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The Longitudinal Effects of Electroconvulsive Therapy on Ictal Interhemispheric Coherence and Its Associations With Treatment Outcome: A Naturalistic Cohort Study

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Abstract

Objectives. Electroconvulsive therapy (ECT) is an effective treatment for severe depression. Electroencephalogram (EEG) measures between ECT sessions seem to be related to the antidepressant efficacy of ECT. In this naturalistic cohort study, we examine longitudinal effects of ECT on interhemispheric EEG coherence measures during seizure activity and its relation to the antidepressant efficacy. *Methods*. This study included 65 patients diagnosed with severe depressive disorder. Depressive symptoms were rated according to the Montgomery-Åsberg Depression Rating Scale before and after the course of ECT. Frequency-specific ictal interhemispheric (fp1-fp2) EEG coherence measures were established during the first and each consecutive sixth treatment session. Linear mixed-effect models were used to determine longitudinal changes in ictal coherence measures during the course of ECT and its relation to treatment efficacy. *Results*. Ictal interhemispheric coherence in the theta and alpha frequency bands increased over the course of treatment, whereas no significant change was found for the delta and beta frequency bands. A main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band was revealed. However, the longitudinal effects of ECT were not associated with treatment efficacy. *Conclusion*. The current study suggests that interhemispheric coherence during ECT-induced seizures increases over the course of treatment. Furthermore, these longitudinal effects seem to be unrelated to the antidepressant efficacy of ECT. These findings contribute to the understanding of the mechanism of action of ECT.

Keywords
electroconvulsive therapy, treatment outcome, EEG, coherence, longitudinal effects

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Introduction

Electroconvulsive therapy (ECT) is an effective treatment for severe depression.[1,2] Remission rates of ECT have been shown to range from 20% to more than 80%.[3] However, the mechanism by which ECT is effective are still largely unknown. During a course of ECT, series of electrical pulses are administered to the brain, thus evoking seizure activity in clusters of neurons. Propagation measures of seizure activity can be established by ictal electroencephalographic (EEG) recording. The use of ictal EEG has provided insight into the working mechanisms of ECT.[4] One measure that is often reported is the coherence of oscillations between the 2 hemispheres. Oscillatory coherence is considered to be a useful indicator of signal propagation through functional connections in the brain.[5] The current study explores interhemispheric seizure propagation using ictal coherence measures during ECT-induced seizures.

Previous studies have shown interictal slowing of oscillations during the course of ECT (ie, inducing oscillations in the theta and delta bands).[6-8] Furthermore, the antidepressant efficacy of ECT has been correlated with increases in slow wave (theta frequency) coherence over the first 4 treatments.[9] These studies used interictal EEGs, that is, recorded between the treatment sessions. A study that acquired EEG during the

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ECT-induced seizure showed that greater slow wave coherence (delta frequency) averaged over the course of treatment correlated with better antidepressant efficacy.[10] Thus, previous research has shown that ECT seems to induce slow frequency oscillations, which may be correlated with antidepressant efficacy. However, the longitudinal effect of ECT on ictal coherence measures has not been established yet.

The main aim of this naturalistic cohort study was to examine the longitudinal effects of ictal interhemispheric EEG coherence during the course of ECT treatment. Furthermore, we assessed whether differences in longitudinal effects of ictal EEG coherence were related to treatment efficacy. Finally, a secondary aim of this study was to replicate a previous finding that revealed an association between treatment efficacy and the ictal EEG coherence averaged over the course of treatment.[10]

Materials and Methods

Patients

Patients, indicated for ECT at the Rijnstate Hospital (Arnhem, the Netherlands), were classified according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (*DSM-IV-TR*), with severe mood disorders and were selected for this study. Patients were excluded if aged <18 years, and if they dropped out of treatment during the ECT course. The severity of depression was determined with the Montgomery-Åsberg Depression Rating Scale (MADRS) by a trained research nurse. The MADRS consists of questions in 10 subcategories,[11] rated 0 to 6, resulting in a score ranging from 0 to 60 (highest level of severity). The percentage change in MADRS scores from pre- to post-ECT were established for each patient and response was defined as a decrease in MADRS score of at least 50% after the course of ECT.

