Restoration of postictal cortical activity after electroconvulsive therapy relates to recovery of orientation in person, place and time

Sven Stuiver[1,2], Julia C.M. Pottkämper[1-3], Joey P.A.J. Verdijk[1,2], Freek ten Doesschate[2], Michel J.A.M. van Putten[1], Jeannette Hofmeijer[1,3], Jeroen A. van Waarde[2]

Affiliations:

[1]University of Twente, Technical Medical Centre, Faculty of Science and Technology, Clinical Neurophysiology, Hallenweg 15, 7522NB, Enschede, The Netherlands.

[2]Rijnstate Hospital, Department of Psychiatry, Wagnerlaan 55, 6815AD, Arnhem, The Netherlands.

[3]Rijnstate Hospital, Department of Neurology and Clinical Neurophysiology, Wagnerlaan 55, 6815AD, Arnhem, The Netherlands.

Corresponding author:

Sven Stuiver, MSc.

Rijnstate Hospital

Department of Psychiatry, P.O. Box 9555, 6800 TA Arnhem, the Netherlands

Phone: 0031 88 005 7766

Fax: 0031 88 005 8929

E-mail: sstuiver@rijnstate.nl

ORCID digit: 0000-0002-5260-0820

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Short title:

Recovery of clinical orientation depends on restoration of cortical activity

Introduction

Electroconvulsive therapy (ECT) has been used for effective treatment of major depression since decades. In ECT-sessions, a short electrical stimulus (< 8 seconds, block pulse) is administered through (parts of) the patients' brains to elicit self-terminating generalized seizure activity. The postictal state follows directly after seizure termination. During this state, patients may show temporary postictal symptoms, such as confusion with disorientation in person, place, or time [1–6]. Understanding the postictal state is important, because its duration has been related to both effectiveness and cognitive side-effects of the ECT-course [7–9].

During the postictal state, patients gradually regain orientation, typically from personal to spatial and temporal orientation [10]. At the bedside, recovery in these cognitive domains is clearly observed and classically assessed by the Reorientation Time (ROT) questionnaire [7]. Increased ROT values indicate a longer postictal state after an ECT-session. This is clinically relevant, since longer ROT has been associated with poorer retrograde autobiographical memory outcome, lasting from a week up to six months after the ECT-course [7,11]. On the other hand, longer ROT was associated with more rapid decline of depressive symptoms and better antidepressant outcome of the ECT-course [9].

The electroencephalogram (EEG) can be used to measure real-time cortical brain activity and also provides measures to quantify the postictal state. Immediately after

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termination of the ECT-seizure, the postictal EEG shows suppression and slowing [6,12,13]. Postictal suppression is defined as amplitude reduction to less than 10 µV within 30 seconds of seizure transmission, lasting > 2 seconds [13,14]. Abnormal EEG slowing is indicated by an increase in the delta (1-4 Hz) and theta (4-7 Hz) frequency ranges, and a reduction of faster frequencies [15,16]. EEG recovery is probably more objective and more sensitive than ROT to quantify postictal recovery. Indeed, while clinical reorientation usually recovers within an hour, postictal EEG slowing may last up to 24 hours and it even takes longer before the EEG has completely returned to baseline activity [17,18].

Currently, it is unknown how restoration of the postictal EEG relates to recovery of clinical orientation after ECT. Such link between EEG and clinical recovery may provide new objective and sensitive measures to quantify the postictal state. In addition, the relation between clinical and electrophysiological recovery may yield novel insights into the mechanisms of recovery of consciousness after seizures. Therefore, we studied whether postictal EEG restoration was related to recovery of clinical orientation by simultaneous continuous EEG recording and intermittent assessment of orientation in person, place and time, immediately after ECT-induced seizures.

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Methods

Study population

This is a *post hoc* exploratory analysis of prospectively collected trial data from 33 depressed patients treated with ECT in Rijnstate Hospital (Arnhem, The Netherlands), who participated in the StudY of effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT (SYNAPSE; NCT04028596). SYNAPSE was a randomized controlled trial with a three-condition cross-over design. Patients received nimodipine, acetaminophen or placebo (i.e., water) in random and counterbalanced order at a maximum of two hours before each ECT-session [19]. Repeated EEG measures before, during, and until one hour after the ECT-sessions were collected to study the effects of the various treatment conditions on postictal recovery. Inclusion criteria for patients were age ≥ 18 years and having a current clinical diagnosis of major depression (i.e., classified as unipolar, bipolar, schizoaffective disorder, according to the Diagnostic Manual of Mental Disorders, fifth edition [DSM-5]) [20]. The local medical ethical committee approved the study protocol (NCT04028596) and all included patients provided oral and written informed consent.

