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# The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy

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**Abstract** The question of how to define a therapeutically adequate electroconvulsive therapy (ECT) has been under discussion since the early days of ECT. Although convention has asserted a demand for minimum seizure times, the complex electrophysiological conditions involved in developing a generalized seizure make it problematic for therapeutic efficacy of ECT to be linked only with seizure duration. Within the framework of an open clinical study of 40 patients, selected parameters of the ictal electroencephalogram (EEG) have now been examined with respect to differentiation between therapeutically effective and ineffective treatments. For this purpose a rating scale covering both quantitative and qualitative features of the ictal EEG was used. Although this study recorded no correlations between seizure duration and clinical improvement, correlations were established between clinical improvement, on the one hand, and the frequency of epileptic discharges and their slowing during the spike-wave phase as well as the stereotypy of the discharge or a "stable" pattern of rhythmic spike-wave or sharp wave complexes, on the other. The results suggest that several of these EEG parameters might be combined to form a marker for therapeutically adequate ECT, and that treatment might be controlled accordingly.

**Key words** ECT · Ictal EEG · Electrophysiological marker · Efficacy · Epileptic discharges

## Introduction

The therapeutic efficacy of individual electroconvulsive therapy (ECT) treatment has not yet been defined. As seizure production per se has historically been suspected to be therapeutically effective ("all or nothing" principle), monitoring was confined to recording the occurrence of a seizure (Weiner and Krystal 1993). With Ottosson (1960) and Kirstein and Ottosson (1960) having found that seizures shortened by lidocaine were less therapeutically effective, the seizure duration asserted itself as the criterion for adequate ECT without Ottosson having explicitly postulated this. In recent years, however, seizure duration has been subject to increasingly critical comments (e.g. Swartz 1993c; Krystal and Weiner 1994; Sackeim 1994) because it has been found that seizures of "adequate" duration may be produced without therapeutic effects. In contrast to the criterion of seizure duration, the findings recorded by Ottosson (1960, 1962) and 20 years earlier by Antrop (1941) in the ictal electroencephalogram (EEG) were virtually ignored, although Antrop had formulated that the factors characterizing a therapeutically effective ECT included generalized epileptic discharges with a polyspike pattern with transition to a spike-wave pattern during the clonic phase, followed by postictal suppression. In last years studies comparing the ictal EEG of the unilateral and bilateral ECT were carried out. They revealed higher amplitudes, more pronounced symmetry and postictal suppression in the bilateral ECT, which had been considered more therapeutically "effective" (Brumback and Staton 1982; d'Elia and Perris 1970; Enderle et al. 1986; Gerst 1982; Krystal et al. 1992; Swartz and Larson 1986). These findings suggested that factors other than seizure duration might be of significance in distinguishing therapeutically effective from ineffective ECT treatments. Based on studies by Nobler et al. (1993), Krystal et al. (1993), Weiner (1982), and Weiner et al. (1991, 1993), which recorded differences between various ECT dosage strategies by means of the ictal EEG, selected ictal EEG parameters were examined with respect to differentiation between therapeutically effective and less effective ECT treatment within the framework of an open clinical study of 40 patients. The hypothesis was that more "intense" epileptic discharges result in increased therapeutically effective ECT.

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**Table 1** Patient sample. HAM-D Hamilton Scale for Depression; BPRS Brief Psychiatric Rating Scale

| | Responders ($n$ = 29) | | Nonresponders ($n$ = 11) | | $P$-value |
|---|---|---|---|---|---|
| | Mean[a] | SD | Mean[a] | SD | |
| Age (years) | 46.24 | 15.6 | 44.22 | 14.00 | n.s.[b] |
| M:F | 14:15 | | 2 : 9 | | n.s.[c] |
| Pre-ECT HAM-D[e] | 35.22 | 5.87 | 24.83 | 4.02 | 0.001[d] |
| Pre-ECT BPRS[f] | 56.16 | 14.39 | 49.33 | 11.42 | n.s.[d] |
| Diagnosis (depressive: schizophrenic) | 20 : 9 | | 7 : 4 | | n.s.[c] |
| Length of current episode (weeks) | 13.96 | 14.12 | 15.16 | 18.68 | n.s.[b] |
| Length of hospitalization until ECT (days) | 45.20 | 44.48 | 41.33 | 21.72 | n.s.[b] |
| Length of hospitalization after start of ECT (days) | 84.28 | 60.17 | 96.44 | 44.32 | n.s.[b] |
| Number of previous psychiatric admissions | 2.24 | 2.02 | 2.77 | 2.52 | n.s.[b] |
| Post-ECT HAM-D[e] | 10.72 | 4.41 | 15.16 | 2.48 | 0.008[d] |
| Post-ECT BPRS[f] | 28.62 | 5.00 | 38.33 | 5.51 | 0.02[d] |

[a] Mean values except for $\chi^2$-test
[b] $t$-test
[c] $\chi^2$-test
[d] U-test
[e] Only depressive patients
[f] Only schizophrenic patients

## Subjects and methods

This open clinical study covered 40 patients treated consecutively with right unilateral ECT. The main patient data appear in Table 1. Of the 40 patients 27 fulfilled ICD-10 criteria for a moderate or severe depressive episode or DSM-IV criteria for major depression (m:f = 12:15), whereas 13 additional patients were classified according to ICD-10 or DSM-IV criteria (m:f = 4:9) as suffering from schizophrenic psychoses. (Only those patients who had undergone at least six ECTs were included; ECT was continued until a plateau of a clinical improvement was reached.) The depressive patients were aged between 26 and 74 years (mean 51.26 ± 13.19 years), and the schizophrenic patients between 23 and 45 years (mean 34.09 ± 11.85 years). All patients were right-handed. Psychotropic medication was discontinued not later than 3 days before ECT; only individual doses of diazepam (up to 5 mg/d) or Pipamperon (40 mg/d) were allowed. Ratings were performed according to the 21-item Hamilton Scale for Depression [(HAM-D) Hamilton 1960] or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) between 4 p.m. and 6 p.m. The response criteria were at least 50% symptom reduction on the HAM-D or 40% on the BPRS. The same criteria were used to evaluate the clinical result up to the fourth ECT (rapid or slow responders).