The Medical Ethical Committee of the hospital approved the research protocol of this study (NL24697.091.09). After receiving full information about the study, written informed consent was obtained from all participants. Characteristics of the patients are described in more detail elsewhere.[9]

Treatment Course and Procedure

ECT was administered using a constant-current (0.9 A), brief-pulse (0.25 ms in right unilateral [RUL] and 0.5 ms in bifronto-temporal [BL] ECT) device (maximum output 1008 mC; Thymatron IV; Somatics Incorporation, Lake Bluff, IL, USA), after induction of anesthesia intravenously with etomidate (0.3 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass) intravenously, and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL, except in patients at high risk for suicidality and/or acute somatic compromised conditions, or if BL ECT had successfully been administered previously. Dosage was set at 6 times initial seizure threshold (IST) in RUL ECT and at 2.5 times IST for BL treatment. Patients were treated twice weekly. RUL electrode placement could be changed into BL electrode placement during the ECT course if the patient did not show (enough) improvement after 6 RUL sessions, based on the clinical decision of experienced psychiatrists. One week before starting ECT, baseline MADRS scores were determined. The course of ECT treatment was terminated when mood had not further improved in the last 2 ECT sessions, based on the clinical decision of the psychiatrists. Within 1 week after the last ECT session, the post-ECT MADRS score was established.

EEG and Interhemispheric Coherence

Ictal coherence was documented by 2-channel EEG recordings as part of the standard clinical practice (using the Thymatron IV device; sampling rate = 250Hz). In this study, only EEG recordings were used that were registered after inducing a suprathreshold therapeutic seizure at the 1st, 6th, 12th, 18th, and 24th treatment session, depending of the total length of the individual course. EEG Ag/AgCl electrodes were positioned at approximately Fp1 and Fp2 and pulse artifacts were avoided by placing the reference electrodes high on the ipsilateral mastoid. An additional ground electrode was placed at the shoulder. Prelubricated and self-adhesive electrodes were used on a cleaned skin (Somatics Incorporation, Lake Bluff, IL, USA). Patients were instructed not to use any face cream or lotion on the day of treatment to increase the adherence of the electrodes. Because of the use of the Thymatron device for EEG recording, no measure of impedance could be determined.

The Thymatron device automatically calculated the interhemispheric coherences per frequency band (δ [0.7-3.5 Hz], θ [3.5-8 Hz], α [8-13 Hz], and β [13-25 Hz]). The device determined the cross-correlation between the power spectrums of the 2 EEG electrodes for each frequency band, adjusted for possible shifts in phase, based on the following equation:

$$\text{Coherence}(f) = \frac{\left|S_{xy}(f)^2\right|}{S_{xx}(f) * S_{yy}(f)}$$

in which $\left|S_{xy}(f)^2\right|$ is the squared magnitude of the complex cross-spectrum function. This function is normalized by the convolution of $S_{xx}(f)$ and $S_{yy}(f)$, which are the real valued power spectra of the individual left and right EEG channels, respectively. Computer-automated EEG measures established by the Thymatron IV device are shown to be reliable,[12,13] though precludes custom data processing and signal-to-noise optimization.

The ictal interhemispheric coherence was quantified during generalized seizures, and the pre- and post-ictal segments of the EEG were excluded from the analysis. The criteria for a generalized seizure were (*a*) visible motor tonic-clonic seizure activity at the nonparalyzed limb (≥20 seconds) and (*b*) typical peak slow-wave EEG signals at Fp1 and Fp2 (≥25 seconds). No outliers in the mean ictal interhemispheric coherence measure could be detected.

Table 1. Descriptive Statistics of the Sample's Demographic, Clinical, and Treatment Parameters.