Electroconvulsive therapy and treatment outcome measures

ECT was administered according to the Dutch treatment guidelines in the context of current care, twice a week, and electrodes were either placed right unilateral (RUL) or bi(fronto)temporal (BL) [21]. ECT stimuli were delivered with a constant-current (900 milliAmpere), square wave, bidirectional and brief pulse (1 millisecond) using the Thymatron System IV device (Somatics Incorporation Lake Bluff, Illinois, USA). In case patients showed a poor response initially, RUL placement was switched to BL placement. Anesthesia was mostly achieved using etomidate (0.2–0.3 mg/kg body

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weight) for sedation and succinylcholine (0.5–1 mg/kg) for muscle relaxation. In case of severe postictal confusion, defined as the clinical necessity to administer sedatives or restraints due to severe motor restlessness, disorientation, agitation or anxiety [22]), midazolam (2.5-5 mg intravenously) was used. Cessation of the ECT-course was clinically decided by the treating psychiatrists, and rated with the Hamilton Depression Rating Scale (HDRS) [23]. Clinical response was defined as a decrease ≥ 50% of post-ECT HDRS-score compared to pre-ECT, and remission as a post-ECT HDRS-score < 8.

EEG registration and pre-processing

Twelve or twenty silver/silver chloride cup electrodes were placed on the scalp according to the International 10-20 system. Cz was used as reference. The electrode-skin impedance was kept below 5 kΩ. EEG was recorded before, during, and after the seizure: recordings started around five minutes before administration of anesthesia and lasted up to one hour after seizure termination. In this study, both ictal and postictal EEG recordings were used. Data were band-pass filtered (0.5-30 Hz; first-order Butterworth filter) and segmented into five-second epochs without artifacts. EEG recordings were visually inspected for artifacts in software of NeuroCenter EEG (Leiden, The Netherlands). Electrodes containing noise or electrodes that were physically removed during the measurements (e.g., due to movement or postictal agitation) were rejected for analyses. All EEG analyses, pre-processing steps and fits were conducted with MATLAB R2023a (MathWorks, Natick, MA, USA).

Restoration of the postictal EEG

The start of the postictal state was defined at seizure termination, that was based on cessation of spike-wave complexes and EEG suppression. Restoration of the postictal

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EEG was quantified with the normalized alpha-delta ratio (ADR), that was calculated and expressed as:

$$ADR = \frac{pow(\alpha) - pow(\delta)}{pow(\alpha) + pow(\delta)} \quad (1)$$

with $pow(\alpha)$ and $pow(\delta)$ the power in the alpha (8-13 Hz) and delta (0.5-4 Hz) frequency bands, respectively. These values were calculated from computing power spectral density (PSD) values using Welch's method [24]. Five-second artifact-free segments with an overlap of 50% were used and median PSD values were determined of the available electrode channels (whole brain). ADR values were averaged per minute and fitted with a sigmoidal function given by:

$$f(t) = \frac{a}{1 + be^{-(c-t)/\tau}} + d \quad (2)$$

with t the duration of the postictal state (with a minimum duration of 40 min), a the distance from d to the lower asymptote, b the transition from rapid to reduced growth, c the initial lag, τ the time constant, and d the upper asymptote. The values of the parameters (a, b, c, τ and d) were estimated using a nonlinear least squares routine. R^2 ≥ 0.7 was considered appropriate for goodness of the fit. Subsequently, the derivative (df/dt) of equation 2 was calculated, given by:

$$\frac{df}{dt} = -\frac{abe^{-(c-t)/\tau}}{\tau(1 + e^{-(c-t)/\tau})^2} \quad (3)$$

to estimate the timepoint where the recovery of ADR was at its maximum (T_{max}). T_{max} was defined as the timepoint where equation 3 had its maximum value. The EEG features we used for postictal EEG restoration were the parameters a and τ from equation 2, and T_{max} from equation 3.

