

Seizures induced in electroconvulsive therapy as a human epilepsy model: A comparative case study

Julia C. M. Pottkämper^{1,2,3}  | Joey P. A. J. Verdijk^{1,2}  | Jeannette Hofmeijer^{1,3}  |
Jeroen A. van Waarde²  | Michel J. A. M. van Putten¹ 

¹Clinical Neurophysiology, Technical Medical Centre, Faculty of Science and Technology, University of Twente, Enschede, The Netherlands

²Department of Psychiatry, Rijnstate Hospital, Arnhem, The Netherlands

³Department of Neurology, Rijnstate Hospital, Arnhem, The Netherlands

Correspondence

Julia C. M. Pottkämper, Technical Medical Centre, Hallenweg 15, 7522 NB, Enschede, The Netherlands.

Email: j.c.m.pottkaemper@utwente.nl

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Abstract

Objective: Standardized investigation of epileptic seizures and the postictal state may contribute to a better understanding of ictal and postictal phenomena. This comparative case study aims to assess whether electrically induced seizures in electroconvulsive therapy (ECT) show sufficient similarities with spontaneous seizures to serve as a human epilepsy model.

Methods: We compared six EEG recordings, three ECT-induced seizures and three generalized tonic-clonic seizures, using quantitative electroencephalography (EEG) analyses. EEG recordings during and after ECT sessions (under general anesthesia and muscle paralysis) were collected prospectively, whereas epilepsy data were selected retrospectively. Time-frequency representations, dominant ictal frequencies, and postictal alpha-delta ratios were calculated.

Results: In all EEG recordings, a decrease in dominant ictal frequency was observed, as well as postictal suppression. Postictal alpha-delta ratio indicated the same trend for all: a gradual increase from predominantly delta to alpha frequencies on timescales of hours after the seizure. Postictal spectral representation was similar. Muscle artifacts were absent in ECT-induced seizures and present in spontaneous seizures. Ictal amplitude was higher in epileptic than in ECT-induced seizures. Temporospectral ictal dynamics varied slightly between groups.

Significance: We show that ictal and postictal characteristics in ECT and patients with generalized tonic-clonic seizures are essentially similar. ECT-induced seizures may be used to investigate aspects of ictal and postictal states in a highly predictable manner and well-controlled environment. This suggests that clinical and electrophysiological observations during ECT may be extrapolated to epilepsy with generalized tonic-clonic seizures.

KEYWORDS

alpha-delta ratio, electroencephalography, ictal, postictal, time-frequency analyses

1 | INTRODUCTION

Standardized investigation of epileptic seizures and the postictal state may contribute to a better understanding of ictal and postictal phenomena and may help identifying new treatment targets for people with epilepsy. However, given the erratic nature of seizures, this research is often difficult in patients with epilepsy.

Animal models may solve this problem only to a certain extent. Rodent models of focal and generalized seizures have allowed identification of seizure thresholds and drug development.¹⁻⁴ Zebrafish and *Drosophila* models have proven useful for low-cost drug testing in genetic epilepsies.¹ Advantages of animal models include the possibility of invasive measurement techniques (eg, hippocampal electrodes measuring pO₂ levels during and after seizures), which are obviously limited in humans. In addition, chronically epileptic animal models (kainite or pilocarpine models) do have some degree of translational relevance, with the disadvantages that seizures are unpredictable, requiring constant monitoring and being time-consuming.^{5,6} Another major disadvantage is that animal models cannot fully represent the structure and function of the human brain, hampering translation to patients with epilepsy.^{3,7-10} A human model of epileptic seizures may facilitate standardized investigation of ictal and postictal features and enhance translation from models to patients.¹¹⁻¹³

Electroconvulsive therapy (ECT) is applied in the context of patient care and is an effective and safe treatment option for severe depressive episodes, as well as for treatment-resistant manic, psychotic, and catatonic episodes.^{14,15} In extraordinary cases, ECT may be used to terminate intractable epileptic seizures.¹⁶ Using short electrical stimuli applied between two electrodes at the patients' head, under anesthesia with proper muscle relaxation, seizure activity is elicited for 30-60 seconds.¹⁷ ECT-induced seizures are highly predictable, reproducible, and take place in a well-controlled environment. This allows standardized investigation of clinical, electrophysiological, and neuroimaging phenomena. ECT-induced generalized epileptic seizures may—therefore—present a unique opportunity to serve as a human seizure model to overcome the limitations of unpredictability of seizures and animal models. However, it is not well established whether seizure activity elicited by ECT compares to seizures in epilepsy.

