

Fractal Dimension of Seizure EEG during ECT Predicts Therapeutic Effects in Depression

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The therapeutic efficacy of ECT in depression is incontrovertible (1). Ottosson and co-workers demonstrated that induction of seizure during ECT is mandatory (2). The antidepressant potency of low dose and in particular, unilateral, stimulus ECT is lesser than other ECT methods (3). This has led to the possibility that with variations in stimulus standards the essential physiology of seizure may be different and hence the therapeutic potency. Krystal et al (4) found that bilateral ECT produced 'robust' EEG seizure than unilateral. The differences included EEG seizure amplitude, coherence and regularity, as well as post-ictal suppression. Patients whose seizure EEG during ECT was characterized by higher ictal amplitude had better therapeutic effect (5). Smaller post-ictal amplitude (better suppression) was associated with better therapeutic outcome (6). In these studies the clinical effect of ECT was not determined by the duration of seizures. Seizure parameters other than duration have hence become important in determining the therapeutic potency of ECT.

The fractal dimension (FD) is a geometrical measure of two-dimensional forms including EEG. Katz (7) described a method to estimate FD. Using this method, Pradhan and Dutt (8) demonstrated that FD reflects changing patterns in the EEG. In digitized EEG data FD is estimated using the following equation:

$$FD = \log(N-1)/(\log(N-1) + \log(d/l))$$

'N' indicates the number of data points in the waveform; 'N-1' indicates the number of steps used for the analysis. 'd' is the maximum 'distance' between the first and the last data point. 'l' is the total 'distance' covered over the waveform.

Clinicians interpret EEG with units of micro volt (Y-axis) and millisecond (X-axis). In an earlier report we hence calculated the 'distance' after calibrating the waveform in units of microvolt and inter-sample distance in units of millisecond⁹. FD itself has no units. At the onset of seizure the FD is about 1.25 and increases with the progression of seizure to values of 1.4-1.8. With seizure termination the FD drops close to unity. The abrupt transition in FD value could be automatically detected and the seizure duration estimated thereof (9). This study examined if EEG seizure FD predicted the therapeutic potency of ECT.

METHOD

Patients: Consenting, right-handed patients with a diagnosis of major depression (10) and who were referred for ECT were the subjects in this study (n=90). During the ECT their medication status was unchanged; most received an antidepressant drug (Table-1). Using Hamilton Rating Scale for Depression (HRSD) (11) we rated the severity of the clinical condition before and weekly during the ECT course.

ECT: ECT was administered thrice weekly using atropine- 0.65mg, thiopentone- 3mg/kg and succinylcholine- 1mg/kg in that order intravenously for modification. Patients received positive pressure ventilation with 100% oxygen till resumption of spontaneous and regular breathing. The stimulus was bi-directional, and of constant current brief pulse waveform. Patients received unilateral ECT (ULECT) as a routine. However for 17 patients, the treating team insisted on bilateral ECT (BLECT). For right unilateral stimulus d'Elia electrode position and for bilateral ECT standard bifronto-temporal electrode position was used. The stimulus

threshold was determined by administering the stimulus from an initial dose of 30mC upwards in steps. Initial two steps were of 15mC and subsequent steps were of 30mC. The dose at which an EEG seizure of at least 25 seconds duration was obtained was the seizure threshold. Supra-threshold stimulus (150% above threshold for ULECT and 60mC above for BLECT) was administered during the other ECT sessions. Motor seizure monitoring was carried out using 'cuff' method' on the right forearm or right leg (12).

EEG was recorded from F3, F4, T3 and T4 sites referenced to linked-mastoids and a ground on forehead. Electrode impedance was below 10KOhm. During stimulus and for six seconds thereafter the amplifiers received only the calibration signal (100 microVolt sinewave) but not the EEG signal. For purposes of duration estimation however this period after the stimulus application containing only calibration signal was considered. The calibration and the following seizure EEG signal were amplified between 0.5 and 35Hz (high and low pass filters) by a factor of about 1000. A 50 Hz notch filter was used. The EEG was instantaneously digitized using a 12-bit A-D converter at a rate of 256 Hz. The signal was displayed on the computer screen online. EEG seizure termination was defined as unequivocal absence of epileptiform transients for five seconds or longer (13). Seizure EEG data acquisition was stopped 30 seconds after seizure termination. The EEG data files were coded and stored. The EEG seizure of second ECT of each patient was used for subsequent analyses without knowledge of their clinical information.

A digital FIR low-pass filter to remove signals beyond 32 Hz was applied. The seizure was displayed in contiguous epochs of six seconds. The seizure duration as noted at the ECT session was confirmed. The onset of early-seizure was the end for calibration signal. The onset of mid-seizure that had most regular spike-wave morphology and also the highest amplitude

during seizure was also noted. The seizure end-point with continuous absence of any EEG transients was marked as post-seizure. Six consecutive seconds of artifact-free EEG epoch of each of these phases was used for analyses. Each phase had four channels of temporally analogous EEG data. The data of each second was baseline-corrected for fractal analysis. Fractal dimension (FD) was computed using the algorithm described by Katz (7) as described above and used in an earlier study (9). The average of six seconds of each phase was obtained for each channel. The FD values from the four channels were averaged for the early-, mid- and post-seizure phases.

