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# AWARD PAPER

# Post-seizure EEG fractal dimension and spectral power predict antidepressant response to unilateral ECT

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## ABSTRACT

Background: Measures of EEG during ECT, for example, smaller post-seizure fractal dimension have predicted antidepressant response. The earlier study on this subject used bilateral ECT. This study aims to examine if this finding holds good even for unilateral ECT, using both fractal dimension and spectral power analysis of EEG. Methods: Fifty-one right-handed, drug-free patients with major depressive disorder received right unilateral ECTs at 2.5 times their seizure threshold. A rater blind to the clinical data measured fractal dimension and spectral power of EEG during their second ECT. Depression was rated using Hamilton's Rating Scale for Depression at baseline and on the 3rd, 7th and 14th days following ECT. Results: Thirty-five good quality EEG recordings were analyzed. Seventeen patients reached criteria for early response of more than median percent improvement on HRSD on both 7th and 14th day. Univariate analysis showed smaller fractal dimension and spectral power (greater post-seizure EEG suppression) in early responders compared to the late responders. This was confirmed by multivariate discriminant function analysis. None of the other clinical, treatment or EEG parameters predicted early response. Conclusions: Effective seizure during unilateral ECT may be characterized by high post-seizure EEG suppression.

**Key Words :** ECT, EEG, Fractal Dimension

## INTRODUCTION

The issue of prediction of response to ECT in depression has gone beyond its correlation with seizure duration. Depending on the stimulus intensity and electrode placement, generalized seizures of adequate duration may be associated with differential therapeutic effects (Sackeim et al 1993). Measures of seizure quality have gained importance in predicting the response (Swartz, 1993). Several attributes of ictal EEG other than its duration are candidates for markers of relative stimulus intensity, viz., amplitude, symmetry, coherence and postictal suppression (Krystal and Weiner, 1994). Effective stimulation results in morphologically well-developed symmetrical, coherent, synchronous, high-voltage seizure activity that is followed by marked postictal suppression (Abrams, 1997). Bilateral ECT and supra-threshold unilateral ECT, which have better antidepressant effects than threshold unilateral ECT, produce EEG characterized by higher amplitude seizure discharges as well as greater postictal suppression than threshold unilateral ECT (Krystal et al., 1993). Similar relationship between antidepressant response and ictal amplitude and postictal suppression have been reported by Krystal et al., (1995) and Nobler et al (1993) respectively. Suppes et al., (1996) replicated the association between postictal suppression and therapeutic response.

Visual analysis of EEG, power spectral analysis and fractal dimension (FD) of EEG are some of the measures for assessing the attributes of the EEG produced by ECT. Most of the studies have used power spectral analysis (e.g., Krystal et al 1995). The only Indian study examining the relationship between the EEG quality and antidepressant response following bilateral ECT reported that smaller post-seizure FD - a measure of post-seizure suppression - predicted better antidepressant effect (Gangadhar et al., 1999). Fractal dimension, unlike power spectral analysis is a less known measure. Unilateral ECT may be preferred in depression as it is equipotent with fewer side effects. This study examines if the findings hold good for supra threshold unilateral ECTs, using both power spectral analysis and fractal dimension to analyze the EEG changes produced by unilateral ECT.

## METHODS

Fifty-one right-handed patients (31 females) with DSM-IV (APA 1994) diagnosis of major depressive disorder participated in a randomized controlled trial, comparing the efficacy of two ECT procedures after informed consent. The pulse frequencies in the ECT stimulus in these two procedures were 50 and 200 pulses per second. None of the patients was on any psychotropic medications, except lorazepam tablet 1mg on as-needed basis for sleep, but was withheld the nights before the ECT sessions. The severity of depression was assessed on 17-item Hamilton Rating Scale for Depression (Hamilton, 1960), before starting ECT and on 3rd, 7th and 14th day thereafter.

