a group of 27 AD patients and a group of 25 control subjects. Patients (12 men and 15 women; mean age 70.1 years; age range: 57–76 years) met the criteria of the National Institute of Neurological and Communicative Disorders and Strokes – Alzheimer's Disease and Related Disorders Association work group [10] for probable AD. They were at a mild to moderate stage of AD as assessed by the Global Deterioration Scale (stages 3 and 4) [11], and their Mini Mental State scores [12] ranged from 12 to 26 (mean: 20.2). Other causes of dementia were ruled out by clinical neurological investigation, computerized tomography scan, Hachinski ischemia score and blood analyses, which included a complete blood cell count, and thyroid, B₁₂/folic acid, VDRL and urine analyses. Twenty-five elderly control subjects (13 men and 12 women; mean age 67.8 years; age range: 60–75 years) were selected, who were without neurological or psychiatric disorders, epilepsy, recent drug or alcohol dependence, or recent injury. Their Mini Mental State scores ranged from 28 to 30 (mean: 28.6). Both patients and control subjects were

free from psychoactive medications for at least 2 weeks prior to their stay in the laboratory. Written consent was given by control subjects and, in the case of AD patients, by both the patient and the spouse after they were given a detailed explanation of the study. The study was approved by the ethics committee of the participating hospital.

EEG Recording and Computer Analysis

To obtain samples of REM sleep EEG, all subjects were recorded for 1 night in the sleep laboratory. Sixteen electrodes were placed over the scalp surface using the international 10–20 system [13], i.e., Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1 and O2. These sites were recorded in a unipolar mode using an average reference. Average reference is more suitable than a linked-ear reference since the latter may contaminate the temporal regions – the regions most affected in AD. EEG signals were amplified with a 6-dB band-pass filter of 0.3–100 Hz, digitized at a rate of 256 Hz and filtered on line with a Finite Impulse Response filter having a cutoff frequency at 64 Hz. Following this filtering, only 128 samples/s/channel were retained and stored on optical disk.

Table 1. Results of statistical comparisons between AD and control groups for absolute and relative activities in the frontal and temporal regions during wakefulness and REM sleep

Activity	Delta	Theta	Alpha	Beta	Total
<i>Wakefulness</i>					
Frontal					
Absolute	↑ (0.0001)	↑ (0.0001)	NS	NS	↑ (0.05)
Relative	↑ (0.01)	↑ (0.00001)	NS	↓ (0.001)	-
Temporal					
Absolute	↑ (0.01)	↑ (0.001)	NS	NS	↑ (0.05)
Relative	↑ (0.01)	↑ (0.0001)	NS	↓ (0.05)	-
<i>REM sleep</i>					
Frontal					
Absolute	↑ (0.001)	↑ (0.05)	NS	NS	NS
Relative	↑ (0.01)	↑ (0.001)	NS	↓ (0.0001)	-
Temporal					
Absolute	↑ (0.00001)	↑ (0.01)	NS	NS	↑ (0.05)
Relative	↑ (0.00001)	↑ (0.00001)	↓ (0.00001)	↓ (0.00001)	-

↑ = More activity for AD subjects with respect to controls; ↓ = less activity for AD subjects with respect to controls; NS = non-significant difference.

Samples of the wakefulness EEG were recorded for a 10-min interval while subjects were lying on the bed with their eyes closed. To prevent drowsiness during the recordings, they were periodically asked to open their eyes. The first artifact-free EEG sections encountered were selected, for a total sample of 96 s. Special care was taken to avoid selecting sections contaminated by eye movements. Samples of the REM sleep EEG consisted of selected sections that were free from muscle and eye artifacts, and sleep spindles, and that were clearly positioned between two bursts of REMs. Total sample size for the REM sleep EEG was also 96 s. REM sleep was defined using the criteria established by Rechtschaffen and Kales [14], namely, the presence of muscle atonia, REMs, and a desynchronized EEG. There was no difficulty in recognizing any of the sleep stages for subjects at this stage of AD.

