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Electroencephalographic Vigilance Dynamics in Multiple Sclerosis during an Acute Episode and after Remission

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Summary. Twenty-three patients with multiple sclerosis were studied during an acute episode and again 4 weeks later. Whereas the patients' clinical condition improved significantly (Kurtzke DSS: from 3.9 (SD 1.4) to 3.3 (SD 1.5), $P < 0.001$), the conventional power spectra of the resting EEG showed no marked changes. Following a 10-min EEG recording under resting conditions the patients performed a visuomotor tracking task, during which a further EEG recording was made. The frequency of the subvigilant non-A epochs of Loomis et al. as calculated for each minute of the resting recording was taken as the basis for evaluating the EEG dynamics of vigilance. A comparison during and after relapse showed differences in the time courses of the numbers of non-A epochs. While the non-A epochs were not time dependent in the acute phase, remission was characterized by a steady increase in non-A epochs across the 10 min of the recording period. This change in the dynamics of vigilance, which approximates a physiological pattern, was accompanied by an improvement in visuomotor tracking performance. Comparison of the power spectra of the EEG recorded during the tracking task showed a bifrontal increase in absolute alpha power during remission.

Key words: Multiple sclerosis – EEG vigilance dynamics – Visuomotor tracking task

Introduction

Visual evaluation of the EEGs of patients with multiple sclerosis (MS) reveals pathological findings in 20%–80% of cases [16], depending on the severity and acuity of the clinical symptoms, and the criteria on which investigators base their assessment.

Interest is focused mainly on irregularities in and slowing of the background activity, and also focal changes. As yet very little attention has been paid to the spatio-temporal characteristics of the recording as a manifestation of EEG vigilance dynamics. Of the investigators who have conducted quantitative EEG analyses in MS [4, 6, 14] only Harrer et al. [6] have discussed the question as to whether the differences they observed between MS patients and a group of normals (reduced alpha activity and increased beta, theta and delta activity) could be interpreted as a sign of a change in vigilance level.

Following on from a previous visual EEG study [2] in which 24% of the MS patients had considerable fluctuations in vigilance, the aim of the present investigation was to make a quantitative study of vigilance dynamics in MS, using a procedure described by Ulrich and Frick [17], and to discover any differences between the acute episode and remission.

Subjects' performance in a visuomotor tracking task (VTT) [8, 18] was measured to serve as external validation for the EEG findings. The results of the VTT have already been published elsewhere [3].

Patients and Methods

Twenty-three patients with MS (17 women, 6 men with an average age of 39.9, SD 9.9 years) were investigated on admission to our clinic during an acute episode, and again 4 weeks later, when they were in relative remission.

Twenty-one of these patients fulfilled the criteria for clinically definite MS. The average duration of disease for these patients was 8.9 (SD 7.7) years. Two of the patients were experiencing their first attack. In these cases the clinical symptoms, cerebrospinal fluid (CSF) findings and results of magnetic resonance imaging were also consistent with a diagnosis of laboratory-supported definite MS [15]. Nineteen patients underwent adrenocorticotrophic hormone (ACTH) therapy. Four went into spontaneous remission. None were receiving any sedative medication.

The extent of neurological deficit and the severity of disablement were assessed during the acute episode and 4 weeks later by an investigator who was not the physician treating the patients, according to the Functional System Scale (FFS) and the Disability Status Scale (DSS) developed by Kurtzke [9].

EEG techniques. The EEG recordings were done on the same days as the clinical evaluations were made. They were also performed at a similar time of day (between 10 and 11 a.m.) with a Mingograph 21 manufactured by Siemens-Elema.