ECT (thrice weekly) was administered under thiopentone (3mg/kg) anesthesia

with atropine (0.65mg) and succinylcholine (0.75mg/kg) used for modification. All received right unilateral ECTs at d'Elia position. ECT device delivered constant current (800 mA) bipolar pulses. Pulse width was 1 millisecond and frequency was 50 pulses per second (in 54.1% of the subjects) and 200 pulses per second (in 45.9%). During the first ECT session, seizure threshold was assessed using titration method by adjusting the train duration (0.125-13.5 seconds). From second ECT onwards, ECT was administered using energy 2.5 times the threshold. All patients obtained at least 15 seconds of motor seizure (Cuff method) and 25 seconds of EEG seizure (Gangadhar et al., 1995a).

Seizure was monitored using 4-channel EEG recording (F3, F4, T3 and T4, referenced to ipsilateral mastoids) on all ECT sessions. The EEG during the 2nd or the 3rd session was used for analysis. The EEG data was digitized (256 Hz, 12 bit), stored in the computer and coded. Calibration pulse (100 μV) train was recorded for each EEG. A trained researcher (J) replayed the EEG on a computer screen to measure seizure duration and identify early- (4 sec), mid- (8 sec) and post-seizure (4 sec) phases (figure 1). The phases of each of the four channels were temporally analogous and free from artifacts. Each phase was divided into 1-sec epochs each of which overlapped by half a second. EEG values in μV (Y-axis) and intersample interval in ms (X-axis) were used to compute FD as described earlier (Katz, 1988. Gangadhar et al., 1997). Arithmetic mean of FDs of the seven epochs yielded the FD of each seizure phase. The average of the FDs of the four channels from the second or third ECT was used for the analysis. Similarly, spectral power (dB) was estimated for 2-6 Hz band (Dummermuth and Molinari, 1987) and the averages of the four channels for each phase were computed. A computer programme automatically computed seizure duration (Gangadhar et al, 1995b)

Good quality EEG records were available for 35 patients in the first week. These 35 patients who formed the sample of this study did not differ from the remaining sixteen on age, sex, baseline HRSD score, number of past episodes, duration of current episode and the number of melancholic features present. The reduction in HRSD scores over the 2-week trial was not different between the two (data not presented). The data was analyzed using SPSS version 10. Chi-square, independent sample t-test, multivariate discriminant analysis were used and the level of significance was fixed at $p < 0.05$.

## RESULTS

Percentage improvement in HRSD scores was calculated at each assessment stage. Median improvement at 7th day was 31.8% and at the end of 14th day was 61.5%. Accordingly, patients, who had more than median improvement at both these time points, were defined operationally as early responders (ER) (n=17), and the remaining, as late-responders (LR) (n=18). The two groups did not differ on any demographic, baseline clinical and ECT variables. They however differed with respect to post-treatment HRSD scores as expected (Table 1 and 2).

The two groups did not differ on seizure duration recorded during the first week's ECT session. The ER group had significantly less post-seizure FD and spectral power than the LR group (Table 2). There was no difference between the two with respect to early- or mid-seizure FD and spectral power. The average post-seizure measures correlated negatively with percent improvement on the 7th day. (Spearman rho: spectral power: $r = -0.340$; $p = 0.046$; FD: $r = -0.282$; $p = 0.10$). There were no correlations between percent improvement on the 14th day and post-seizure FD. None of the other measures of EEG showed any correlations with improvement.