Seizure duration

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Seizure duration was defined as the time-interval between seizure onset and offset points, which were determined visually in the EEG. Seizure onset was defined as onset of rhythmicity of spike-wave complexes, including waveform repetition with relatively uniform morphology and duration. Seizure offset was the timepoint where the seizure terminated, which was defined as the onset of generalized postictal suppression of at least two seconds [17,25,26].

Recovery of clinical orientation

Before each ECT-session, ROT questions were asked to assess orientation at baseline. After the ECT-stimulus, ROT questions were asked every five minutes to assess recovery of clinical orientation [7]. The ROT questionnaire consists of five questions to assess orientation in person (name, birthday), place (name of hospital), and time (age, day of week). Time to reorientation in all three domains was determined separately, by registration of the time (in minutes) until the question regarding a specific cognitive domain was answered correctly for the first time. Since the domains person and time consisted of two questions, these values were averaged, resulting in a single time to reorientation value for each domain. In case patients were not orientated at baseline in a specific domain, this domain was ignored for analysis.

Statistical analyses

Variables were described by using numbers and percentages (%), means and standard deviations (SD), and medians and interquartile range (IQR), as appropriate. Pre- and post-ECT HDRS-scores were compared using Wilcoxon signed-rank test, with $p < 0.05$ was regarded as statistically significant. Statistical analyses were computed using MATLAB and R version 4.3.1 using the lme4 and report packages [27,28].

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Recovery of clinical orientation. Time to reorientation values in the three cognitive domains person, place, and time were averaged (median and IQR) across subjects. Wilcoxon signed-rank tests were used to test whether these values in person, place and time differed.

Restoration of the postictal EEG and recovery of clinical orientation. Because of the inherently correlated data structure, three linear mixed models (LMMs) were fitted to predict clinical postictal recovery, one for each. Fixed effects, derived from the postictal EEG, were T_{max}, a and τ. Fixed effects related to patient- and ECT-parameters were electrical charge of the ECT-stimulus (in millicoulombs [mC]), seizure duration (in seconds), administration of midazolam, the applied electrode placement, the number of the ECT-session of the ROT measurement, sex, and age (in years). Random effects (slope and intercept) were subject and T_{max}, which specification was chosen based on avoiding singularity [29]. Separate analyses were performed in measurements without midazolam, to account for its known effects on EEG recordings [30].

Restoration of the postictal EEG and ECT-parameters. For each postictal EEG feature (i.e., T_{max}, a and τ), LMMs were fitted to predict postictal restoration, one for each (Supplementary Table S3).

LMMs assume that random effects deviations and residual errors are normally distributed, which were verified. All fixed effects were checked for multicollinearity, where a variance inflation factor < 5 was considered as a low correlation and tolerable. Because of the relatively small sample size (N = 33), the restricted maximum likelihood was used as estimation method. 95% Confidence intervals (CI) and *p*-values (alpha = 0.05) were computed using a Wald t-distribution approximation.

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Results

Patient and treatment characteristics

Out of the SYNAPSE database (N = 33), we included 272 pairs of ictal-postictal EEGs and clinical measures from 32 patients, because one patient had to be excluded due to poor EEG quality. Patient and treatment characteristics are shown in Table 1. Mean age was 54.2 ± 13.9 years and eighteen patients (56%) were female. Postictal EEG recordings of 90 ECT-sessions (34.2%) were registered after RUL stimulation, the remaining after BL stimulation. Immediately after 101 ECT-sessions (37.1%; N = 13 patients), midazolam was administered intravenously. At group level, patients received a median of 14 (IQR = 4.9) ECT-sessions during the completed ECT-course, with a mean applied electrical charge of 349.3 ± 162.4 mC. Mean seizure duration was 58.5 ± 29.9 seconds. HDRS-scores decreased significantly after the ECT-course (median pre-ECT HDRS-score = 23.5, IQR = 10; median post-ECT HDRS-score = 12, IQR = 9; $p < .001$). After the ECT-course, sixteen patients (50%) showed clinical response and seven (22%) remission.