### Performance of ECT

With the informed consent of the patients, all ECTs were performed with a THYMATRON-DGx device (Somatics Inc., Lake Buff, IL, USA) in brief-pulse technique (1 ms, 0.9 As). ECT monitoring was done with a cuff on the right arm compressed above systolic blood pressure and by EEG. All patients received right unilateral ECT; the stimulus electrodes were placed in the d'Elia position. Stimulus dosage was based on a modified age-dependent strategy. For patients aged between 30 and 60 years, the stimulus dosage (as a percentage of maximum energy) was based on age. To prevent the risk of underdosage, stimulation of the 9 younger patients (< 30 years) was set at 151 mC (= 30% of maximum energy); for the remaining 9 patients aged over 60 years, treatment was done with 302 mC (= 60%) to avoid unnecessarily high stimuli. If seizure times were less than 25 s (cuff) or less than 30 s (EEG), the stimulation was repeated with an additional 10% (10 ECT) and an additional 20% of maximum stimulus energy in the case of a second restimulation (2 ECT). The patients received 0.5 mg atropine sulphate prior to anesthesia and were preoxygenated with 100% oxygen by means of a mask. The anesthesia itself was performed with a mean 1.35 mg/kg methohexital (i.v.) and 0.7–1.0 mg/kg i.v. succinylcholine for partial relaxation. The doses were maintained throughout the series. The ventilation rate was kept constant at 12–15 breaths per min. Monitoring was done before, during and after ECT by ECG and continuous measurement of blood pressure and pulse rate.

### EEG monitoring and analysis

EEG monitoring was done with bifrontomastoid EEG leads (Fp1–A1, Fp2–A2, international 10–20 system, Ag/AgCl electrodes). The gain was set for all patients to 5 mm = 100 uV; calibration was performed at the start, in the middle and at the end of the data collection time by the authorized dealer. A rating schedule in part adopted from Krystal et al. (1993), Nobler et al. (1993), and Weiner et al. (1993) was used for visual analysis of the ictal EEG, with both qualitative and quantitative parameters taken into account. In addition, the parameters determined by the THYMATRON-DGx (postictal suppression and concordance) were included. Evaluation was done separately according to the individual phases: latency phase (immediately after stimulation until the beginning of the recruitment phase), recruitment phase (high-frequency rhythmic activity, epileptic recruitment rhythm), polyspike phase (chaotic polyspike activity, gradual transition from tonic to clonic activity), spike-wave phase (high-amplitude regular epileptic activity, "delta-firing," running synchronously with the motor discharges), and termination phase (irregular slow-wave activity, diminishing amplitudes). The factors ascertained in the individual EEG phases were duration, frequency, and maximum peak-to-peak (mean values from three successive discharges) amplitude. In the spike-wave phase, stereotypy (0–6) and symmetry (+3 right/0/-3 left) were also evaluated on the corresponding scales, and the EEG pattern was classified by visual analysis [(poly-) spike wave, sharp slow wave, irregular polyspike theta, irregular theta groups]. In the spike-wave phase the frequency [maximum, minimum (at least three successive spike-wave complexes if a clear-cut rhythm was perceptible on visual analysis), slowing amount of epileptic discharges (short: amount of slowing) during spike-wave phase (difference between maximum and minimum frequency) was determined together with the time at which slowing began [start slowing (lowering of frequency at least 0.4 Hz)]. The strength of the entire seizure was also determined by visual evaluation and classified on a scale from 0 to 6. Values were determined both for individual ECTs and for series (up to the fourth ECT, up to the end of

the series). Thanks to careful preparation in accordance with APA recommendations (1990), only six EEG strips from the total of 291 ictal EEGs were unserviceable or could be only partially evaluated because of excessive artifact superimposition. In an additional 29 EEGs some timely limited artifacts were visible. In these cases an artifact-free section was chosen for analysis. All EEG ratings were performed by one and the same rater (H.F.). Reliability was verified by having 50 randomly selected EEGs examined by a second rater (Falko Rath, a colleague) according to the same criteria; the correlation coefficients were between 0.76 and 0.85. The EEG raters were not informed of the patient data at the time of EEG evaluation, and the clinical raters were blind to EEG data.

### Temporal aspect of the onset of the therapeutic effect of ECT

The electrophysiological parameters were related not only to the clinical result up to completion of the ECT series, but also to the improvement up to the fourth ECT. Various reasons lead to this strategy: The main aspect was that several EEG changes (Weiner 1980a) occurred during ECT series [particularly increase in delta power after fourth ECT (Rosen and Silferskiöld 1987) and the rise in seizure threshold (Sackeim et al. 1991), lower ictal amplitudes, and lower postictal suppression during ECT series (Krystal et al. 1995)] conflicting with the interesting EEG features in this study. On the other side, from a clinical point of view very few studies have dealt with the temporal aspect of the onset of the therapeutic effect of ECT (Price et al. 1978, Post et al. 1987; Scott and Whalley 1993; Rodger et al. 1994).

### Statistics

For the exploratory analysis of differences between response groups the paired *t*-test (two-tailed), U-test, $\chi^2$-test, and single multivariate ANOVA were used. In a second step multivariate analysis of variance (MANOVA) of EEG measures was conducted using age, methohexital dose, gender, and diagnosis as covariates and response status as factor. The statistical distribution of the covariates for the different levels of response status was examined previously and in cases of significant differences between the groups considered. For correlations the Pearson coefficient was calculated. The significance level was set at $P < 0.05$.