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Ag/AgCl adhesive electrodes were placed according to the international 10–20 scheme at positions F_3, F_4, O_1 and O_2, each referenced at the ipsilateral ear; time constant 0.3; filter 70. Ipsilateral ear reference represents an essential of the quantification procedure we made use of, since it underlies the assessment of the anterior-posterior relationship of the alpha amplitude which determines subdivision of stage A [17]. The electrode-skin impedances were less than 5 kΩ. The patients were sitting in a semirecumbent position. Their eyes were closed and they remained undisturbed for the duration of the recording. A 10-min recording was simultaneously recorded on a paper chart and stored on FM analogue tape.

Table 1. Mean values on the Kurtzke scale during an acute episode and following remission in 23 patients with multiple sclerosis

Kurtzke scale	Acute episode	Remission	*t*-test (two-tailed)	
			t	*P*
Functional system scale	13.9 ± 4.8	11.1 ± 5.5	−5.13	< 0.001
Disability status scale	3.9 ± 1.4	3.3 ± 1.5	−3.73	< 0.001

Following the resting EEG the patients performed a VTT [8] with simultaneous EEG recording. For the test the patients were presented with a target signal (a cross) on a monitor which was in continuous stochastic movement in the horizontal plane. Their task was to pursue this target signal as closely as possible with a response signal (an arrow) also displayed on the screen and controlled by a small joy-stick.

The test lasted 200 s and was divided into four 50-s sections of varying difficulty. The measure of difficulty was the mean angle velocity of the target signal. The subtests with the lowest (angle velocity 3.8°/s) and highest (angle velocity 5.3°/s) degrees of difficulty were evaluated.

Tracking analysis. The accuracy of control was determined by calculating the information rates transmitted between the target and response signals exactly in bits per second. The methods used to analyse the signals have been described elsewhere [8]. No substantial learning effect with re-tests at a 1-week interval showed up in a previous study [18].

EEG analysis. All four leads of the resting EEG were analysed quantitatively as described by Ulrich and Frick [17]. AD conversion was done with a sampling frequency of 256 Hz. Artefacts were not eliminated, as this would have interfered with the process of determining the time dependency of the subvigilant EEG patterns.