RESULTS

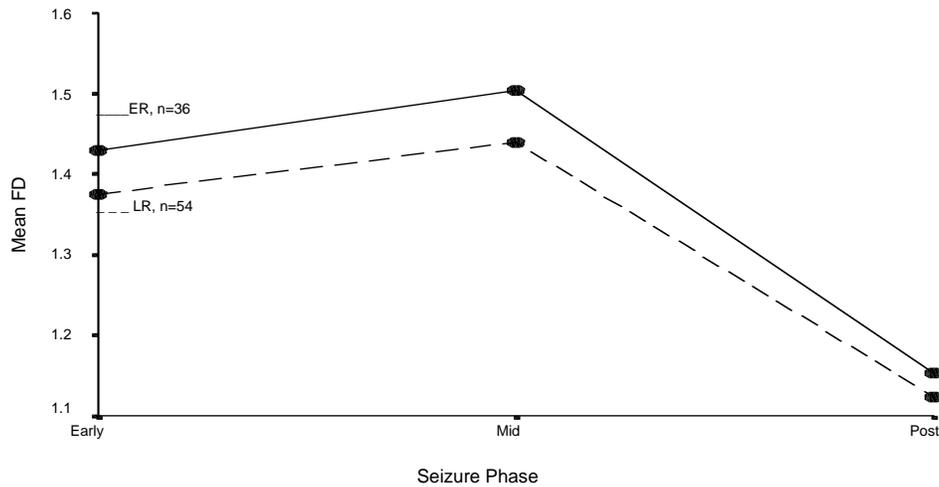
Thirty-six patients achieved 'remission' (HRSD<8) at the end of one week and maintained this till the end of two weeks, 'early remitters' (ER). The rest (n=54) will be referred to as 'late remitters' (LR) as most remitted at the end of two weeks or later. The groups were comparable on clinical variables except the initial HRSD scores; the ER group had lower scores to begin with (Table-1).

The graph below indicates the mean FD across the early (ER) and late remitters (LR) over the three phases of the ECT seizure. The ER group had significantly higher FD (RMANOVA; group effect; $F=6.9$, $df=1,88$, $p=0.01$). The difference was however significant at the early- and mid- seizure phases ('t' test; $p=0.04$ & 0.01 respectively).

We compared nine clinical and three FD variables between the two groups. All these variables with significance (p) below 0.5 in the univariate statistics were entered into Linear discriminant analysis model with leave-one-out analysis. Only two variables accounted for significant difference between the two groups; baseline HRSD ($F=7.9$, $df=1,88$, $p=0.006$) and mid-seizure FD ($F=6.4$, $df=2,87$, $p=0.003$). Together the two variables classified 67% of the patients correctly and 63% after cross-validation.

Table-1: Demographic and clinical differences between the ER and LR groups

Group→ Variable↓	Early Remitter ER (n=36)	Late Remitter LR (n=54)	Statistic t / χ^2	P value
Age (yrs)	30.7±0.3	32.9±11.2	0.97	0.33
Sex (M:F)	16:20	27:27	0.27	0.61
Illness Duration (mo)	5.4±8.5	5.5±6.6	0.03	0.98
Medication (Yes:No)	13:23	10:44	3.50	0.06
Baseline HRSD	22.8±6.1	26.5±6.6	2.81	0.006
Stimulus dose (mC)	188±70	199±80	0.68	0.5
Laterality (BL:UL)	7:29	10:44	0.01	0.91
EEG Seizure (sec)	85.2±36.5	72.4±33.3	1.71	0.091
Motor Seizure (sec)	57.8±21.9	53.4±19.7	0.98	0.33



DISCUSSION

ECT produced remission early in course of treatment in nearly 40% of patients. Neither demographic parameters nor ECT variables and seizure duration predicted early remission. Patients with lesser severity of illness remitted early. Interestingly, the FD of seizure EEG at second ECT session was a predictor. Early remitters had significantly higher FD during early- and mid- seizure phases. In the multivariate model, only two variables differentiated the two patient groups significantly. One of these was the high FD of mid-seizure EEG.

With progression of seizure the FD of the EEG increases, being highest in the mid- and lowest in post- seizure. It may hence indicate the overall amplitude of the EEG signal. Higher amplitude discharge in

the EEG may also point to more intense physiological state during the seizure. Rhythmic 3-3.5 Hz spike and wave complexes typically characterize the mid-seizure (14). The physiology of this phase is linked to GABA-ergic neurotransmission. With higher amplitude in this phase it is likely more GABA is released. ECT seizures which are successful in more pronounced GABA response may be more therapeutic. There is some support to this hypothesis. GABA-ergic drugs are used in the treatment of affective disorders (15) and GABA-ergic effects are suggested in mechanisms of ECT action (16).

The findings of this study are in keeping with some observations by Nobler et al (5). We were unable to confirm better postictal suppression in early remitters. Lower postictal FD was associated with early remission in an earlier study (6) from this center. In the last study we used only

bilateral ECT in patients who were not on medication. In contrast this sample received mostly unilateral ECT and were on anti-depressant medication.

The sample was a series of consecutive patients referred for ECT without control over medication status and stimulus laterality, which could have affected the seizure parameters. However this has strength in that the results are generalizable to representative ECT patients with depression. Remission definition was limited to only two weeks of treatment. This was because a majority of the patients were discharged at the end of two weeks. However, as the ECT seizure assessed was collected in the first week (second ECT), the results must necessarily focus on the acute effects at the end of one week. Had ECT seizure analysis been extended to later ECT sessions, viz., 2nd and 3rd week, it would have been more fruitful. In summary, seizure EEG's FD of ECT session of first week predicts early therapeutic effect; higher ictal FD was associated with early remission in depression.

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