## Results

### Influencing variables of the ictal EEG

A number of variables influencing the ictal EEGs were identified in our patients. Patients aged over 42 years (median) displayed a significantly ($P < 0.000$) shorter seizure duration. This overall duration with a mean shortening of just under 10 s was due essentially to the similarly significant ($P < 0.000$) shortening of the spike-wave phase (10.9 s). Significantly lower maximum amplitudes (polyspike, spike-wave phase) were also recorded. In addition, the stereotypy of the spike-wave phase was less pronounced in these patients (> 42 years). However, higher doses of methohexital (1.44 vs 1.30 mg/kg; $P < 0.007$) were also necessary in patients over the age of 42 years.

Higher doses of methohexital (> 1.44 mg/kg) led to a significantly (mean 4.7 s) shorter seizure duration (42.4 vs 47.1 s), with the spike-wave phase significantly ($P < 0.001$) shorter and the amplitudes during the spike-wave phase significantly ($P < 0.01$) lower. Moreover, the tonic phase of the seizure was prolonged with methohexital doses in excess of 1.44 mg/kg. The stereotypy of the spike-wave phase was significantly less pronounced ($P < 0.001$) and the amount of slowing during the spike-wave phase significantly reduced ($P < 0.008$).

The known lower seizure threshold for women was expressed in the significantly shorter duration of the recruitment phase (1.5 vs 1.9 s) and in the significantly higher amplitudes (polyspike, spike-wave phase); the slight differences in seizure duration between men (46.8 s) and women (44.3 s) fell short of significance level. The mean stimulus dosage was 241.5 mC for women and 251.5 mC for men.

Single multivariate ANOVA analysis of the influence of the variables age, gender, and methohexital dosage/kg (in each case in relation to the median of the values) on seizure duration revealed that the age-dependent effect (F 40.1; $P < 0.000$) played the greatest role. However, gender (F 7.2; $P < 0.008$) and methohexital dosage related to body weight (F 5.5; $P < 0.02$) were also recorded as influencing variables.

### Ictal EEG parameters as markers for therapeutically adequate ECT

#### *Responders up to the end of ECT series*

A total of 29 (72.5%) from the 40 patients fulfilled the above-listed response criteria ("responders") after completion of ECT therapy. There were no significant differences between responders and nonresponders in distribution of diagnostic groups, gender, age, and methohexital dosage. The univariate statistics for each EEG variable for responders and nonresponders appear in Table 2.

The mean amplitudes during the spike-wave phase were higher (but not reaching significance) among responders (related to the entire ECT series), and there was a positive correlation ($P < 0.05$) between reduction in Hamilton ($r = 0.40$) or BPRS ($r = 0.45$) scores and spike-wave phase amplitudes. Among responders there were more frequently regular spike-wave or sharp wave patterns (Fig. 1), whereas irregular, "less organized" patterns were predominant among other patients. Slowing of discharges during the spike-wave phase started earlier and was more pronounced among responders (but not reaching significance); (Table 2). At the same time there were positive correlations ($P < 0.05$) between clinical improvement (reduction in Hamilton and BPRS scores) and amount of slowing. The relationship between slowing and the temporal course of the spike-wave phase is shown in Fig. 2. Among responders symmetry was more pronounced during the spike-wave phase (0.03 vs 0.55; $P < 0.01$). No correlations were found between the baseline Hamilton score (significant difference between responders and nonresponders; see Table 1) and the ictal EEG measures.

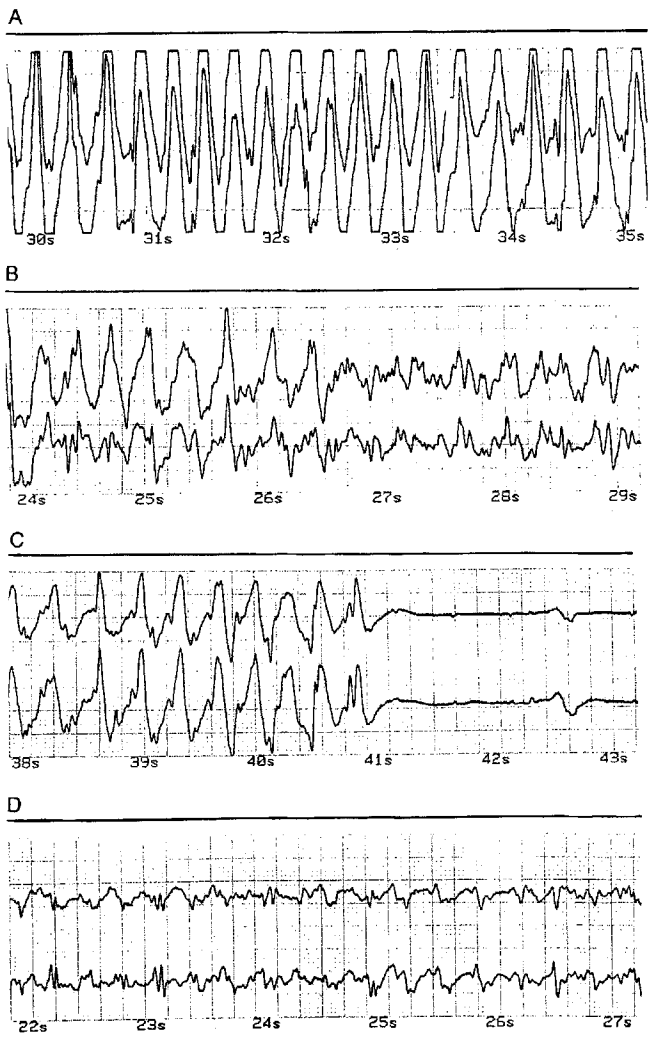
In addition, multivariate analysis of variance (MANOVA) of EEG features (recruitment phase duration, symmetry, strength) was conducted using age, methohexital dose, gender, diagnosis as covariate, and response status