Clinical manifestations, electroencephalographic, and neuroimaging findings of ictal and postictal states show similarities between epileptic and ECT-induced seizures.¹⁸ In patients, an ECT stimulus elicits seizure activity showing tonic-clonic characteristics of a generalized seizure, presenting with whole body stiffening, followed by generalized jerking muscle contractions, and showing postictal sleep and confusion afterward.¹⁹⁻²¹ With the current use

Key Points

- Investigating ictal and postictal states in epilepsy patients is challenging as seizures are typically unpredictable
- EEG and clinical features of ictal and postictal states of ECT-induced seizures show strong similarities with those in epilepsy patients
- ECT-induced seizures allow systematic analysis of ictal and postictal characteristics in a well-controlled environment that can be extrapolated to epileptic seizures
- ECT-induced seizures present a human model system to study effects of treatments to ameliorate postictal symptoms

of general anesthesia and muscle relaxants, instant loss of consciousness will not be observed and the convulsive movements become manifest only in an isolated limb using a cuff, inflated above the systolic blood pressure just before administering the muscle relaxant.²² Postictal confusion, unresponsiveness, headaches, muscle pain, and cognitive impairments are frequently reported after generalized seizures in epilepsy and after ECT-induced seizures.^{14,23-29} Duration of the postictal state varies widely in patients with epilepsy as well as in ECT patients, often comprising more than an hour after generalized seizures.^{20,27,30} Both in generalized spontaneous seizures and ECT-induced seizures, stereotypical electroencephalographic (EEG) characteristics include ictal large amplitude rhythmic and hypersynchronous activity along with postictal suppression.³¹⁻³⁵ Ictal hyperperfusion of the brain and postictal hypoperfusion have been established in both epilepsy and ECT patients.^{7,15,36,37} Investigating tonic-clonic seizures is of increased value because clinical manifestation (ie, tonic and clonic phase), electroencephalographic characteristics (ie, generalized EEG spike-wave complexes and postictal suppression), and neuroimaging findings (ie, ictal hyperperfusion and postictal hypoperfusion) are similar compared to ECT-induced seizures. The neurobiological mechanisms involved in seizure termination and the postictal state may be similar as well, which may present new candidate treatments suitable for both populations.

In the present study, we study the electroencephalographic characteristics of epileptic and ECT-induced seizures. We hypothesize that ictal and postictal electroencephalographic characteristics show similarities and argue that ECT-induced seizures present a unique opportunity to systematically study ictal and postictal characteristics in humans, including treatments to ameliorate postictal symptoms in randomized controlled trial designs.

2 | METHODS

2.1 | Study design

In this comparative case study, we included three patients with severe depressive disorder treated with ECT and three epilepsy patients having generalized tonic-clonic seizures (GTCS). We compared EEG characteristics of ictal and postictal states using qualitative and quantitative EEG analyses. EEG recordings during ECT sessions were collected prospectively in Rijnstate Hospital, Department of Psychiatry, Arnhem, The Netherlands, as part of a pilot experiment that was approved by the Dutch Central Ethical Committee (NCT04028596). Epilepsy data were selected retrospectively from the hospital database of Medisch Spectrum Twente, Department of Clinical Neurophysiology, Enschede, The Netherlands, and Epilepsy center Kempenhaeghe, Heeze, The Netherlands.

2.2 | Patients

Inclusion criteria of ECT patients were a regular indication for ECT (ie, treatment-resistant depressive episode), having no contraindications for EEG (ie, sensitive scalp), and the ability to give informed consent. Criteria for including epilepsy patient data were seizure type (ie, GTCS) and the availability of ictal and postictal EEG recordings as long as possible. Oral and written informed consent was obtained from all ECT patients prior to participation.

2.3 | ECT procedure

Electroconvulsive therapy was administered by using right unilateral (RUL) according to d'Elia or bifrontotemporal (BL) electrode placement and executed according to standard treatment guidelines in The Netherlands.^{38,39} ECT stimuli were characterized as constant-current (0.9 Ampère), bidirectional, square wave, brief pulse (1 ms) and were delivered by the Thymatron System IV device (Somatics Incorporation Lake Bluff, Illinois, USA). Delivered charges (and electrode placements) were 252 mC (BL), 302.4 mC, and 327.6 mC (RUL), for patients ECT1, ECT2, and ECT 3, respectively.

Patients were oxygenated at 100% O₂ starting before administration of anesthetic (etomidate 0.2-0.3 mg/kg), and ventilation was continued with positive pressure during anesthesia until resumption of spontaneous respiration. Succinylcholine (0.5-1 mg/kg) was used as muscle relaxant. EEG and motor seizure duration were determined based on visual inspection, respectively. End of the motor seizure duration was defined as the last clonic jerk. Electromyography (EMG), heart rhythm,

blood pressure, and oxygen saturation were monitored throughout the procedure and postictally. Antidepressant, antipsychotic, analgesic, and other medication pre- and post-ECT was in the context of current care and left to the discretion of the treating psychiatrist.