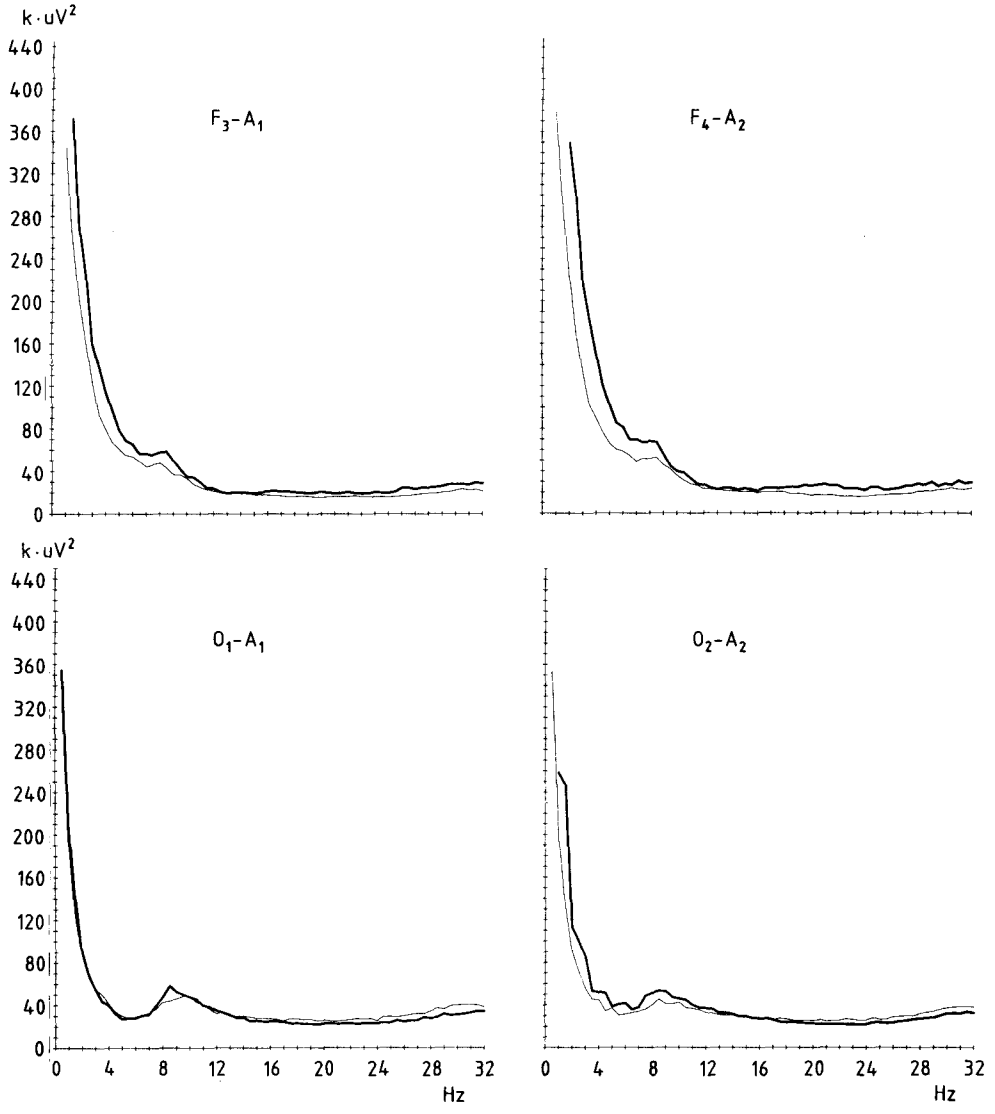

Fig. 1. Mean power spectra in leads F_3–A_1, F_4–A_2, O_1–A_1, O_2–A_2 of the resting EEG during the acute episode and after remission ($n = 23$). —— Acute episode; ▬▬ remission