**Table 2** Results of EEG monitoring up to the end of ECT series

| | Responder ($n$ = 29) | | Nonresponder ($n$ = 11) | | $P$-value |
|---|---|---|---|---|---|
| | Mean[a] | SD | Mean[a] | SD | |
| Age (years) | 46.24 | 15.6 | 44.22 | 14.00 | n.s.[b] |
| mg/kg | 1.41 | 0.37 | 1.33 | 0.35 | n.s.[b] |
| Seizure duration (EEG) | 46.49 | 11.15 | 45.00 | 12.01 | n.s.[b] |
| Recruitment phase (s) | 1.65 | 0.62 | 1.98 | 0.55 | 0.04[b] |
| Spike-wave ampl (uV) | 513.18 | 114.99 | 490.54 | 130.63 | n.s.[b] |
| Spike-wave pattern[d] | 108:121 | | 22:38 | | $\chi^2$ 1.63, $P < 0.20$[c] |
| Concordance (%) | 80.52 | 13.56 | 68.53 | 38.14 | n.s.[b] |
| Symmetry (+3–0/–3 left) | 0.03 | 0.48 | 0.55 | 0.57 | 0.01[b] |
| Start slowing (%) | 60.83 | 14.61 | 66.83 | 13.62 | n.s.[b] |
| Amount of slowing (Hz) | 1.21 | 0.49 | 1.01 | 0.60 | n.s.[b] |
| Stereotypy (0–6) | 4.62 | 0.40 | 3.69 | 0.79 | n.s.[b] |
| Strength (0–6) | 4.55 | 0.75 | 3.60 | 0.72 | 0.09[b] |

[a] Mean values for the two groups compared except for $\chi^2$-test
[b] $t$-test
[c] $\chi^2$-test
[d] Rhythmic spike wave, sharp wave complexes against other irregular ictal pattern

as factor. A significant effect (F = 6.48; $P < 0.002$) of response status could be detected. The in the MANOVA analysis included univariate F-tests showed for the variable recruitment phase duration a significant effect of response status (F = 9.36; $P < 0.005$). Age ($P < 0.01$) and gender ($P < 0.01$) were identified having significant effects as covariates. Again for the variable symmetry the response status showed a significant effect (F = 5.48; $P < 0.02$) with no effects of the covariates. For the variable strength a trend for a significant effect of the response status was found (F = 3.02; $P < 0.09$). The covariates failed to show significant effects.




*Rapid responder (up to fourth ECT)*

In a further step the ictal EEG recordings of the 22 patients who had fulfilled the response criteria (rapid responders) fast (i.e., by the fourth ECT) in comparison with the other 18 patients were examined. The clinical course, divided according to diagnoses, is shown in Fig. 4. Significant differences in clinical rating (HAM-D, BPRS) were recorded in the depressive patients after the second ECT and in the schizophrenic patients after the fourth ECT.

Again, no significant differences between the two groups were found with respect to age, gender, diagnostic

**Fig. 1 A–D** Examples of seizure ratings. **A** Second ECT, 151.2 mC, seizure duration (EEG) 70 s "cuff" 52 s, spike-wave phase duration 48 s, max (3.60 HZ) and min (1.90 HZ) frequency during spike-wave phase (sw phase), max amplitude (peak to peak) 830 uV, stereotypy 6 (sw phase), symmetry +2, good "organized" spike-wave pattern, overall strength 5, postictal suppression 86%. **B** Fourth ECT, 327.6 mC, seizure duration (EEG) 49 s "cuff" 30 s, spike-wave phase 25 s, max amplitude (peak to peak) 390 uV, stereotypy 3, symmetry -2, irregular discharges with theta-waves, overall strength 4, postictal suppression 73%. **C** Third ECT, 252.0 mC, seizure duration (EEG) 41 s "cuff" 41 s, spike-wave phase 31 s, max (4.20 HZ) and min (2.30 HZ) frequency (sw phase), max amplitude (peak to peak) 490 uV, stereotypy 5, symmetry 0, (poly-) spike-wave pattern, overall strength 5, postictal suppression 95%, "fit switch" at the end of seizure. A movement artifact (42–43 s) and an ECG artifact are visible. **D** Tenth ECT, 302 mC, seizure duration (EEG) 32 s "cuff" 32 s, spike-wave and termination phase 24 s, max amplitude (peak to peak) 280 uV, stereotypy 3, symmetry +1, low-amplitude irregular less-organized polyspike-wave pattern, overall strength 2, postictal suppression 65%. [Fp1-A1 (upper channel), Fp2-A2 (lower channel), international 10–20-system, all EEG traces (A–D) from different patients]

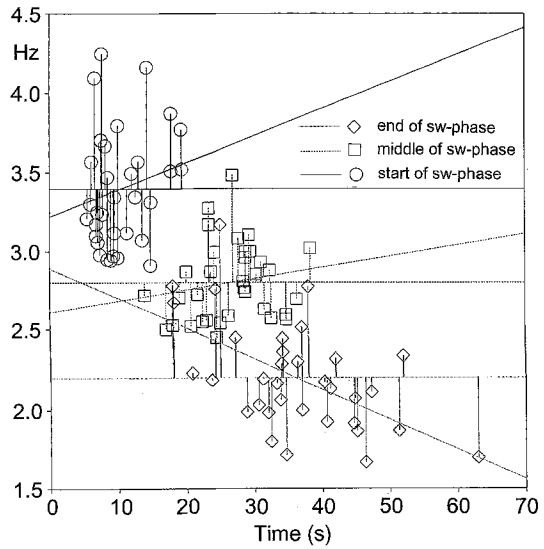



**Fig. 2** Slowing of epileptic discharges during spike-wave phase (mean values of the whole ECT series). Frequency of the epileptic discharges at the beginning (–○–), in the middle (–□–), and at the end of the spike-wave phase (–◇–). First with ongoing time there are increasing frequency baseline values, during the middle section of the spike-wave phase this trend is diminished, and until the last part of the spike-wave phase this positive correlation (see linear fit lines) between frequency (HZ) and time (s) become negative. The *horizontal lines* indicate the mean frequency values during the different part of the spike-wave phase