Predictive power of variables, which showed least p values in univariate analysis, was tested using discriminant function analysis. HRSD baseline score, seizure duration, average early-, mid- and post-seizure FD, were the independent variables. We used stepwise multivariate discriminant analysis with revalidation using leave-one-out procedure. Only post-seizure FD could significantly discriminate the early and late responders. It could predict 69% of the patients correctly into early or late responders. Discriminant analysis was

**TABLE 1**: Comparison between late responders and early responders: clinical and ECT variables.

| Variable | Late responders (n=18) | Early responders (n=17) | Statistics |
|---|---|---|---|
| Mean age in years (SD) | 36.92 (9.0) | 33.47 (9.7) | t=1.09; df=32.3; p=0.28 |
| Sex ratio (male : female) | 6:12 | 7:10 | Fisher's exact 0.44 |
| Mean duration of illness in weeks (SD) | 17.44 (23.3) | 21.64 (29.0) | t =0.498; df =33; p=0.62 |
| Mean number of melancholic features at baseline (SD) | 6.23 (1.0) | 5.88 (1.2) | t =1.02; df =33; p= 0.31 |
| Mean HRSD score at baseline (SD) | 36.1 2 (4.7) | 27.73 (6.9) | t =1.69; df =33; p=0.09 |
| Mean HRSD score - 7th day (SD) | 24.61 (4.6) | 14.64 (6.7) | t=5.04; df =28.11; p < 0.001 |
| Mean HRSD score - 14th day | 15.83 (4.6) | 6.70 (4.2) | t=6.04; df=33; p<0.001 |
| Frequency of ECT pulses (50pps:200pps) | 9:9 | 9:8 | ?2 = 0.97; df =2; p=0.61 |

**TABLE 2:** Comparison between late responders and early responders: Seizure variables.

| Variable | Late responders (n=18) | Early responders (n=17) | Statistics |
|---|---|---|---|
| Variable | Late responders (n=18) | Early responders (n=17) | Statistics |
| Seizure duration (seconds) | 49.13 (21.9) | 65.30 (36.9) | T= -1.58; df=33; p=0.122 |
| FD of early-seizure EEG | 1.17 (0.07) | 1.13 (007) | t =1.73; df =33; p=0.092 |
| FD of mid-seizure EEG | 1.21 (0.07) | 1.17 (0.08) | t =1.47; df =33; p=0.15 |
| FD of post-seizre EEG | 1.016 (0.01) | 1.009(0.006) | t =2.16; df =33; p=0.038 |
| Spectral power of early-seizure EEG | 54.56 (4.7) | 51.45 (5.3) | t =1.80; df =33; p=0.08 |
| Spectral power of mid-seizure EEG | 56.71 (3.4) | 54.38 (5.0) | t =1.31; df =28.19; p=0.201 |
| Spectral power of post-seizure EEG | 41.06 (6.4) | 36.97 (4.6) | t =2.13; df =33; p=0.04 |

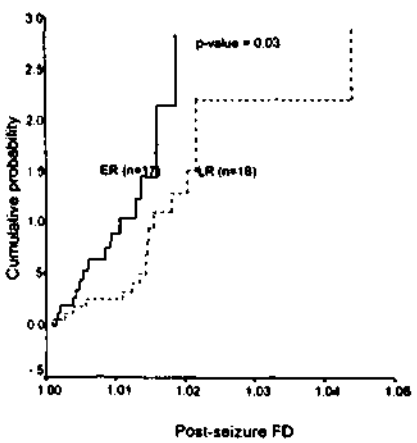


**Figure 2:** Kaplan-Meier survival curve for cumulative probability of being in either ER or LR groups depending on the FD of post-seizure EEG

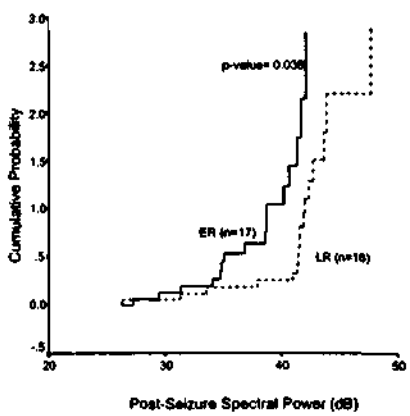


**Figure 3:** Kaplan-Meier survival curve for cumulative probability of being in either ER or LR groups depending on the spectral power of post-seizure EEG

repeated with spectral power values replacing FD values. Only post-seizure spectral power could significantly discriminate the early and late responders. It could predict 63% of the patients correctly into early and late responders. Kaplan-Meier survival analysis indicated that smaller post-seizure FD and lesser spectral power increased the cumulative probability of the patient being in the ER group (Figure 2 and 3).