2.4 | EEG recordings

In ECT patients, continuous EEG was recorded before and during the ECT session, continued up to approximately 1 hour after the treatment. EEG electrodes were attached at the clinical neurophysiology department. A total of six seizures were evaluated, with one seizure of each patient. For patient ECT1, the seizure was acquired during the maintenance treatment with ECT sessions, while for ECT-naïve patient ECT2 and ECT3, the seizure was recorded during their initial index ECT course. Patients received ECT in the operating room, recovered at the recovery ward and afterward at the psychiatric department. A detailed overview of EEG acquisition methodology is presented in Table 1.

A systematic search was performed in the MST and Kempenhaeghe databases from January 2008 to March 2021. Neurophysiological EEG reports and conclusions were searched with terms including 'generalized', 'tonic-clonic', 'ictal', or 'postictal'. Following this, EEG recordings associated with identified reports were selected based on visual identification of baseline, ictal, and postictal states.

In ECT patients, EEGs were recorded using a NeuroCenter EEG recording system (Clinical Science Systems) and a full-band DC-coupled amplifier (TMSi). Twenty-two silver/silver chloride cup electrodes were applied according to the international 10-20 system and fixated using collodion. For ECT patients treated with BL electrode placement, F7 and F8 were placed 0.5 cm above the defined position due to ECT electrodes. In case of RUL electrode placement, only Cz was placed 0.5 cm to the left. Impedances were kept below 5 kΩ. Recordings were sampled at 256 Hz.

In epilepsy patients, electrodes were in concordance with the international 10-20 system, with either individual silver/silver chloride cup electrodes or a titanium nitride electrode cap (ElectroCap International, Inc). A Schwarzer Ahns amplifier (Natus) or 32-channel acquisition amplifier (Brain quick SD, Micromed) was used. All EEGs were acquired with BrainRT software (OSC) and sampled at 250 Hz.

In all patients, baseline resting-state EEG consisted of 1 minute eyes-closed segments. The third epilepsy patient was asleep before and during the recording, of which an artifact-free sixty-second segment was chosen as baseline.

TABLE 1 Patient characteristics

Patient ID	ECT1	ECT2	ECT3	EPL1	EPL2	EPL3
Age	45	40	34	77	14	30
Gender	Female	Male	Male	Female	Female	Male
Condition	MDD	MDD	MDD	Seizures induced by hypocalcemia	Primarily generalized epilepsy	Primarily generalized epilepsy
No. of previous seizures (type of ECT course)	52 (maintenance)	9 (index)	10 (index)	NK	NK	NK
No. of seizures analyzed	1	1	1	1	1	1
ECT electrodes (charge, in milliCoulomb [mC])	BL (252 mC)	RUL (327.6 mC)	BL (302.4 mC)	NA	NA	NA
Anesthesia	Etomidate (30 mg)	Etomidate (24 mg)	Etomidate (20 mg)	NA	NA	NA
Muscle relaxant	Succinylcholine (100 mg)	Succinylcholine (125 mg)	Succinylcholine (100 mg)	NA	NA	NA
Additional medication during postictal state	Lorazepam and ondansetron (1 and 4 mg, post-ECT)	Ondansetron and propofol (4 and 50 mg, post-ECT)	Midazolam (3 mg, post-ECT)	NA	NA	NA
Postictal clinical symptoms	Severe confusion and restlessness, unapproachable	Headache, slightly confused	Quickly awake, no signs of confusion, sleep	NA	Sleep	Muscle ache, fatigue
EEG acquisition						
Method	Silver/silver chloride cup electrodes with international F8 placed 0.5 cm above the defined position due to ECT electrodes	Silver/silver chloride cup electrodes with international 10-20 placement; BL: F7 and F8 placed 0.5 cm above the defined position due to ECT electrodes	Titanium nitride electro-cap with international 10-20 placement			Silver/silver chloride cup electrodes with international 10-20 placement
Software; amplifier	NeuroCenter EEG ^a ; Full-band DC-coupled amplifier ^b (sampling frequency: 256 Hz; impedances <5 kΩ)			BrainRT ^c ; Schwarzar Ahns amplifier ^d (sampling frequency: 250 Hz; impedances <5 kΩ)		BrainRT ^c ; 32-channel acquisition amplifier ^e (sampling frequency: 250 Hz; impedances <5 kΩ)
Center	Rijnstate Hospital			Medisch Spectrum Twente		Epilepsy center Kempenhaeghe

Abbreviations: BL, bifrontotemporal; ECT, electroconvulsive therapy; ECT, electroconvulsive therapy; EEG, electroencephalography; EPL, epilepsy; MDD, major depressive disorder; NA, not applicable; NK, not known; RUL, unilateral.