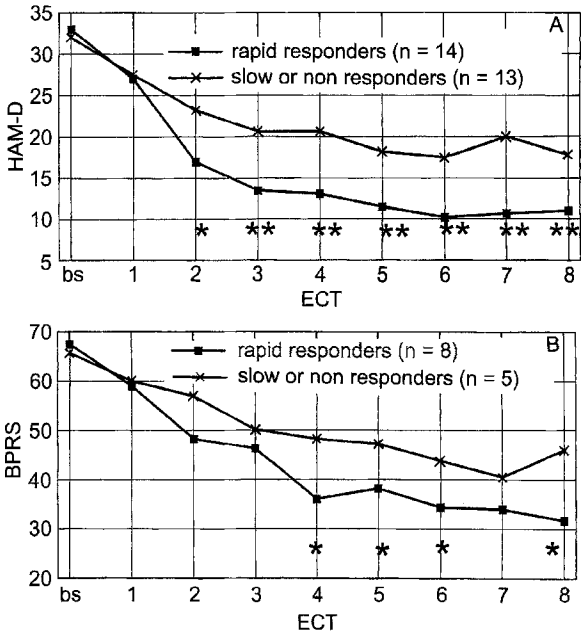



**Fig. 3 A, B** Clinical improvement of depressive and schizophrenic patients. Different clinical improvement of **A** the 27 depressive (HAM-D) patients and **B** the 13 schizophrenic (BPRS) patients; mean values of rapid (–■–) responders (up to fourth ECT) and slow- or nonresponders (–×–) during time course of ECT series (differences between groups compared * $P < 0.05$, ** $P < 0.01$; U-test)

classification, and methohexital dosage. The univariate statistics for the examined EEG variables for responders and nonresponders appear in Table 3. The 22 patients in whom ECT had had an exceptionally fast therapeutic effect displayed regular, stereotypic spike-wave or sharp wave patterns significantly more often. Concordance between the different measurements of the seizure duration (EEG, cuff) was higher and postictal suppression was also more pronounced among rapid responders, but failed to reach the significance level. Significant differences were recorded with respect to the amount of slowing during the spike-wave phase; this applied not only to the series up to the fourth ECT, but also to individual treatments (Table 3 a). Related to the series up to the fourth ECT, slowing started earlier (25.2 vs 28.8 s; $P < 0.05$), although there were no significant differences in the duration of the spike-wave phase. The amount of slowing (Table 3 b) was more pronounced among rapid responders (1.58 vs 0.87 Hz; $P < 0.0001$). There was a negative correlation between the amount of slowing and time when slowing started ($r = -0.68$; $P < 0.000$), i.e., the earlier the onset of frequency slowing, the more pronounced it was. At the same time there was a positive correlation ($P < 0.05$) between energy index (seizure duration/stimulus energy) and amount of slowing. Positive correlations ($P < 0.05$) were discernible between the reduction in Hamilton or BPRS scores up to the fourth ECT on the one hand, and the amount of slowing ($r = 0.62$; $P < 0.003$), stereotypy and pattern during the spike-wave phase ($P < 0.05$) or a negative correlation ($r = -0.55$; $P < 0.01$) at the start of slowing, on the other.

Moreover, multivariate analysis of variance (MANOVA) of five EEG features of spike-wave pattern and frequency (maximum, minimum, amount of slowing, start of slowing) was conducted using age, methohexital dose, gender, diagnosis as covariates, and response status (rapid responders vs slow- or nonresponders) as factor. Again, a highly significant effect of response status ($F = 4.87$; $P < 0.003$) was discernible. For all five EEG measures a significant effect of response status could be proven in the subsequent univariate F-tests. The results are shown in Table 4 inclusive of the effects of the covariates. The amount of slowing was the EEG measure with the most significant effect of response status ($F = 25.52$; $P < 0.000$). Age was identified having a significant effect as covariate ($t -2.93$; $P < 0.01$).

Of the 22 patients who had undergone a substantial improvement by the fourth ECT, 19 (rapid responders) displayed a further improvement by the end of the ECT series; however, this result could not be upheld in 3 patients. Of the 18 patients in whom no substantial improvement had been recorded by the fourth ECT, 10 underwent a marked improvement during the further course of the ECT series and then fulfilled the given response criteria.

**Table 3a** Results of EEG monitoring (first and fourth ECT) comparing rapid responders to slow- and nonresponders

| | Rapid responder ($n = 22$) | | Slow- and nonresponder ($n = 18$) | | $P$-value |
|---|---|---|---|---|---|
| | Mean[a] | SD | Mean[a] | SD | |
| *Seizure duration (EEG, s)* | | | | | |
| First ECT | 50.21 | 15.03 | 49.60 | 19.84 | n.s.[b] |
| Fourth ECT | 47.31 | 23.73 | 46.35 | 17.83 | n.s.[b] |
| *Max frequency spike-wave phase (Hz)* | | | | | |
| First ECT | 3.59 | 0.34 | 3.20 | 0.42 | 0.05[b] |
| Fourth ECT | 3.51 | 0.50 | 3.19 | 0.42 | 0.05[b] |
| *Min frequency spike-wave phase (Hz)* | | | | | |
| First ECT | 2.09 | 0.52 | 2.29 | 0.29 | n.s.[b] |
| Fourth ECT | 1.99 | 0.44 | 2.38 | 0.39 | 0.05[b] |
| *Amount of slowing (Hz)* | | | | | |
| First ECT | 1.50 | 0.64 | 0,90 | 0.39 | 0.008[b] |
| Fourth ECT | 1.52 | 0.62 | 0.81 | 0.60 | 0.004[b] |
| *Start Slowing* (% of total seizure time) | | | | | |
| First ECT | 52.84 | 21.31 | 63.76 | 16.21 | n.s.[b] |
| Fourth ECT | 59.29 | 20.29 | 65.84 | 25.51 | 0.10[b] |