## DISCUSSION

The important finding of this study is that the degree of post seizure EEG suppression predicts antidepressant response to right unilateral ECT. No other seizure measure predicted response. The finding of low FD in post-seizure EEG found in univariate analysis is unlikely to be a chance finding, as it alone stood out to predict early response in multivariate analysis, where other possible confounders were controlled for. Estimation of FD, however, is a less conventional method of analyzing EEG. Hence we conducted power spectral analysis also and found that early responders had lower spectral power than the late responders. Again, this was confirmed by multivariate analysis.

Positive association between the degree of post-seizure EEG suppression and antidepressant response with bilateral ECT has been reported by Nobler et al., (1993), Suppes et al., (1996) and Gangadhar et al., (1999). Given the pronounced cognitive advantage of unilateral ECT over bilateral ECT, clinicians might prefer unilateral ECT to bilateral ECT wherever possible (Abrams, 1997) and a considerable proportion of patients would receive unilateral ECT. Replication of the finding of positive association between post-seizure suppression of EEG and antidepressant response suggests that both unilateral and bilateral ECTs share a common mechanism of action. Krystal et al., (2000) also reported similar findings with unilateral ECTs. Seizure duration did not predict antidepressant response. This is again in conformity with the current knowledge that seizure duration has no positive correlation with antidepressant action of ECT (Nobler et al., 1993; Abrams, 1997).

Median average FD for post-seizure EEG of the four channels for the entire sample was 1.0129. When average FD of only the frontal leads was taken, the median was 1.014. This value is similar to the one reported by Gangadhar et al., (1999) based on two frontal channel EEG analysis (1.016). Median or less than median post-seizure FD identified correctly twelve of the seventeen (71%) in the ER group, whereas, more than median post-seizure FD identified twelve of the eighteen (67%) in the LR group, suggesting a good predictive value for post-seizure FD.

In this study, early responders were defined as those who had more than median percent improvement on both