Restoration of postictal EEG

The typical recovery of the postictal EEG in the first hour followed a sigmoid-like recovery of ADR (Figure 1). At group level, averaged values for postictal EEG parameters were: a = 0.33 ± 0.27 (ΔADR), τ = 6.3 ± 3.1 min, and T_{max} = 29.4 ± 8.6 min. While ADR values increased over time during the postictal state, no patient reached baseline ADR values within one hour after the seizure.

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Recovery of clinical orientation

In Figure 2, violin plots of the median time to reorientation values in person, place and time are shown. At group level, patients recovered firstly in person (median = 24.0 min, IQR = 5.2, $p < .001$), compared to time to reorientation in place (median = 28.6 min, IQR = 15.0, $p < .001$) and time to reorientation in time (median = 33.0 min, IQR = 18.7, $p < .001$). Also, patients recovered faster in place compared to reorientation in time ($p = .012$). Nineteen patients (61%) reached recovery of orientation in the exemplary sequence: person-place-time. None of the patients showed reorientation in time before reorientation in the other two domains.

Restoration of postictal EEG in relation to recovery of clinical orientation

Timepoint of maximum recovery (T_{max}). In all three cognitive domains, relationships between T_{max} and time to reorientation were observed (see Figure 3); i.e., positive relations between T_{max} and time to reorientation in person ($\beta = 1.5$, 95% CI [0.4, 2.6], $p = .007$), place ($\beta = 3.3$, 95% CI [1.3, 5.4], $p = .002$) and time ($\beta = 2.4$, 95% CI [0.5, 4.4], $p = .016$).

Extent of recovery (a). Negative relations were found between the extent of recovery (a) and time to reorientation in person ($\beta = -1.2$, 95% CI [-2.3, -0.1], $p = .036$) and in time ($\beta = -2.8$, 95% CI [-4.8, -0.8], $p = .007$). No relationship was found with reorientation in place ($\beta = -1.2$, 95% CI [-3.0, 0.7], $p = .171$).

Time constant (τ). No relationships were found between time constant τ and time to reorientation for all three domains (in person: $\beta = -0.7$, 95% CI [-0.1, 1.5], $p = .094$; in place: $\beta = -0.7$, 95% CI [-2.0, 0.6], $p = .300$; in time: $\beta = -0.3$, 95% CI [-1.8, 1.2], $p = .699$).

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Seizure duration in relation to recovery of clinical orientation

Positive relations were found between seizure duration and time to reorientation in person (β = 2.5, 95% CI [1.5; 3.5], $p < .001$), in place (β = 3.1, 95% CI [1.5, 4.8], $p < .001$) and in time (β = 3.3, 95% CI [1.6, 5.1], $p < .001$) (Figure 3).

Recovery of orientation in relation to patient- and ECT-parameters

Age. Higher age was related to longer duration of reorientation in time (β = 4.0, 95% CI [1.3, 6.7], $p = .004$). No significant associations were found in the other two domains.

Electrode placement. BL (compared to RUL) electrode placement seemed associated with longer time to reorientation in place (β = 5.2, 95% CI [-0.4, 10.8], $p = .070$), however this finding was not significant. In the other two domains, no associations were found.

Electrical charge of the ECT-stimulus. Electrical charge of the ECT-stimulus was positively related with time to reorientation in place (β = 2.6, 95% CI [0.5, 4.8], $p = .014$). No significant associations were found in the other two domains.

Postictal midazolam. Administration of midazolam was associated with longer time to reorientation in person (β = 4.4, 95% CI [1.3, 7.4], $p = .005$), in place (β = 8.3, 95% CI [3.5, 13.2], $p < .001$) and in time (β = 5.6, 95% CI [0.4, 10.7], $p = .034$).

The results of all fixed effects, random effects designs, formulas, and model performances of the LMMs for recovery of clinical orientation in all three cognitive domains (i.e., person, place and time) are shown in Supplementary Table S1. Analyses of data from measurements without midazolam (N = 171 measurements; N = 20 subjects) showed similar results (Supplementary Table S2). In Supplementary Table

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S3, associations of the postictal EEG features (T_{max}, a, τ) and other patient- and ECT-characteristics are shown.