NOTE: Response criteria after fourth ECT series
[a] Mean values for the two groups compared
[b] $t$-test

**Table 3b** Results of EEG monitoring until fourth ECT

| | Rapid responders ($n = 22$) | | Slow- and nonresponders ($n = 18$) | | $P$-value |
|---|---|---|---|---|---|
| | Mean[a] | SD | Mean[a] | SD | |
| Age (years) | 42.73 | 14.89 | 49.46 | 14.77 | n.s.[b] |
| mg/kg | 1.45 | 0.39 | 1.37 | 0.45 | n.s.[b] |
| M:F | 9:13 | | 7:11 | | n.s.[b] |
| Seizure duration (EEG, s) | 48.89 | 16.21 | 47.16 | 10.48 | n.s.[b] |
| Spike-wave ampl (uV) | 511.20 | 130.05 | 507.11 | 103.77 | n.s.[b] |
| Spike-wave pattern[d] | 49:35 | | 29:41 | | $\chi^2$ 5.87; $P < 0.01$[c] |
| Concordance (%) | 85.44 | 11.42 | 76.82 | 23.09 | n.s.[b] |
| Symmetry (+3–0/–3 left) | 0.15 | 0.54 | 0.16 | 0.66 | n.s.[b] |
| Max frequency (Hz); (spike-wave phase) | 3.53 | 0.37 | 3.22 | 0.29 | 0.10[b] |
| Min frequency (Hz); (spike-wave phase) | 2.03 | 0.27 | 2.42 | 0.33 | 0.001[b] |
| Slowing amount (Hz) | 1.58 | 0.38 | 0.87 | 0.39 | 0.0001[b] |
| Start slowing (%) | 54.66 | 12.21 | 67.48 | 12.98 | 0.006[b] |
| Stereotypy (0–6) | 4.25 | 0.45 | 3.88 | 0.79 | n.s.[b] |
| Strength (0–6) | 4.09 | 0.75 | 3.89 | 0.74 | n.s.[b] |
| Postictal suppression (percent) | 73.94 | 8.40 | 70.22 | 7.80 | n.s.[b] |

[a] Mean values for the two groups compared except for $\chi^2$-test
[b] $t$-test
[c] $\chi^2$-test
[d] Rhythmic spike wave, sharp wave complexes against other irregular ictal pattern

**Table 4** Multivariate analysis of variance (MANOVA) of spike-wave pattern, frequency (maximum, minimum, amount of slowing, start of slowing) with age, methohexital dose, gender, diagnosis as covariates, and response status (rapid responders vs slow- or nonresponders) as factor

| | Rapid response | | Covariate age[a] | Covariate methohexital dose[a] | Covariate gender[a] | Covariate diagnosis[a] |
|---|---|---|---|---|---|---|
| | F-value | Significane of F | | | | |
| Spike-wave pattern | 4.75 | 0.03 | –1.61 (0.12) | 0.79 (0.44) | –0.94 (0.35) | –1.66 (0.11) |
| Max frequency | 7.38 | 0.01 | –5.13 (0.00) | 1.33 (0.19) | –1.70 (0.98) | –2.34 (0.03) |
| Min frequency | 12.30 | 0.002 | –1.59 (0.13) | 2.96 (0.01) | 0.10 (0.92) | –0.82 (0.42) |
| Amount of slowing | 25.52 | 0.000 | –2.93 (0.01) | –1.44 (0.16) | –1.59 (0.12) | –1.30 (0.20) |
| Start slowing | 8.09 | 0.03 | –0.02 (0.98) | 0.86 (0.40) | 0.54 (0.59) | 0.32 (0.75) |

[a] $t$-value and significance of $t$ for covariates

## Discussion

### Stimulus dosage

Although the seizure threshold was not determined by titration, stimulation in this study can be assumed to have been performed well above the seizure threshold with our modified age-dependent stimulus dosage. This is suggested on the one hand by the EEG findings themselves, and on the other hand by comparison with the ictal EEG findings of other authors. Beale et al. (1994) determined the mean value of seizure threshold for women with 106.6 mC. Considering a mean stimulus dosage of 241.5 mC for women in our study, the mathematic stimulation value would be 227%. Among the men (251.5 mC) stimulation would have been performed at 218.7% according to the values (seizure threshold 115.7 mC) quoted by Beale et al. (1994). If computation is based on the lower values for the seizure threshold with exclusively unilateral stimulation quoted by Sackeim et al. (1993) with a mean seizure threshold of 73.5 (± 29.5) mC and by McCall et al. (1993) with a mean seizure threshold of 62.9 (± 26.9) mC, stimulation would have been performed at 338% / 395% with a mean stimulus of 248.7 mC. On the other hand, the stimulus dosage used in this study is below that quoted by Swartz (1994), who also used an age-dependent stimulus dosage (3.5–5 times patient age in milliCoulombs) with a mean stimulus of 292 mC. However, an up to 20-fold interindividual variability (Sackeim et al. 1991) in the seizure threshold, which could not be taken into account in this study, has to be borne in mind.