Variable	Mean ± SD or Count (%)
Age, years	57.0 (±14.5)
Sex, female	40 (62)
Pre-ECT MADRS	36.1 ± 8.4
Post-ECT MADRS	13.2 ± 10.1
Bipolar depression	12 (18)
Psychotic features present	20 (31)
Known DSM-classified personality disorder	21 (32)
Concomitant medication use during ECT	
Antidepressants	39 (60)
Benzodiazepines	42 (65)
Antipsychotics	44 (67)
Antiepileptics	5 (8)
RUL/BL/switch RUL to BL during course	25 (35) / 13 (20) / 27 (42)
Total no. of ECT sessions during ECT course	17.8 ± 7.0
Initial seizure threshold (in mC)	63.4 ± 34.7
Dosis succinylcholine (in mg)	86.8 ± 16.1
Dosis etomidate (in mg)	22.1 ± 5.0

Abbreviations: ECT, electroconvulsive therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; DSM, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; RUL, right unilateral electrode placement; BL, bifrontotemporal electrode placement.

Statistical Analysis

Linear mixed-effect models were performed in R studio with the lme4 package.[14,15] Assumptions for homoscedasticity and normality were checked by visual inspection and did not show deviations. Separate models were run for each frequency band (as the dependent variable). First, the effect of time (ie, treatment number) on the ictal coherence measures was analyzed. Time and electrode placement were entered as fixed effects, a by-subject random slope for time and random intercepts for age and sex were included. The main effect of time was inferred from the linear mixed-effect model. Second, the effect of treatment efficacy on the ictal coherence measures was analyzed. Percentage change in MADRS scores, time, and electrode placement were entered as fixed factors, and random intercepts were included for subject, age and sex. The main effect of percentage change in MADRS scores was inferred from the linear mixed-effect model. Additional analyses were performed to assess whether the effects of treatment efficacy on the ictal interhemispheric coherence were unique for each frequency band. This was established by adding random intercepts for the frequencies that did not serve as the independent variable to the latter analysis. Third, the interaction effect of time by efficacy on the ictal coherence measures was analyzed. Time, percentage change in MADRS scores (pre- to post-ECT), electrode placement and a time by percentage change in MADRS interaction effect were entered as fixed factors, a by-subject random slope for time, and random intercepts for sex and age were also included. As additional analyses and for the purpose of visualization, the analyses on the main and interaction effects of treatment efficacy were also performed using the dichotomized treatment response score (split at 50% change in MADRS scores). Finally, to test for confounding effects, potentially confounding variables were added to the models that revealed a significant result. This was done by adding random intercepts for the following variables: length of the EEG, pre-ECT MADRS score, use of antidepressants (yes/no), antiepileptics (yes/no), benzodiazepines (yes/no) and antipsychotics (yes/no), and the presence of a bipolar disorder (yes/no), psychosis (yes/no), or a known comorbid DSM personality disorder (yes/no). For all analyses, P-values were obtained by likelihood ratio tests of the full model with the effect of interest against the model without the effect of interest. The statistical threshold was set at $\alpha = .05$ and Cramer's V values were reported as a measure of effect size.

Results

Descriptive statistics of the sample's (n = 65) demographic, clinical, and treatment parameters are presented in Table 1.

The analyses on the effect of time revealed that the ictal interhemispheric coherence in the theta, $\chi^2(1) = 7.52$, $P = .006$, $V = 0.18$, and alpha, $\chi^2(1) = 13.01$, $P < .001$, $V = 0.25$, bands increased significantly over time. No effect of time was observed in the delta, $\chi^2(1) = 1.54$, $P = .214$, $V = 0.08$, and beta, $\chi^2(1) = 0.924$, $P = .337$, $V = 0.06$, frequencies (Figure 1). The effect of time on theta, $\chi^2(1) = 6.54$, $P = .01$, $V = 0.18$, and alpha, $\chi^2(1) = 12.1$, $P < .001$, $V = 0.24$, coherence remained significant after adjusting for the effects the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of medication.