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Discussion

In this analysis of prospectively collected clinical and EEG data, gradual restoration of the postictal EEG was related to gradual recovery of clinical orientation in all three cognitive domains (i.e., in person, place and time) after ECT-induced seizures. Slower restoration of postictal EEG was associated with longer time to reorientation in all domains. Longer seizure duration and postictal administration of midazolam were related to later time to reorientation. Clinical reorientation mostly recovered within one hour after the ECT-stimulus, but ADR values never reached baseline values in that time-frame. Our findings show that EEG is more sensitive than ROT to measure postictal recovery at one hour post seizures, and suggest that recovery of orientation after ECT is related to gradual restoration of cortical synaptic recovery.

Derived from the postictal EEG, the parameters a (indicating the extent of EEG restoration) and T_{max} (indicating the timepoint where EEG restoration was at its maximum) were related to reorientation time values. The EEG is dominated by postsynaptic potentials and restoration of the postictal EEG probably reflects the gradual recovery of cortical synaptic activity. Alpha oscillations have been theorized to play a key role in cognition and are present during (relaxed) wakefulness [31]. Restoration of this rhythm, indicated by an increase in ADR, probably relates to recovery of cortical synaptic activity. Our chosen EEG feature, the ADR, serves as proxy for this postictal EEG restoration, which as we show typically follows a sigmoidal function in the first hour. In most patients, clinical orientation recovered within an hour, while ADR values never normalized. This shows that a clinical psychometric instrument, such as the ROT [7], has ceiling effects and that EEG provides a more sensitive measure to estimate recovery of the postictal state. Previous work has shown

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that longer ROT is associated with retrograde amnesia, an important side effect of ECT [7,11]. We hypothesize a similar relationship with slower restoration of the postictal EEG, which may be a more sensitive measure for predicting retrograde amnesia. Our observed relationships between postictal EEG features and patient- and ECT-parameters support this hypothesis. EEG recordings beyond one-hour post-seizure may reveal important aspects (including prolonged disturbances of brain activity) of the postictal state that are currently neglected by clinical measures of reorientation.

Longer seizure duration was related to later time to reorientation in all domains. This finding is in line with previous findings [17]. During a seizure, there is an increase in energy consumption and cerebral blood flow, oxygen consumption and glucose metabolism [32,33]. Prolonged seizure activity may result in more (local) deprivation of oxygen and energy, inducing longer postictal synaptic depression and slower cortical synaptic recovery. Our results show a larger effect size of seizure duration on time to reorientation with an increase in complexity of the cognitive domain, from person to place to time. It has been shown that amnestic effects of ECT are greatest for impersonal memory (i.e., knowledge about the world) compared to personal memory, for recent compared to distinctly remote events, and for less salient events [34]. Therefore, domains involving impersonal memory and more recently stored information (i.e., orientation in time and place) may be more vulnerable to the effects of ECT-induced seizures, especially in longer seizures.

More than half of the patients recovered in orientation in the sequence person-place-time, and never in time before the other two domains. The specific order of reorientation in person-place-time is in line with earlier findings [10,35] and was also observed in patients recovering from closed-head injury [36]. Furthermore, this finding is also in line with observations in patients with dementia, where orientation disappears

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in counterorder [37]. The sequence of recovery in person-place-time may again point towards differences between personal and recently stored information, or at distinct restoration processes of consciousness, possibly in different parts of the human brain or functional networks [37].

Previous research found that the length of postictal disorientation tends to increase with more numbers of previous ECT-sessions and with the application of BL electrode placement.[35] In this study, we show that higher age was related to longer duration of reorientation in time. Furthermore, higher applied electrical charge and BL electrode placement (and at trend level with RUL, p = .070) were related with longer reorientation time in place. According to modeling studies, these ECT-parameters determine spread of current density in the brain during electrical stimulation [38]. Postictal administration of midazolam was associated with later time to reorientation in all domains. Use of this agent is known to increase delta power and decrease of alpha power [30]. Therefore, midazolam may delay postictal ADR restoration, resulting in longer reorientation times. Separate analyses without midazolam showed similar findings regarding the relationships with postictal EEG and clinical reorientation. Our findings indicate that some patient characteristics and ECT-parameters may only affect reorientation time values of specific domains, while others show persistent effects in all domains of orientation.