^aClinical Science Systems, The Netherlands.

^bTMSi, Oldenzaal, The Netherlands.

^cOSG, Runst, Belgium.

^dNatus, Munich, Germany.

^eBrain quick SD, Micromed, Mogliano Veneto, Italy.

2.5 | Data analysis and presentation

2.5.1 | EEG analysis

Preprocessing

Artifact detection was manually performed offline based on visual inspection in a bipolar montage with NeuroCenter EEG (Clinical Science Systems). Channels with excessive noise, flatlines, or epochs with excessive artifacts (eg, movement) were marked and removed entirely from recordings for further analyses. Data were inverse filtered using a reconstruction filter and bandpass filtered between 1 and 25 Hz (first-order Butterworth filter) and converted to a bipolar montage.

Qualitative analysis

Qualitative analysis was done by visually inspecting EEGs in bipolar montage, without transforming the data. Ictal and postictal EEG characteristics were classified based on American Clinical Neurophysiology Society (ACNS) criteria.⁴⁰ In the literature, ECT-induced seizures have been previously divided into phases: Phase I refers to rhythmic beta activity (14–22 Hz), Phase II includes arrhythmic polyspike activity, and Phase III refers to rhythmic spike or polyspike wave activity (2.5–3.5 Hz).⁴¹ In our qualitative analysis, Phase I up to Phase III were investigated. Ictal amplitude of waves was defined as trend (ie, increase or decrease) including absolute peak-to-through value in a channel or region in which the pattern was most readily appreciated (ie, frontal, central, temporal, parietal; Phase II & III). Ictal frequency of waves was characterized as the typical, minimum, or maximum frequency rate or range in the majority of the epoch (eg, 0.5/s; Phase II & III). Seizure onset was defined as first occurrence of rhythmicity (Phase I). Rhythmicity was defined as waveform repetition with relatively uniform morphology and duration (Phase I & II).⁴⁰ Seizure duration comprised onset of rhythmicity up until postictal generalized suppression (Phase I–III). Spreading pattern referred to the spatial evolution of ictal activity (Phase I & II). Postictal suppression referred to a generalized and isoelectric EEG with amplitudes below 10 μ V.⁴² Recovery was defined as the first occurrence of slow waves (ie, 0.5–4 Hz) in the postictal state.

Quantitative analyses

Quantitative analyses refer to transforming the data using computerized programs (ie, MATLAB, R). Power spectral densities and time-frequency analyses were performed during baseline, ictal, and postictal states. Time-frequency power plots from short-time Fourier transform were created using the function “spectrogram” in MATLAB with a window length of 2 s. To illustrate spectral EEG evolution, one-minute epochs were analyzed and averaged across all channels (ie, baseline, ictal state, postictal 1 minute, and

the last artifact-free postictal epoch). To determine dominant ictal frequencies, spectral analysis was performed with Welch's method using a 5 s window length, which was averaged across all channels. Dominant ictal frequency has been shown to decrease as seizure termination approaches.⁴³ The frequency range in all time-frequency analyses was set to 1–20 Hz and averaged across all artifact-free channels.

Normalized alpha-delta ratio (ADR) was used as a global measure of spectral content to quantify temporal EEG evolution after epileptic and ECT-induced seizures. The ratio was defined as

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

with α , the power in the 8–13 Hz range and δ in the 0.5–4 Hz range. Power spectral densities were calculated using Welch's method with windows of 5 s with an overlap of 50%. The temporal evolution of the ADR was subsequently fitted using the sigmoid

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

with t the time (minutes) and a , b , c , d , and τ . The constants were estimated using a nonlinear least squares fit routine. The time constant τ effectively serves as the characteristic recovery time of the EEG. Goodness of fit of the sigmoid model was indicated by R^2 , where values of 1 indicate a good fit.

All analyses were performed using MATLAB version 9.6.0 (R2019a). The statistical program R was used to visualize the results yielded by quantitative analyses.⁴⁴

2.5.2 | Comparative analysis

No sample size calculation was performed as this was a pilot study. Between-group differences were analyzed in a descriptive way, based on qualitative, visual analyses. Subsequently, quantitative EEG parameters were compared by means of visual pattern identification and synthesis of similarities and differences in a descriptive way. Alpha-delta ratios were compared to postictal clinical manifestation.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are given in Table 1. All ECT patients had major depressive disorder. Two patients received ECT with BL electrode placement, while one was treated with RUL placement. The number of previously administered ECT

sessions (and consequently the number of former seizures) differed across patients (range: 9-52 sessions). Postictal clinical symptoms included confusion, agitation, and headache.