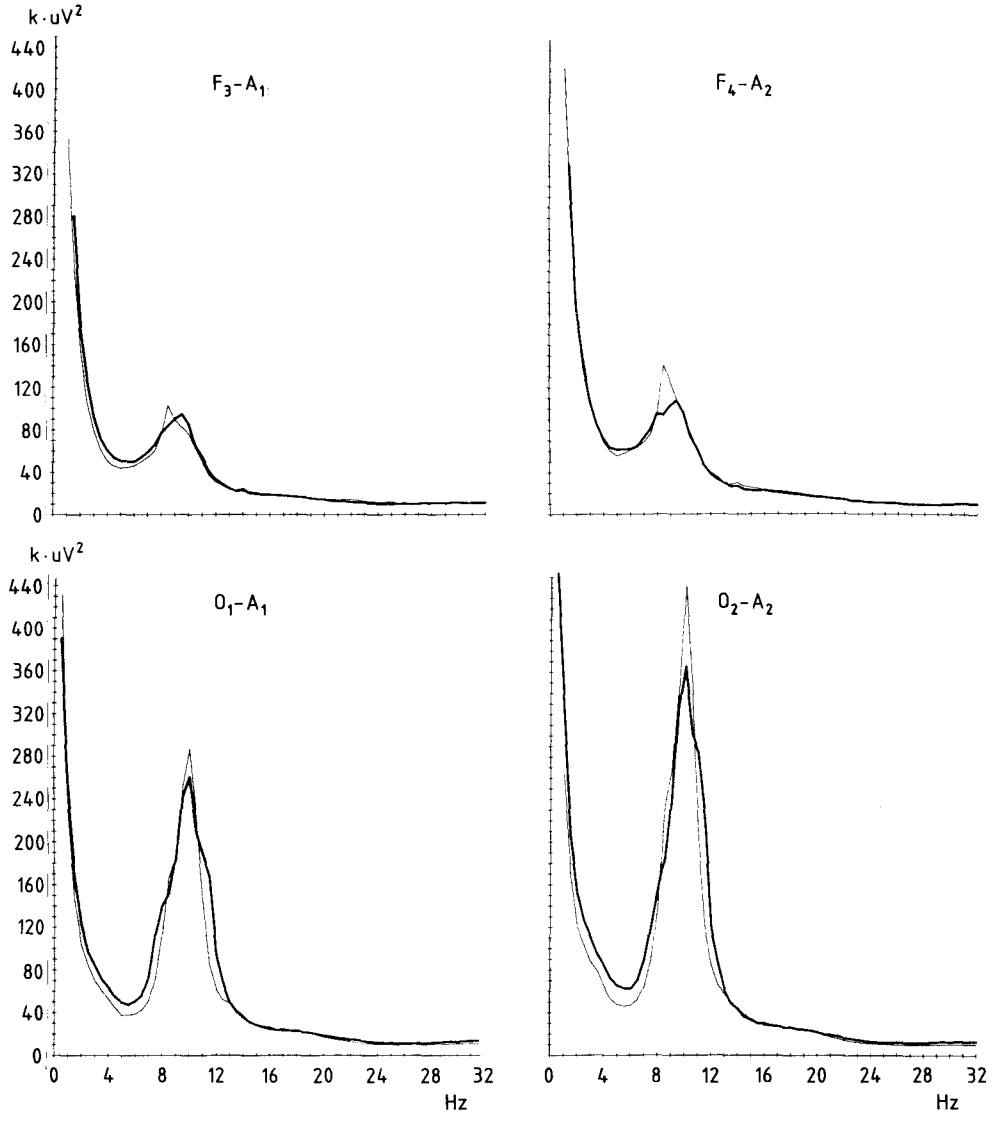

Fig. 2. Mean power spectra of the EEG recorded simultaneously with the visuomotor tracking task during the acute episode and after remission. Leads F_3–A_1, F_4–A_2, O_1–A_1, O_2–A_2 ($n = 23$). —— Acute episode; ▬▬ remission

The digitized EEG was plotted to serve as the control (DA conversion). With this method recordings with marked disturbances can be excluded from further analysis. The traces were segmented consecutively into 2-s epochs and the absolute power spectrum between 0 and 32 Hz was determined for each epoch [fast Fourier transformation (FFT); spectral resolution: 0.5 Hz]. The 300 2-s periodograms thus obtained for each EEG served as the data base for the subsequent computations. The proportion of the total activity (0–32 Hz) accounted for by alpha activity between 7.5 and 13 Hz was determined for each 2-s segment. This step was conducted as a preliminary to distinguishing between stage A epochs and stage non-A epochs [13].

The criterion for stage A was that the alpha power should constitute at least 50% of the total power in at least one of the four leads. The frequency of occurrence of the non-A epochs was determined for each minute of the 10-min recordings. For the EEG recorded during the VTT we determined the mean power spectrum for the whole test (duration: 4×50 s, equivalent to 100 2-s segments.

Results

Clinical Symptoms

Clinical improvement was defined as a percentage reduction in the total scores on the Kurtzke scales (DSS and FSS). Nineteen patients showed a 7%–62% (mean 26.3%) regression of their symptoms within the 4-week study period. Three patients showed no change and one patient deteriorated slightly (−7%). Table 1 gives an overview of the FSS and DSS means obtained in the acute episode and after 4 weeks' hospital treatment. The differences are highly significant.

EEG Parameters

Mean power spectra in the resting EEG. Figure 1 shows the mean power spectra for leads F_3–A_1, F_4–A_2, O_1–A_1 and O_2–A_2 during the acute episode and after remission. As the profiles had given reason to expect, the comparisons calculated with the *t*-test showed no significant differences for the conventional frequency bands.