Strengths and limitations

Strengths of this study include the prospective collection of large number of repeated measures of ictal and postictal EEG data (N = 272), the use of continuous EEG monitoring and the analysis of time to reorientation values in three domains. Furthermore, this study included systematically measured postictal brain activity up to one hour after seizure termination together with direct clinical measures of

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reorientation. However, some limitations apply to this study. First, the study was not powered for this post-hoc evaluation of time to reorientation in the three distinct cognitive domains. Second, we did not account for possible confounding effects of the concomitant use of medication (i.e., antidepressants, antipsychotics, anti-epileptics and benzodiazepines) during the ECT-course. Finally, the remission rate of ECT in this study cohort was low (22%), compared to reported ECT remission rates of 51-58% [39], probably due to the patient selection for ECT in The Netherlands (i.e., often only indicated as treatment-of-last-resort).

Conclusion

We found a clear relationship between clinical recovery of orientation and restoration of EEG activity after ECT-induced seizures. Longer time to reorientation was related to slower restoration of the postictal EEG. Despite complete clinical reorientation, the EEG showed enduring postictal disturbances at one-hour post-seizures, pointing towards a higher sensitivity of EEG than ROT to estimate postictal recovery. In addition, longer seizure duration and postictal administration of midazolam were related to increased time to reorientation values. Our results imply that clinical reorientation probably depends on gradual cortical synaptic recovery, and that longer seizures lead to longer postsynaptic suppression.

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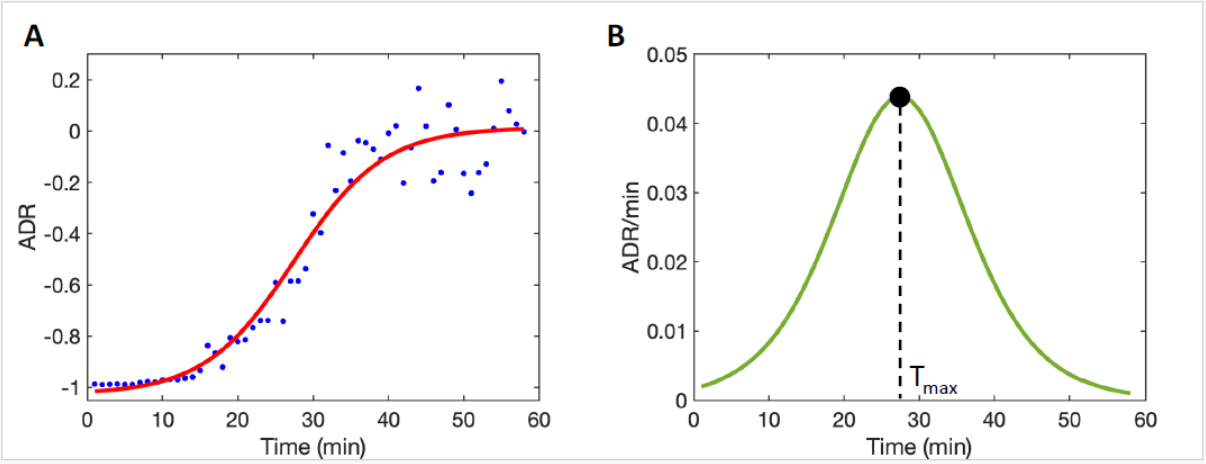
Figure captions

Figure 1. Restoration of the postictal electroencephalogram (EEG) expressed as the evolution of the normalized alpha/delta ratio (ADR; equation 1). (A) Averaged ADR values per minute (blue dots) followed a typical sigmoidal evolution in the postictal state, starting at values close to -1. The evolution of ADR is well described by the sigmoidal curve (solid red line), defined by equation 2. Here, a = 1.0 ± 0.1 (ΔADR) and τ = 5.9 ± 4.4 min. (B) From the derivative (green solid line), defined by equation 3, T_{max} is estimated. Here, T_{max} = 27 min. These data are from subject 2 in this study.



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364 **Figure 2.** Median time to reorientation values in person, place and time after
365 electroconvulsive therapy (ECT)-induced seizures. Patients firstly recovered in person
366 (median = 24.0 min, IQR = 5.2) compared to the domains place (median = 28.6 min,
367 IQR = 15.0 min, $p < .001$) and time (median = 33.0 min, IQR = 18.7, $p < .001$).
368 Reorientation in place was faster than reorientation in time ($p = .012$).