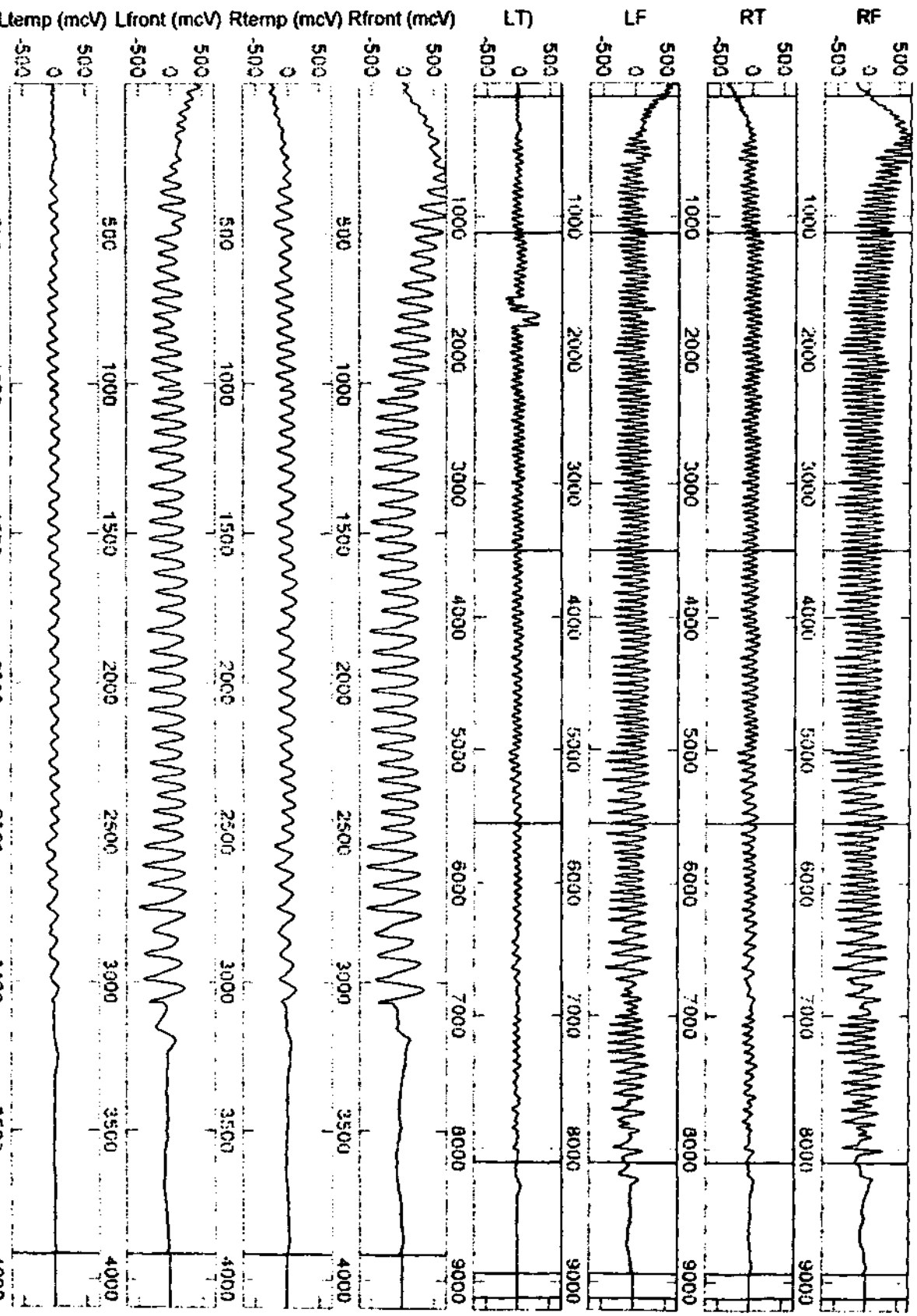


**Figure 1. A typical EEG recording during ECT depicting early- mid- and post-seizure phases chosen for analysis**

7th and 14th day. On the 14th day, their mean HRSD score was 6.70 (± 4.2). Spectral power of the post-seizure EEG had a significant negative correlation (Spearman's rho = -0.38; p <0.05) with percent improvement on HRSD scale on the 7th day. Such a correlation was not found on the 14th day (Spearman's rho = -0.14; p = 0.4). This is possibly because post-seizure suppression of EEG following ECT during the first week may be more closely associated only with improvement during the first week. Whether similar correlation exists between post-seizure suppression of EEG following ECT during the second week and antidepressant response during the second week was not examined in this study.

The implications of this positive association between post-seizure suppression of EEG and therapeutic response can only be speculative at this stage. It is known that failure to elevate the seizure threshold during the course of ECT is associated with poor antidepressant effect (Sackeim et al 1987), indicating that anticonvulsant action of ECT is in someway related to its therapeutic effect. Sackeim et al (1983) for example have suggested that enhanced GABAergic activity perhaps underlies the anticonvulsant and therapeutic action of ECT. GABA mediates the seizure termination and this in turn may cause post-seizure suppression of EEG. Measuring post-seizure EEG amplitude (by FD or spectral power) could hence reflect GABAergic response following seizure.

Strengths of this study are that it used four channels to analyze EEG and a rater blind to the clinical status of the patients analyzed EEGs. FD and spectral power analyses were done and both of these produced similar results, adding to the consistency of the findings. That whether the improvement during the first two weeks sustained in weeks to follow was not examined in this study and this remains to be examined. The measures of EEG seizure from all ECT sessions may help to find an answer.

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