Further analyses revealed a main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band. That is, a greater percentage change in MADRS scores was associated with greater ictal interhemispheric coherences in the

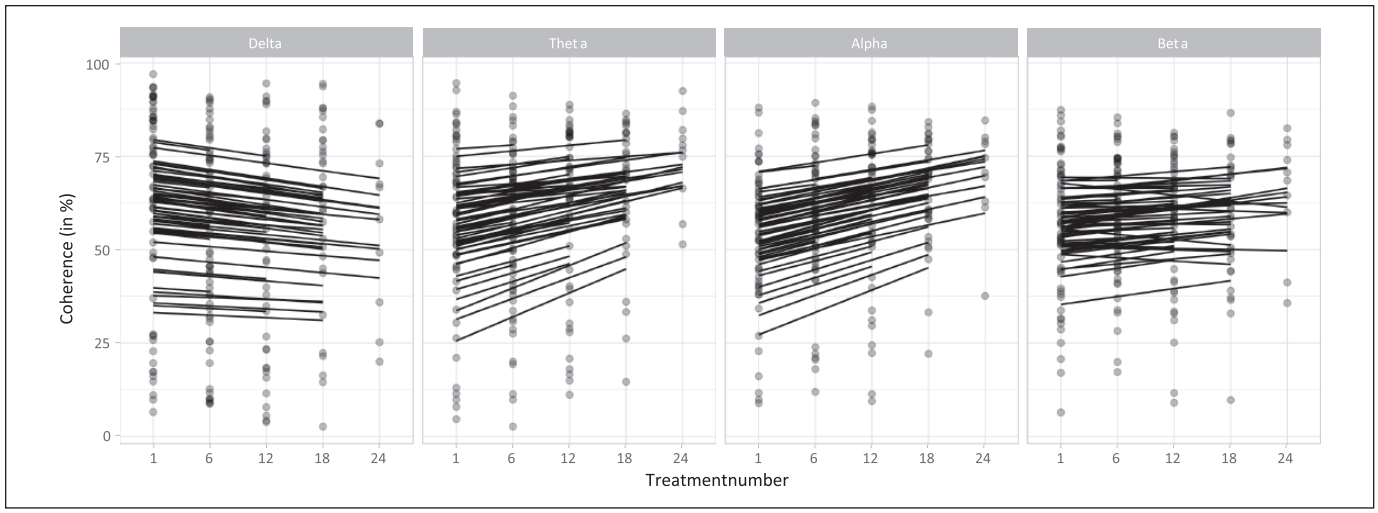

Figure 1. Regression plots for the effect of time on the ictal interhemispheric coherence for all frequency bands. Data points represent the actual measured ictal interhemispheric coherence, whereas the lines represent regression slopes for each patient as fitted by the linear mixed-effect models.