Mean power spectra in the EEG recording during the VTT. Figure 2 shows the mean power spectra of the EEGs recorded during the VTT. In contrast to those obtained under resting conditions these recordings showed an increase in 7.5–13 Hz alpha activity at both frontal leads ($t = 2.17$; $P < 0.05$; *t*-test, two-tailed) after 4 weeks.

Table 2. Group means $\sqrt{(\text{maximally } 30)}$ and standard deviations of the non-A epochs for each 10 min period of the resting recording during the acute episode and after remission ($n = 23$)

		Recording-time min									
		1	2	3	4	5	6	7	8	9	10
Acute episode	Mean	11.4	11.5	12.9	12.3	12.6	12.0	12.0	12.2	11.5	11.9
	SD	11.2	10.8	11.8	12.2	12.2	11.6	11.0	11.7	10.6	10.5
	%	38	38	43	41	42	40	40	41	38	40
Remission	Mean	9.2	9.7	10.2	10.0	10.7	11.9	12.7	13.6	14.9	14.1
	SD	9.4	10.6	10.2	10.3	10.1	10.3	9.5	10.4	10.4	10.1
	%	31	32	33	33	36	40	42	45	50	47

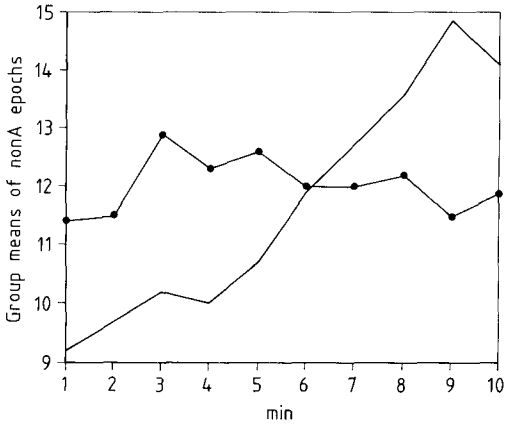

Fig. 3. Graph showing the group mean values for the non-A epochs during the 10-min resting recording in 23 patients with multiple sclerosis. The vigilance dynamics in the acute episode were significantly different from those after remission (two-factor analysis of variance, see text). ●—● Acute episode; —— remission

Table 3. Relationship between normalization of EEG vigilance and improved performance on the visuomotor tracking task; 4-fold frequency distribution (Fisher's exact test, see text)

	Patients *(n)* with above-average performance in the tracking task	Patients *(n)* with below average performance in the tracking task	Total
Patients *(n)* with EEG normalization	10	1	11
Patients *(n)* with only a slight, or no trend towards EEG normalization	4	7	11
Total	14	8	22

EEG vigilance dynamics. Table 2 lists the group means for the non-A epochs for each $\sqrt{\text{minute}}$ of the 10-min periods during the acute episode and after remission. The graph (Fig. 3) shows the pre-/post differences. While in the acute phase the group means for the number of non-A epochs did not indicate any dependency on time, after remission there was a trend towards an increase in the frequency of non-A epochs during the course of the recording, the initial level being somewhat lower. The data were analysed statistically by two-way ANOVA with repeated measurement for both factors. The factors selected were "day" (acute phase and remission) and "minute" (min 1...10). While a significant main effect was found for the factor "minute" ($F_{9,198} = 2.43$; $P < 0.02$), none was found for the factor "day" ($F_{1,22} = 0.04$; NS.). As evidenced by the interaction effect between "day" and "minute" ($F_{9,198} = 3.35$; $P < 0.001$), there was a difference between the time-dependent frequencies of non-A epochs in the patients' recordings in the acute phase and 4 weeks later, i.e. there was a difference between the EEG vigilance dynamics at these two times.

Relationships between clinical symptoms, EEG and performance in the VTT

Neither in the acute episode nor 4 weeks later were significant correlations observed between the spectral powers in the different frequency bands and the extent of clinical impairment according to Kurtzke's FSS and DSS scales. In a previous report on visuomotor tracking performance alone [3] it was found that the patients showed an improvement in remission, but the difference was significant only in the subtest with the lowest level of difficulty (2.35 bits/s in the acute phase vs 2.58 bits/s after 4 weeks' treatment; $t = 2.59$; $P < 0.05$, two-tailed).