In the period of 2008-2021, three EEGs with adequate ictal and postictal registration were available for our analyses. Epilepsy patients had different medical conditions that led to a generalized tonic-clonic seizure, for which they were monitored in the hospital (ie, hypocalcemia-induced seizures and primarily generalized epilepsy). The included seizures self-terminated spontaneously without additional antiepileptic medication. No detailed information was available on postictal clinical symptoms in epilepsy patients (see Table 1).

3.2 | EEG evolution

Figure 1 shows typical examples of an epileptic seizure (patient EPL2 (1)) and an ECT-induced seizure (patient ECT1 (2)). Generalized seizure activity is clearly noticeable in both patients (B), followed by postictal suppression in all channels (C; amplitudes $<10 \mu\text{V}$) and subsequent postictal slowing (D). Higher frequencies in (D) are due to movement artifacts. Upon visual inspection, the evolving ictal and postictal EEG patterns are largely similar in both patients.

3.3 | Qualitative analysis

All EEGs of ECT patients ($n = 3$) and epilepsy patients ($n = 3$) were qualitatively analyzed with respect to amplitude, frequency, location of ictal onset, (location of) rhythmicity, subsequent spreading pattern, postictal suppression, and recovery. Key characteristics are presented in Table 2.

Similarities between the ECT and epilepsy patients were as follows. Rhythmicity preceded formation of epileptic peaks in both patient populations, except in patient ECT3. Ictal frequency followed a similar pattern with a decrease from 7 to 2 Hz (patient EPL1) and 4 to 2 Hz (patient EPL3) in epileptic seizures and from 12 to 2 Hz (patients ECT2, and ECT3) and 6 to 2 Hz (patient ECT1) in ECT-induced seizures. Due to muscle artifacts in patient EPL1 and EPL3, ictal amplitude and frequency could not be determined reliably. Seizure duration was comparable (ie, 72-78 seconds for ECT-induced seizures, 73-136 seconds for epileptic seizures; min-max). Both groups showed generalized postictal suppression in all channels at seizure termination, which was present for 0.6-6.3 minutes in ECT-induced seizures and 0.6-2.5 minutes in epileptic seizures (min-max). Recovery toward alpha activity was comparable between populations with 40-410 seconds and 57-150 seconds (ECT-induced seizures and epileptic seizures, respectively; min-max). Recovery was characterized by a pattern of initial diffuse slow-wave activity in the early postictal state (ie, postictal 10-20 minutes) toward normal activity in the late postictal state (postictal 60 minutes).

Differences included the following. Ictal amplitude was higher in epileptic seizures compared to ECT-induced seizures (min-max: 400-1000 μV ; min-max: 70-400 μV , respectively). Hemispheric involvement at seizure onset differed slightly within and between populations. In BL stimulation, immediate bilateral spreading (patient ECT1) or a minimal time delay was observed (patient ECT3). With RUL stimulation (patient ECT2), right regions were involved first. In epileptic seizures, seizure onset occurred in several regions first (patient EPL1: bilateral frontal; patient EPL2: right central and posterior), followed by involvement of other regions (patient EPL1: posterior; patient EPL2: left frontal).