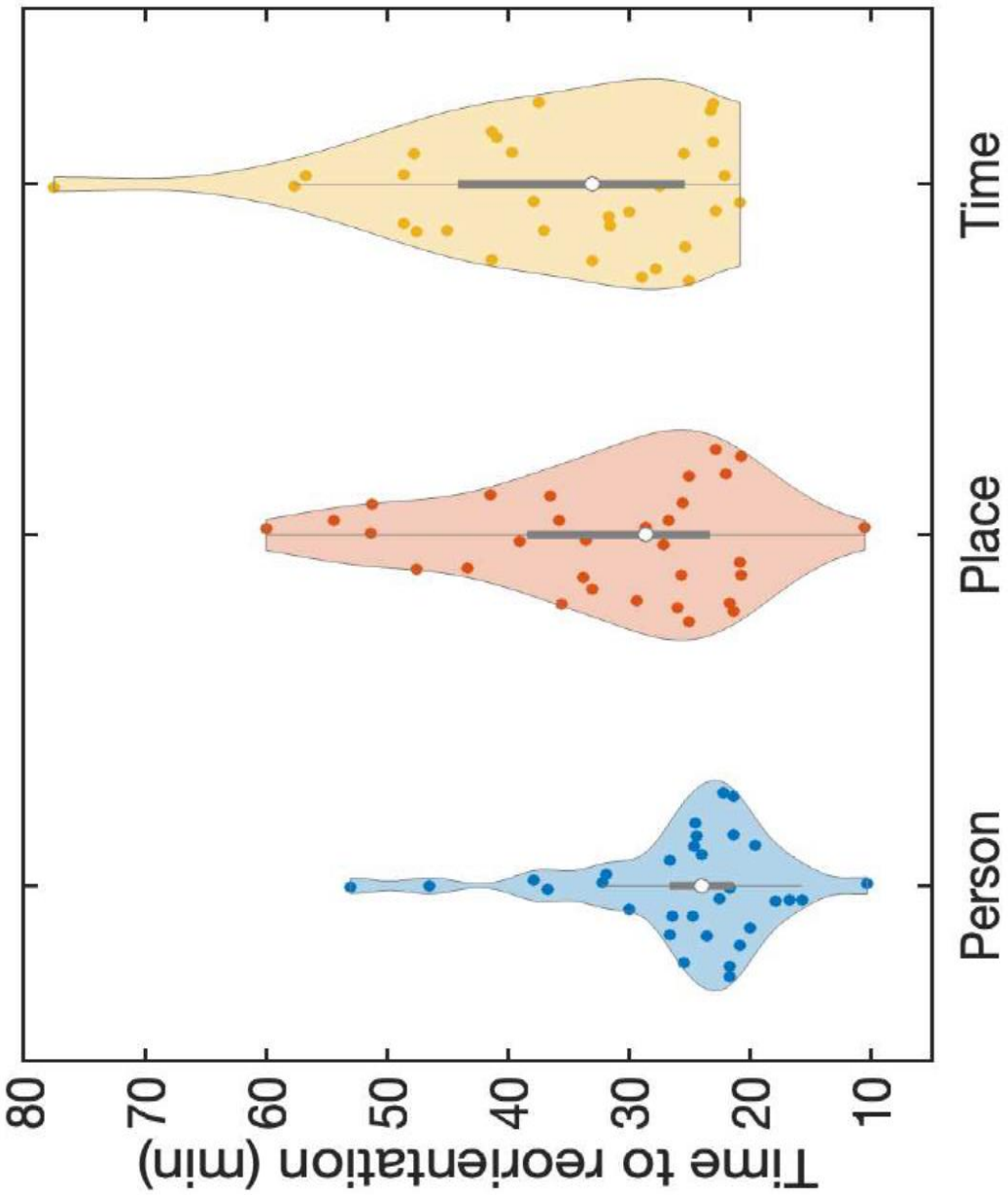

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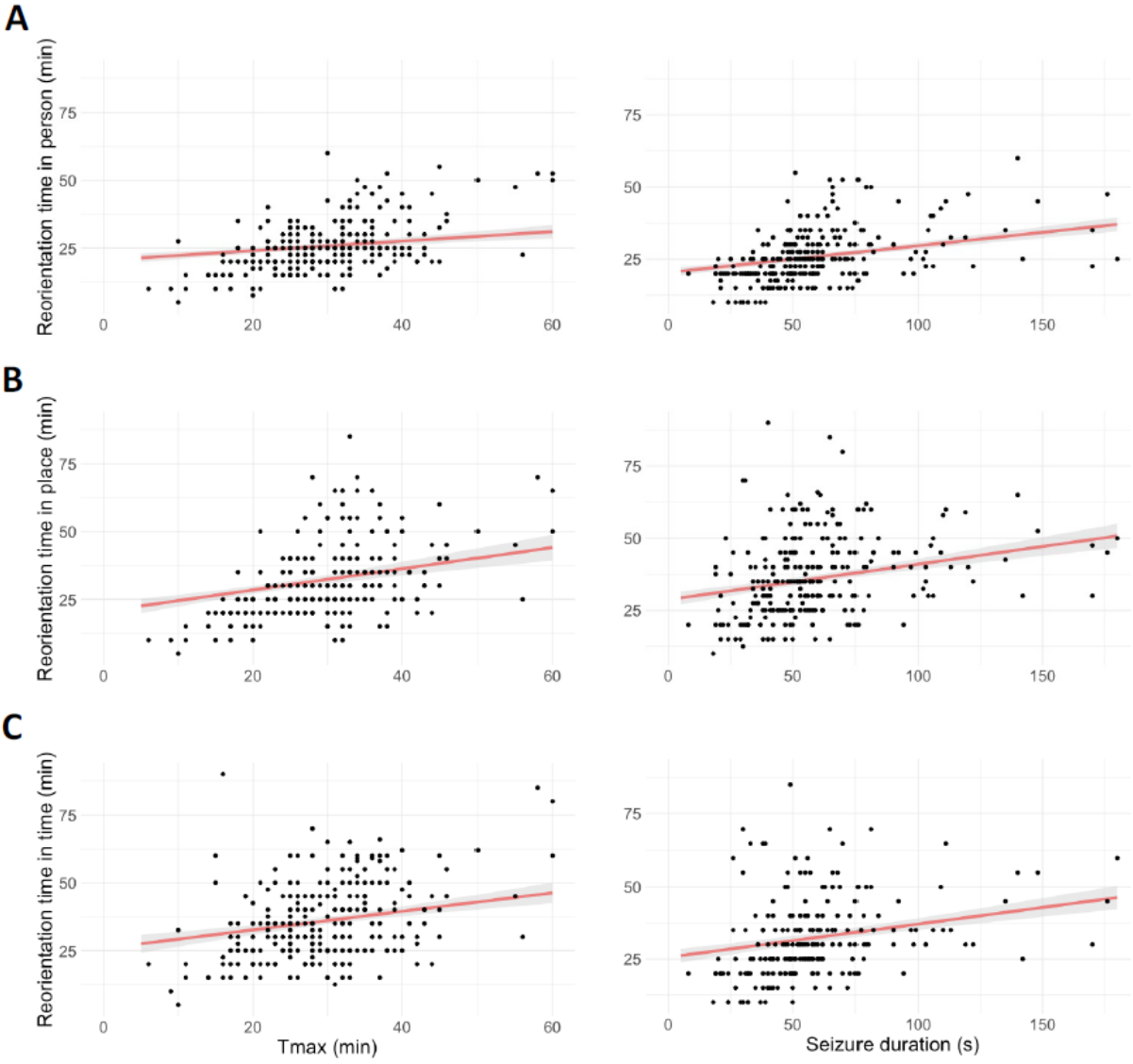
Figure 3. Positive correlations between T_{max} (i.e., the timepoint where the recovery of the electroencephalogram [EEG] was maximized) and seizure duration and time to reorientation in three cognitive domains (i.e., person [A], place [B] and time [C]). Marginal effects (red lines) and 95% CI (shaded errors) are estimated from the models.



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Author contributions

Conceptualization: SS, MvP, JH, JvW; Formal analysis: SS; Investigation: SS, JP, JV; Writing-original draft: SS, JvW; Review and editing: SS, JP, JV, FtD, MvP, JH, JvW; Supervision: MvP, JH, JvW.

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Ethical standards

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The authors declare that the study was approved by the local medical ethical committee (registered as NCT04028596) and all persons who participated in this study gave their oral and written informed consent prior to the study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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