In the present study we investigated whether this improvement in test performance was reflected in the spectral profile of the EEG. The result was negative for both the resting EEG and that recorded during the test.

However, there was a relationship between performance in the VTT and vigilance dynamics. The relationship between tracking performance and vigilance dynamics was determined as follows. First, the differences between the non-A frequency in the second half of the recording (min 6–10) and the first half of the recording (min 1–5) were determined. Since in physiological vigilance dynamics the frequency of non-A epochs would be expected to be much higher in the second half, these difference scores can be taken as a rough measure of vigilance dynamics. In a second step we determined for each patient the changes (differences) in these difference scores between the 2 days on which the recordings were made. The patients were then ranked according to their change scores, the highest score representing the most pronounced normalization of the vigilance dynamics. Two groups were formed by dividing the sample at the median (the median class was eliminated), one with stronger and one with weaker or completely lacking normalization of vigilance dynamics.

The patients were similarly divided into two groups on the basis of the extent of the changes in their test performance (subtest with the lowest level of difficulty) between the 2 test days.

Table 3 shows the resulting 4-fold frequency distribution. We found that normalization of vigilance dynamics was associated with an improvement in tracking performance (Fisher's exact test, $P < 0.02$, one-tailed).

Discussion

The only change found by Colon et al. [4] in their longitudinal EEG study in ten patients with MS was an increase of 1 Hz in the dominant alpha frequency. We were unable to confirm this finding.

Also, in contrast to Colon et al. [4], we found no relationships between the severity of illness and the spectral powers within the conventional frequency bands. Our findings are more consistent with those of older, visually evaluated EEG studies reported in the literature, according to which there is no relation between clinical symptoms and EEG findings [5, 16].

We feel that in view of the lack of comparable findings and relevant models it would be premature to attempt to interpret the increase in frontal alpha activity we observed in the EEG recorded during the visuomotor test after clinical remission.

We consider that the main finding of this study is the confirmation of a relation between clinical remission and the time-dependent frequency of subvigilant non-A epochs as determined quantitatively using the method proposed by Ulrich and Frick [17].

As suggested by the findings obtained for the groups of young healthy subjects, in physiological dynamics the frequency of subvigilant non-A epochs remains unchanged for about 4–6 min under resting conditions. Thereafter there is a constant rise in the frequency of non-A epochs, which on the level of the sleep-wake dimension corresponds to a shift in the direction of sleep [19].

In contrast, in the acute phase the group of MS patients exhibited a relatively high percentage of non-A epochs right from the start of the recording, and there was no trend towards an increase in the course of the recording. After remission, however, the vigilance dynamics showed a pattern similar to that considered to be physiological.

Since conventional analysis of the resting EEG, which is based on mean power spectra and is thus a static measure, has failed to reveal any relationships between EEG findings and clinical remission, vigilance dynamics is gaining significance as a sensitive indicator of pathologically altered patterns in the system as a whole. The procedure we employed can also be considered to be a function test under defined conditions (resting, duration of recording). Referring to a paper by Head [7], Bente [1] stated that a disturbance of the mechanisms regulating vigilance is an indication that not merely a single aspect – e.g. regulation of the sleep-wake rhythm in the strict sense of the term – is impaired, but that there is a generalized disturbance of the differentiation and availability of adaptive functions. In light of this, the impairment of EEG vigilance dynamics (German: *Funktionswandel*) observed in the MS patients in an acute phase can be related to descriptions on a different level, such as those concerning impairment of information processing in MS [10–12]. The correlation between normalization of the EEG vigilance dynamics and improved performance on the VTT is empirical evidence of this.

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