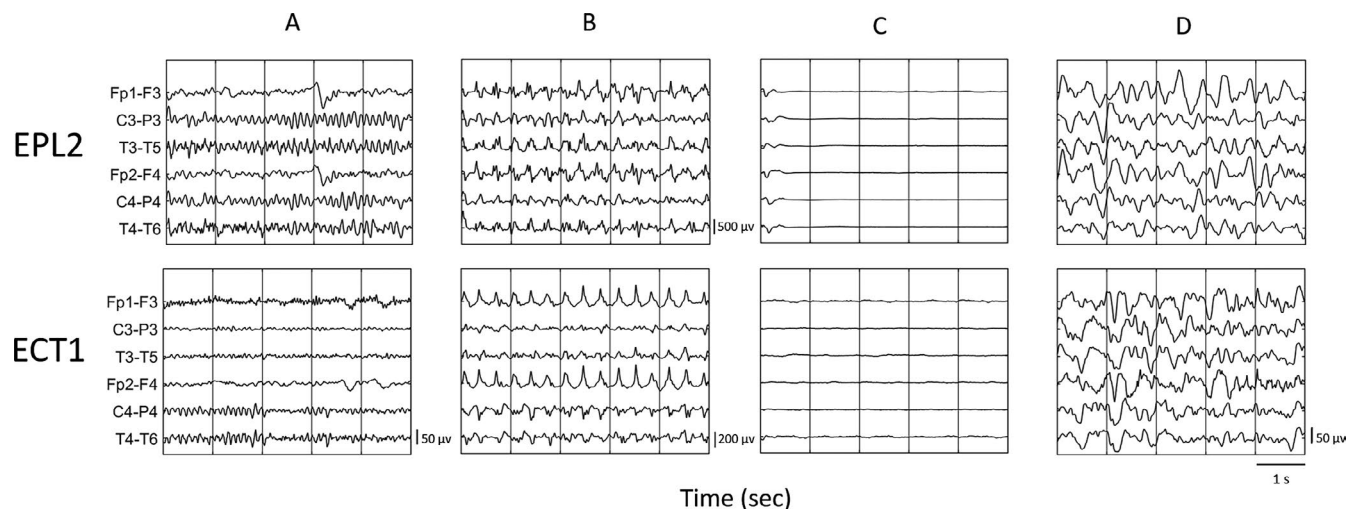


FIGURE 1 EEG epochs from patient EPL2 with spontaneous seizures (top row) and ECT-induced seizure of patient ECT1 (bottom row). A, Baseline (eyes closed). B, Seizure activity is followed by postictal suppression (1C $t = 32$ s postictal, 2C $t = 3$ s postictal) and postictal slowing (1D, 2D $t = 25$ min postictal). Filter settings 1-25 Hz. Epoch length 5 s. Vertical scale bar: 50 μV for A, C, and D; 200 μV for B; 500 μV for 1B

TABLE 2 Qualitative ictal and postictal characteristics

Patient	Duration stimulus (electrode placement ^a)	Δ Stimulus – start seizure	Seizure duration Phase I – III ^b	Hemispheric involvement Phase I & II	Rhythmicity and morphology, Phase I & II	Ictal amplitude, Phase II & III	Ictal frequency, Phase II & III	Postictal suppression	Postictal recovery
ECT- induced seizures	ECT1 3.7 s (BL)	1.5 s	74 s	Both hemispheres involved simultaneously	Bilateral rhythmic peak synchronization preceded spike waves; peak wave complexes 20 s after start seizure	Increasing amplitude (bilateral frontal and central regions: 150–400 μ V; left occipital and parietal regions: 70–250 μ V; right occipital: 70–120 μ V; temporal: 80–210 μ V)	Frequency increased to 6 Hz, then declined to 2 Hz	Present immediately after seizure in all channels (2.3 min)	Recovery of delta activity at 140 s
	ECT2 3.6 s (RUL)	10 s	78 s	Start seizure in the right hemisphere; after 19 s involvement left hemisphere	Frontal rhythmicity preceding spike waves; less overall involvement of left hemisphere; peak wave complexes 20 s after start seizure	Increasing right amplitude (frontal and central: 80–400 μ V; right occipital and parietal: 80–170 μ V) followed by increasing left amplitude (frontal and central: 160–320 μ V; occipital and parietal: 80–170 μ V); bilateral temporal increase (100–290 μ V)	Frequency increased to 12 Hz, then declined to 2 Hz	Exchange of ictal discharges and postictal suppression; suppression in all channels (6.3 min)	Recovery of delta activity at 410 s
	ECT3 3.1 s (BL)	5 s	72 s	Start seizure in the left hemisphere; after 1 s involvement right hemisphere	Frontal bilateral synchronous sharp epileptic peaks; rhythmicity in central and posterior regions without epileptic peaks; peak wave complexes 45 s after start seizure	Increasing frontal amplitude (125–200 μ V) declined to 80 μ V 12 s after start seizure; increased bilateral occipital amplitude (100–230 μ V); bilateral temporal increase (80–190 μ V)	Frequency increased to 12 Hz, then declined to 2 Hz	Present immediately after seizure in all channels (0.6 min)	Recovery of delta activity at 40 s

(Continues)

TABLE 2 (Continued)

Patient	Duration stimulus (electrode placement ^a)	Δ Stimulus – start seizure	Seizure duration Phase I – III ^b	Hemispheric involvement seizure onset, Phase I & II	Rhythmicity and morphology, Phase I & II	Ictal amplitude, Phase II & III	Ictal frequency, Phase II & III	Postictal suppression	Postictal recovery
EPL1	NA	NA	52 s	Start seizure in the frontal regions; after 12 s involvement posterior regions	Frontal rhythmicity preceded spike waves; peak wave complexes 20 s after start seizure	Could not be determined reliably due to muscle artifacts	Could not be determined reliably due to muscle artifacts	Exchange of ictal discharges and postictal suppression; suppression in all channels (2.5 min)	Recovery of delta activity at 150 s
EPL2	NA	NA	72 s	Start seizure in the right central and posterior regions, after 2 s involvement right frontal regions followed by left regions	Central and posterior rhythmicity preceded spike waves; peak wave complexes 20 s after start seizure	Increasing right frontal (400-900 μV) followed by left frontal (400-780) amplitude; increasing left (440-1130 μV) and right (490-1000 μV) occipital amplitude; bilateral temporal increase (500-900 μV)	Frequency increased to 7 Hz, then declined to 2 Hz	Exchange of ictal discharges and postictal suppression; suppression in all channels (1.2 min)	Recovery of delta activity at 70 s after the end of seizure; delta activity remained until the end of the recording (postictal sleep)
EPL3	NA	NA	90 s	Could not be determined reliably due to muscle artifacts	Could not be determined reliably due to muscle artifacts	Could not be determined reliably due to muscle artifacts	Frequency increased to 4 Hz, then declined to 2 Hz	Exchange of ictal discharges and postictal suppression; suppression in all channels (0.9 min)	Recovery of delta activity at 57 s after the end of seizure; delta activity remained until the end of the recording (postictal sleep)