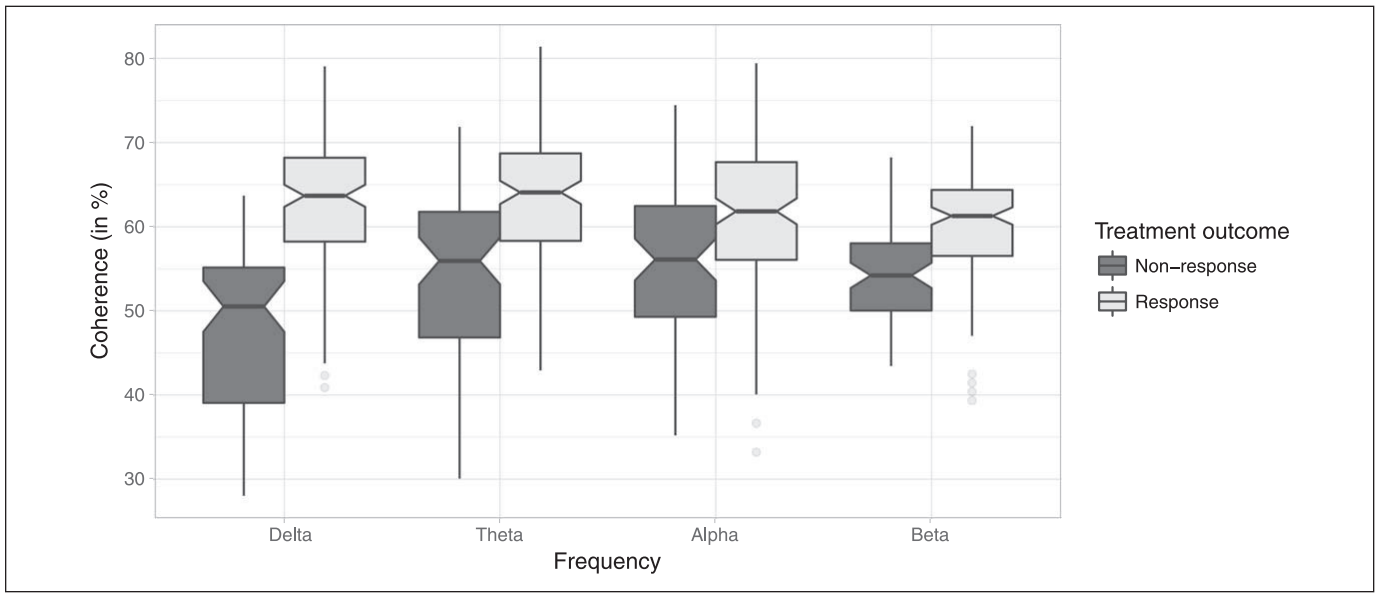

Figure 2. Notched boxplot for the effect of response on the ictal interhemispheric coherence for all frequency bands. Data predicted by the linear mixed-effect models on the effect of response were used to create the boxplots.

delta, $\chi^2(1) = 4.74$, $P = .029$, $V = 0.15$, and theta, $\chi^2(1) = 4.11$, $P = .043$, $V = 0.14$, frequencies, whereas no significant effect was shown in the alpha, $\chi^2(1) = 2.38$, $P = .123$, $V = 0.11$, and beta, $\chi^2(1) = 2.72$, $P = .099$, $V = 0.11$, frequencies. Additional analyses showed that the effect of treatment response remained significant after adjusting for the coherence measures in the other frequency bands for the delta, $\chi^2(1) = 4.77$, $P = .029$, $V = 0.14$, and theta, $\chi^2(1) = 5.14$, $P = .023$, $V = 0.16$, frequency bands, but not for the alpha, $\chi^2(1) = 2.06$, $P = .151$, $V = 0.10$, and beta, $\chi^2(1) = 1.73$, $P = .188$, $V = 0.09$, frequency bands. Furthermore, the significant main effect of percentage change in MADRS scores on delta, $\chi^2(1) = 5.00$, $P = .025$, $V = 0.15$, and theta, $\chi^2(1) = 4.88$, $P = .027$, $V = 0.15$, coherences was not confounded by the effects of the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of psychotropic medication. Analyses on the main effects of treatment response using the dichotomized treatment response scores (split at 50% reduction) revealed similar results (Figure 2).

Finally, analyses on the interaction between time and treatment efficacy on the ictal interhemispheric coherence did not reveal a significant effect in any of the frequency bands (for delta: $\chi^2(1) = 0.67$, $P = .414$, $V = 0.06$; for theta: $\chi^2(1) = 0.23$, $P = .633$, $V = 0.03$; for alpha: $\chi^2(1) = 0.15$, $P = .69$, $V = 0.06$;