### Influencing variables of the ictal EEG

A number of known influencing variables of the ictal EEG were identified in this study. A shortening of seizure times and lower amplitudes were recorded with increasing age. Similar age-dependent effects have been described by numerous authors (Abrams 1992; Sackeim et al. 1987, 1991; Rasmussen et al. 1994; Weiner 1980b). Besides age, methohexital dosage was of special significance in the height of the amplitudes and in stereotypy during the spike-wave phase. Whereas methohexital is known, for example, to have proconvulsive characteristics in low doses (Folkerts 1995), increasing doses of methohexital may delay the spread of epileptic activity in the human brain. The tonus phase often lasts longer, and the clonus phase is reduced with increasing doses (Tresise et al. 1968; Gerst et al. 1982). The ECT seizure duration is shortened by methohexital, especially at higher doses (above 1.5 mg/kg; Miller et al. 1985; Krueger et al. 1993). Very high doses well above 1.5 mg/kg with then-pronounced anticonvulsive characteristics were associated by Swartz (1993b) with a lower ECT-induced improvement rate, a finding that could not be reproduced in this study. The absence of diagnosis-specific differences in ictal EEG parameters reflected findings by McCall et al. (1993) and other authors.

### Electrophysiological markers for the efficacy of ECT

Since the early days of electroconvulsive therapy, the question of how to define a therapeutically adequate ECT has been under discussion. The first crucial step on this path was the theory that the seizure represents the conditio sine qua non for the therapeutic effect of ECT (Cerletti 1956). In the meantime a demand for minimum seizure times has asserted itself as a "standard" (APA 1990; Abrams 1992). This demand has, however, been subjected to increasingly critical discussion in recent times (i.e. Swartz 1993a, c; Krystal and Weiner 1994; Sackeim 1994). No clear-cut correlation was established in the present study between seizure duration and clinical result. This finding confirms those of Sackeim et al. (1987) and Nobler et al. (1993). Consequently, this finding contributes to the evidence that motor and EEG seizure duration have only weak relation to therapeutic effect of ECT.

The aim of this study was to evaluate ictal EEG parameters for therapeutically effective (adequate) ECT. For this purpose a two-step analysis strategy (up to the end of ECT series and up to the fourth ECT) was performed. This was based (beside clinical point of view) on the presumable effects of treatment number on the ictal EEG, because the number of ECT treatments could confound the clinical implementation of ictal EEG indices. Recently, Krystal et al. (1995) reexamined data from two previous own studies. In the first, seizure threshold determination was carried out at treatments 1 or 2 for both nondominant unilateral and bilateral ECT; in the second study unilateral seizure threshold titration was carried out at treatments 1 and 6. The authors found that the ictal EEG at treatment 1 had greater amplitude than either treatments 2 or 6, and a trend was found for greater postictal suppression at treatment 1 than at treatment 6. These results (in part independently of changes in the seizure threshold) suggest that analysis of ictal EEG parameter may need to take treatment number into account particularly if unilateral ECT and treatment 1 data are utilized. This, the known rise in seizure threshold (Sackeim et al. 1991), and other changes during ECT series [e.g., particularly increase in delta power after fourth ECT (Rosen and Silferskiöld 1987)], led to the strategy to investigate not only the EEG indices up to the end of the ECT treatment, but also up to the fourth ECT.

Our study has identified a number of ictal EEG measures that promise utility in separating therapeutically adequate from inadequate seizures. Thus, relationships were established between responders up to the end of ECT series on the one hand, and the duration of recruitment phase, the symmetry, and the rating of strength of the seizure on the other. In addition, significant correlations were found between rapid responders (up to the fourth ECT) and the frequency of epileptic discharges, their slowing (start, amount) during the spike-wave phase and the stereotypy of the discharges and a "stable" pattern of rhythmic spike-wave or sharp wave complexes. These results are consistent with the hypothesis that more "intense" seizure activity leads to therapeutically more effective ECT.

Although no previous work has directly focused on the differences of EEG parameters between responders and nonresponders, other relevant work is in agreement with our results. A series of studies reported findings of EEG parameter comparing forms of ECT that differ in efficacy. Ottosson et al. (1960, 1962) described that lidocaine (possibly affecting seizure threshold?) not only shortened the seizure duration, but also displayed effects on the ictal EEG morphology. Under lidocaine, for example, spike-wave activity was reduced, "escapes" of the ictal spike-wave discharges were caused, amplitudes were lower, and postictal suppression was reduced with a simultaneously poorer clinical result. Also EEG findings relating to "more intensive" epileptic discharges under bilateral stimulation (regarded as the therapeutically most effective treatment) with higher amplitudes, more pronounced symmetry, and regularity (d'Elia and Perris 1970; Krystal et al. 1992; Sackeim et al. 1993; Swartz and Larson 1986) are in line with the results of our study. Findings by Krystal et al. (1993) reporting higher EEG amplitudes, more pronounced symmetry, and higher regularity (using the same rating scale as in this study) with bilateral ECT than with unilateral stimulation should be considered similarly. Depending on relative stimulus intensity, amplitudes were higher and postictal suppression more pronounced with bilateral than unilateral ECT and with higher dosage (2.25 threshold) compared with barely suprathreshold stimuli. Nobler et al. (1993) reported findings in the same direction: The high-intensity conditions [bilateral ECT, high dose (2.5) relative to threshold] resulted in stronger and more stereotyped seizures. The authors moreover postulated a correlation between these ictal parameters and the clinical result, where a correlation was also established between clinical improvement and higher regularity during the spike-wave phase. The findings in our study of a significant relationship between the ictal pattern, stereotypy, and response are consistent also with results from a recent study from McCall and Farah (1995). In their study 17 patients randomly received either titrated moderately suprathreshold or high-fixed-dose (403 mC) right-unilateral ECT. The authors found for the fixed-high-dose ECT group a more rapid clinical effect with significant greater mean regularity ratings.