The fast Fourier transform was computed on epochs of 512 points, corresponding to a duration of 4 s for the sampling rate of 128 Hz, and yielded a 0.25-Hz frequency resolution. Prior to computation of the transform, the mean value of each epoch was subtracted from all points; the data were then tapered with a cosine window occupying 40% of the epoch. Each periodogram was computed for each epoch: for each Fourier coefficient, the real and imaginary components were squared. The periodograms of all epochs selected for analysis were then averaged to obtain the power spectrum. Four frequency bands were defined as delta (0.75–3.75 Hz), theta (4.00–7.75 Hz), alpha (8.00–12.75 Hz) and beta (13.00–31.00 Hz). The absolute and relative activity in each frequency band in both states was calculated for both groups. EEG slowing was assessed by the ratio of activity in slow frequencies (delta + theta) over that in fast frequencies (alpha + beta).

Topographic Mapping and Statistical Analysis

The paradigm for brain mapping [15] includes an algorithm for interpolating values to fill in scalp areas between the recording electrodes on the topographic display. In our case, an enhanced spherical

spline interpolation was used [16]. Probability mapping was developed in order to quantify statistical and topographical differences in electrical activity [17]. The t-statistic map represents Student t scores obtained from between-group mean comparisons. Recently, we enhanced t-statistic mapping by introducing the probability map (p-map). The latter topographically represents the probabilities associated with t values computed under the unequal variance hypothesis [18]; the p-map highlights regions with significant between-group differences. Discriminant analyses (BMDP-7M) were also performed for the regions which the mapping analyses indicated most distinguished AD patients from controls in each state; the spectral ratio was used as the discriminant measure.

Results

Group Comparisons

Visual inspection of the mean ratio maps (fig. 1) reveals EEG slowing for both wakefulness and REM sleep in AD patients relative to controls. EEG slowing was more striking for REM sleep than for wakefulness. The p-maps show at a glance the extent to which activity in different regions significantly discriminated the two groups. Although the EEG slowing index was significantly higher over all regions in both states for the AD group, the regions most markedly affected were, for wakefulness, the frontal regions followed by the temporal regions and, for REM sleep, the parieto-temporal regions.

Differences in absolute and relative activity in the four frequency bands for the two states are shown in table 1.

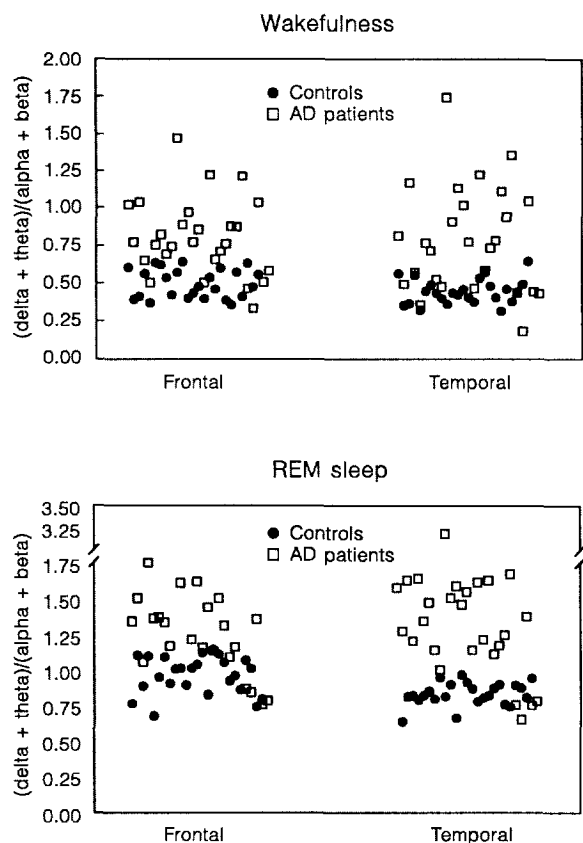


Fig. 2. Individual mean ratio values for six frontal leads and four temporal leads reflecting the mean ratio in wakefulness (top) and in REM sleep (bottom) for controls and AD patients. The variables most discriminative of the two groups were the mean frontal ratio for wakefulness and the mean temporal ratio for REM sleep. Greater overlap between the two groups was seen for wakefulness than for REM sleep.

The significance probability values presented in the table are average values for frontal and temporal regions which were extracted from the *p*-maps of each frequency band.