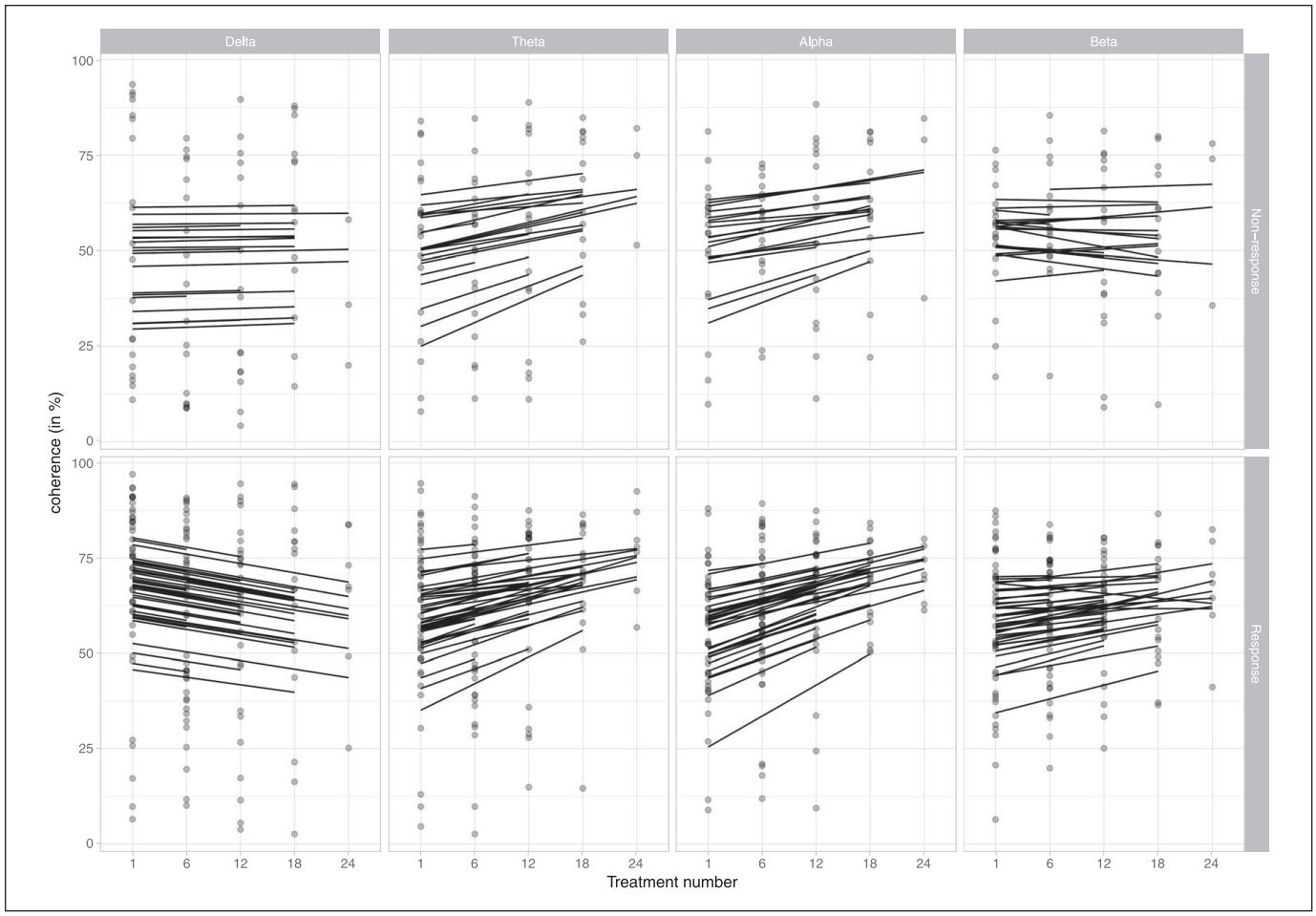

Figure 3. Regression plots for the time by treatment response interaction effect on the ictal interhemispheric coherence for all frequency bands. Data points represent the actual measured ictal interhemispheric coherence, whereas the lines represent regression slopes for each patient as fitted by the linear mixed-effect models. None of the models revealed a significant interaction effect.

for beta: $\chi^2(1) = 1.24$, $P = .266$, $V = 0.08$). In line with these results, no significant effects were revealed by analyses on the interaction effects between treatment response and time using the dichotomized treatment response scores (Figure 3).

Discussion

This naturalistic cohort study showed that the ictal interhemispheric EEG coherence in the theta and alpha bands increased during the course of ECT, whereas no such changes over time were found for the delta and beta band frequencies. The longitudinal alterations in ictal interhemispheric coherence were not associated with the antidepressant efficacy of ECT for any of the frequency bands. Finally, a main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band was revealed. That is, patients with greater reduction in MADRS scores showed greater ictal interhemispheric EEG coherence in the delta and theta bands, which confirms and extends a previous finding.[10] The significant effects were independent from the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of psychotropic medication.

The current study suggests that interhemispheric EEG measures during an ECT session increase over the course of treatment. Similarly, previous studies showed an increase in slow-wave activity between ECT sessions,[6-8] although the increase in EEG measures was found in a slightly lower frequency range (3.5-13 Hz in our study compared with 0.5-7Hz in others). Differences in the type and time of measurements used in the studies may explain this contrast in findings. That is, previous studies used activity measures between treatment sessions whereas our current study examined coherence measures during an ECT-induced seizure. Nevertheless, these studies showed that ECT increases multiple frontal EEG measures, both during and in between treatments. These findings support the neuroplasticity hypothesis of ECT,[16,17] which states that ECT induces synaptic growth, which may facilitate increased signal propagation.