^aElectrode placement is bifrontotemporal (BL) or right unilateral (RUL).

^bPhase I, II, and III refer to a classification scheme provided by Brumback et al.⁴¹

3.4 | Quantitative EEG analyses

Quantitative ictal and postictal EEG characteristics are summarized in Figure 2.

3.4.1 | Temporal frequency representation

Figure 3 shows a typical example of a time-frequency representation of an epileptic seizure (patient EPL2) and an ECT-induced seizure (patient ECT1) in different states (ie, baseline, ictal, immediate postictal, and late postictal). Time-frequency representations of the other four patients are presented in the Supporting Information (Figure S1).

Baseline peak alpha activity was essentially similar in all patients (min-max 7-10 Hz for ECT-induced seizures, 8-12 Hz for epileptic seizures). ECT-induced seizure activity was preceded by the ECT stimulus artifact. A similar

pattern in decreasing dominant ictal frequency was present in both groups. Ictal frequency decreased to 2 Hz in ECT-induced seizures and epileptic seizures. Postictal suppression containing movement artifacts followed seizure termination in all patients. EEG activity recovered to 4-12 Hz in patient EPL1 at $t = 18$ minutes and 2-15 Hz in patient ECT2 at $t = 60$ minutes.

3.4.2 | Alpha-delta ratio

Postictal evolution of alpha-delta ratio showed a similar trend in ECT-induced and epileptic seizures (Figure 4). In both groups, a steady increase from predominant delta toward alpha frequency occurred. Speed of postictal EEG recovery was faster in epilepsy patients than ECT patients (τ min-max: 1.93-10.55 minutes in epilepsy patients, 8.32-13.43 minutes in ECT patients). In ECT-induced seizures, predominant