In wakefulness, AD patients showed higher levels of absolute and relative activity for the delta and theta bands, and lower relative activity for the beta1 and beta2 bands. Similarly, in REM sleep, AD patients showed overall higher absolute and relative delta and theta activities and lower relative alpha and beta activities. Absolute delta activity was globally higher over all regions in wakefulness for AD patients, with the most significant difference occurring at the frontal pole. However, the global difference for delta activity was even more striking for REM

sleep. In this state, areas of highly significant differences were found in both temporal and frontal regions. Absolute theta activity was also greater for AD patients over all regions in both states; the most significant differences for theta were found in parieto-temporal and frontal regions.

Discriminant Analyses

A series of discriminant analyses (jackknife classification) were performed using the ratio of slow over fast frequencies for different individual leads or lead combinations. For wakefulness, the best classifier was the mean ratio from the six frontal leads: it allowed correct classification of 80.8% of subjects (sensitivity 66.7%, specificity 96%). For REM sleep, correct classification of 90.4% of subjects (sensitivity 81.5%, specificity 100%) was obtained with the mean ratio from either the anterior temporal leads, the posterior temporal leads or the four temporal leads. The ratio was more discriminative than either the delta or the theta activities alone. Individual data points for the best classifiers in each state are presented in figure 2. The lack of dispersion of ratio values for REM sleep in the control subjects is noteworthy.

Discussion

In dementia of the Alzheimer type, several studies have demonstrated EEG slowing during wakefulness [3, 6, 19–24]. This EEG slowing is also correlated with severity of the disease [6, 23]. Some studies have reported an increase in delta and theta power as well as a decrease in alpha and beta power [21, 22]. Others have reported changes in various combinations of the four bands in the early stages of AD [3, 20, 23, 24]. In the present study, examination of absolute activity in the four frequency bands revealed that both wakefulness and REM sleep EEG slowing in AD patients results more from an increase in slow activity than from a decrease in fast activity. EEG slowing during wakefulness was especially marked in frontal and, to a lesser extent, in temporal regions. During REM sleep, the greatest EEG slowing was observed in parieto-temporal regions. These findings are in agreement with the results obtained in previous studies. Duffy et al. [4], using topographic mapping of the waking-state EEG, have also found right temporal slow activity in younger AD patients, and frontal slow activity in older AD patients. Breslau et al. [3] performed a wakefulness EEG topography comparison between AD patients and elderly controls and reported a significant and selective increase in delta activity in parieto-temporal

regions. Analysis of regional activity observed with positron emission tomography indicates decreased parieto-temporal metabolic rates without occipital decreases [25–27]. Postmortem studies also report degeneration to be more severe in temporo-parietal and frontal regions [28] with the presence of a high level of neuritic plaques and neurofibrillary tangles [29]. In summary, the EEG patterns observed in wakefulness and REM sleep in the present study are consistent with the findings of neuroimaging and neuropathology studies.

The discrimination rate obtained in this study with REM sleep quantitative EEG (90.4%) is one of the highest among the previously published single-variable discriminant analyses – especially considering that our population is of mild to moderate AD patients. With quantitative analyses of the awake EEG, Soininen et al. [30] obtained a discriminative power of 86% (sensitivity 82%, specificity 89%) while Brenner et al. [20] obtained a sensitivity of 66% and a specificity of 93%. However, samples in both studies included a high proportion of severely demented patients, thus inflating the sensitivity estimates. In fact, when Brenner et al. considered only mildly demented patients, their sensitivity estimate dropped to only 36%.

Quantitative and statistical mapping of the REM sleep EEG are very useful research tools and are probably the best biological markers of AD to be developed so far. ApoE testing does not provide a definitive answer. First, about 80% of familial and only 64% of sporadic AD have at least one copy of the apoE4 allele [31], yielding a sensitivity below 80%. Second, 31% of people who will not develop AD possess at least one copy of the ApoE4 allele [31]; thus specificity is low. Brain-imaging methods, although very helpful for ruling out other causes of dementia, are not sensitive enough to be used for early diagnosis. Indeed, despite efforts made by a group of experienced neuroradiologists to establish an MRI interpretation protocol for diagnosing AD, the latter has not yielded satisfactory results [32]. Similarly, SPECT was found to be less sensitive than REM sleep EEG in evaluating cortical impairments due to AD [33].

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