In the current study, a main effect of treatment efficacy on the slow-wave ictal interhemispheric coherence during ECT-induced seizures was revealed. A previous study posed that

> the field has misinterpreted these associations as reflecting the therapeutic potency of ongoing treatment. Instead, we suggest that these associations derive from differences among patients in neurophysiological response to seizure provocation and that these individual differences, independent of ECT treatment parameters, are linked to therapeutic outcome.[10]

In line with this hypothesis, our findings show that ictal EEG measures that depend on the amount of time in treatment (ie, the longitudinal ictal interhemispheric coherence) were not associated with treatment outcome, whereas measures independent of the amount of time in treatment (ie, the ictal slow-wave coherence averaged over the course of treatment) did correlate with efficacy of ECT. In our study, the main effect of treatment efficacy on interhemispheric coherence measures survived after adjusting for the pre-ECT symptom severity and other comorbid disorders. This further supports the hypothesis that the association between treatment efficacy and ictal interhemispheric coherence indeed reflect differences among patients in the neurophysiological response to seizure provocation, rather than preexistent states of illness. Differences in response to seizure provocation may be due to differential brain states between patients at baseline. To test this hypothesis, future research should aim to reveal whether the treatment efficacy of ECT is also associated with pre-ECT functional connectivity measures. The association between ictal slow-wave EEG measures and treatment outcome might be explained by a possible working mechanism of ECT. That is, slow-wave ictal oscillations originate from the firing of inhibitory GABAergic interneurons.[18,19] The activation of GABAergic interneurons may underlie termination of induced seizure activity, which is proposed as a working mechanism of ECT.[20] Thus, we suggest that the magnitude of ictal slow-wave EEG measures reflect individual differences in the strength of seizure termination processes which determine the antidepressant efficacy of ECT.

Several caveats of this naturalistic cohort study should be considered. The main limitation of this study is that the ictal interhemispheric coherence measures were automatically computed by the ECT device without visual screening for artifacts. Although computer-automated EEG measures established by the Thymatron IV device are shown to be reliable,[12,13] this may have reduced the signal-to-noise ratio. Second, coherence and global power measures seem to have a similar association with ECT efficacy.[10] Global power measures were not included in this study and, therefore, we could not assess whether the relation between coherence and treatment efficacy may be confounded by global power measures. The reported findings should thus be interpreted in terms of EEG features in general rather than effects of coherence measures in specific. Additionally, volume conduction effects are known to increase the coherence between moderately separated electrodes.[21] Therefore volume conduction effects may have amplified the results in this study. Furthermore, patients did not terminate psychotropic medication treatment during treatment. The use of these medication may have influenced the ictal interhemispheric coherence measures, since antidepressants and benzodiazepines seem to affect brain oscillations.[22] However, additional analyses revealed that medication use had no statistically significant influence on the reported results. Another potentially confounding factor is the known degradation of seizure quality over the course of treatment. Because of the lack of a valid measure of seizure quality in this study, we were not able to control for this effect which may have biased the analyses on the longitudinal effects of ECT on the interhemispheric coherence measure. Finally, the interhemispheric coherence was only determined at a limited amount of time points. Thereby, we were not able to detect subtle changes in interhemispheric coherence measures during the course of treatment.

In conclusion, the current naturalistic cohort study suggests that the interhemispheric functional connectivity during ECT-induced seizures increases over the course of treatment. Furthermore, these longitudinal effects seem to be unrelated to the antidepressant efficacy of ECT. The found ictal interhemispheric coherence increase was specific for the theta and alpha frequency bands. The findings of the current naturalistic cohort study may contribute to further understanding of the working mechanism of ECT.

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Author Contributions

F. ten Doesschate contributed to conception and design; contributed to the acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. G.A. van Wingen contributed to the analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. B.J.H.B. de Pont contributed to the acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. M. Arns contributed to the analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. J.A. van Waarde contributed to conception and design; contributed to the acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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