The two ictal EEG features provided by the THYMATRON-DGx failed to show significant differences between responders and nonresponders; concordance (as a possible measure of generalization of seizure activity) between the different measurements of seizure length (EEG, cuff) and postictal suppression were greater on average among responders, but failed to attain significance level because of the substantial scatter of values among nonresponders. This is consistent with the findings of Pritchett et al. (1994) showing that the concordance index or the postictal suppression index on the THYMATRON-DGx failed to detect a difference between right-unilateral and bilateral ECT. Nevertheless, some authors found evidence that higher-dose treatment, such as bilateral ECT, result in greater postictal suppression (Small et al. 1970; Robin et al. 1985; Krystal et al. 1993). In addition, Nobler et al. (1993) could identify postictal suppression using a manual rating on a three-point scale as the only EEG parameter providing correlations with the clinical result. In contrast to this finding, such a correlation was not replicated in our study, possibly due to the relative susceptibility of this parameter to artifacts during manipulation at the end of anesthesia.

The highly significant relationship between ictal slowing (start, amount) of the spike-wave activity and clinical improvement was proven for the first time in this study. This and the other finding of our study necessitates some neurophysiological considerations as to which mechanisms contribute toward generalizing epileptic activity.

During the spike-wave phase (clonic phase) there are regular high-amplitude discharges as though organized by some pacemaker or generator mechanism (Enderle et al. 1986; Staton et al. 1986). Occurrence of these regular discharges and maintenance of this rhythm are probably the outcome of a complex interaction between cortex and subcortical structures (Rossi and Gentilomo 1972; Gloor et al. 1979). The thalamus is essentially (co-)responsible for generalization of the epileptic activity. According to Staton et al. (1988), the precondition for development of a stable spike-wave rhythm is the recurrence of synchronized, prolonged periods of intense inhibitory current flow (hyperpolarization) and associated rebound spike bursts, driven or at least organized by inhibitory circuit relationships or inhibitory GABA neurotransmitters (Jahnsen and Linás 1984; Halasz 1991) and intrinsic electrophysiological properties of thalamic neurons (Staton et al. 1988; McLachan et al. 1984). The (primarily cortical?) discharges (Kostopoulos and Antoniadis 1992) with excitatory corticothalamic activation during the polyspike (tonic) phase are suspected to promote the development of intensified hyperpolarization and subsequent bursts in thalamic neurons (Gutnick et al. 1975). The large number of interconnecting thalamic paths could be responsible for the rapid spread of synchronous discharges. These discharges (delta waves or spike bursts) are suspected to be of crucial importance to the therapeutic effect of ECT during the spike-wave phase and to induce a cascade of neurochemical changes. Observation of the progressive frequency slowing toward the end of the spike-wave phase suggests that this activity is not controlled by an "on/off" mechanism, but rather that these findings comply with the model of increasing fatigue. Thus, this contributes to the hypothesis that more efficacious forms of ECT have an earlier and more potent ability to involve subcortical structures in seizure activity and may also be more effective in eliciting seizure inhibitory processes (Krystal and Weiner 1994; Sackeim et al. 1991). These seizure inhibitory processes are reflected by the slowing of ictal discharges, and secondarily by the rise of seizure threshold during the course of ECT.

The correlations between individual ictal EEG parameters and clinical result recorded in 40 patients within the scope of the present study require further verification, however. Whether these correlations, which are significant in terms of group statistics, are indeed suitable (speci-

ficity, sensitivity) and practicable for distinguishing effective from noneffective ECTs would first have to be demonstrated on larger numbers of patients. In addition, some limitations of this study must be considered. It would be desirable to determine the seizure threshold of each patient to obtain a marker for the relative stimulus dosage. Due to a uniform gain sensitivity (with the aim to avoid problems with uncontrolled changes of gain sensitivity), a few numbers of EEG traces showed a certain saturation (clipping). This could possibly lead to an underestimation of voltage measurements. A further problem for all studies dealing with EEG data is the presence of artifacts (e.g., caused by movements, underlying ECG signal; see Fig. 1). These artifacts confound especially the postictal measures. Moreover, low adherence of EEG electrodes (various artifacts) and low succinylcholine dosage (high-frequency muscle artifacts, especially for the first ECT) could confound EEG measures. On the other side, the main target of this study, the slowing of ictal discharges, is not or is only slightly affected by these problems. Augmentation with computer-assisted EEG analyses (compressed spectral assay, brain mapping) might provide additional information, but does not resolve these general problems with EEG data.

## Conclusions

Apart from the very global statement that a generalized seizure is the conditio sine qua non for the therapeutic effect of ECT, there are no secured, verified predictors capable of distinguishing adequate from inadequate ECT. In view of the complex neurophysiological interactions involved in spreading, maintaining and terminating epileptic activity, the (still) widespread convention of measuring the efficacy of therapy solely by the duration of epileptic discharges can be considered abortive from the very outset. Ictal EEG parameters of the spike-wave phase (i.e., amplitude, pattern, stereotypy, slowing, postictal suppression) may instead be suited to differentiating therapeutically effective from ineffective ECT treatments. However, it seems questionable whether a single of these EEG parameters can be suited to this purpose. What is conceivable, on the other hand, is that several of these EEG parameters might be combined into one marker for relative stimulus intensity. A randomized study already under way is therefore aimed at drawing a comparison between fixed stimulation (2.5 times the seizure threshold in milliCoulombs on the one hand and ECT therapy controlled (or "titrated") by EEG criteria, on the other. Identification of specific and sensitive markers for the efficacy of ECT would best serve our understanding of the mechanisms of action underlying ECT and possibly of the etiology of psychiatric disorders.

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