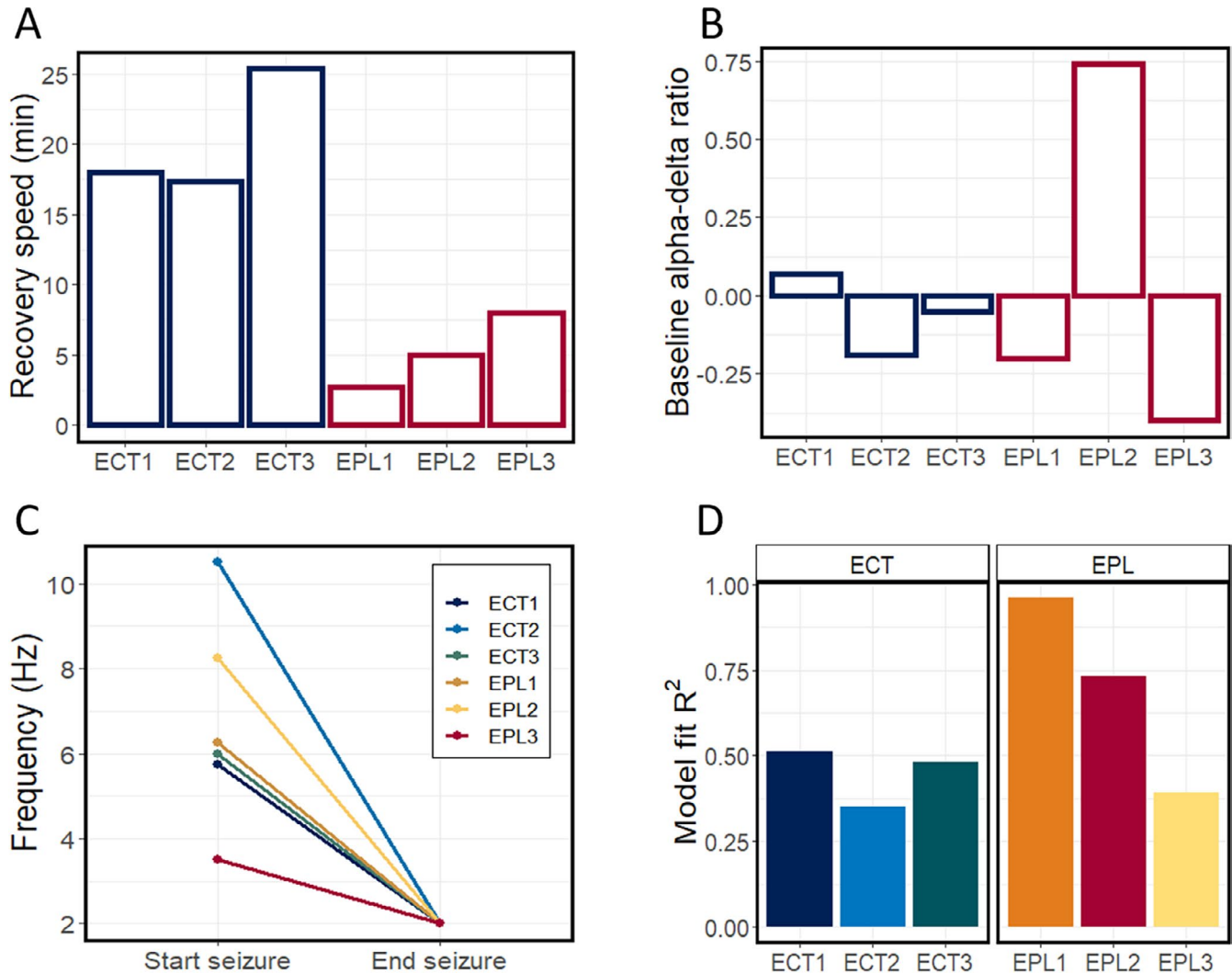


FIGURE 2 Postictal time constants, baseline alpha-delta ratio, dominant ictal frequency, and model fit. A, Postictal recovery speed in minutes (τ) for each patient. B, Baseline alpha-delta ratios. C, Dominant ictal frequency at the start and end of the seizure. Each line corresponds to one patient. D, R^2 values representing the fit of the sigmoid model to the data, grouped by ECT patients (ECT) and epilepsy patients (EPL)

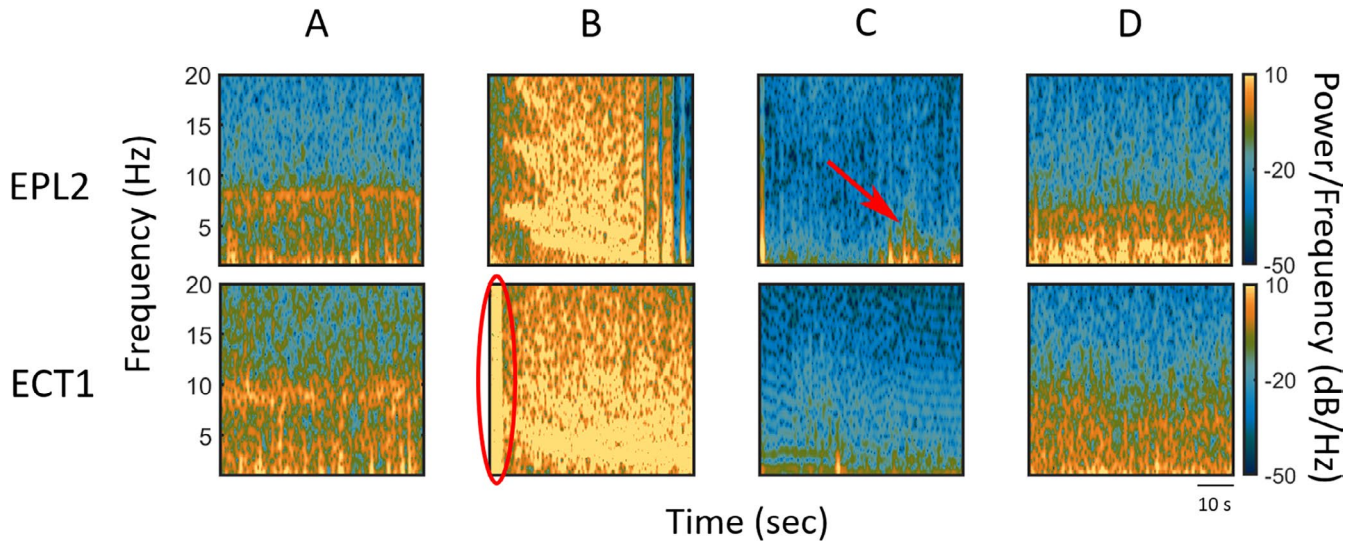


FIGURE 3 Spectrograms of an epileptic generalized seizure (patient EPL2) and an ECT-induced seizure (patient ECT1). A, Baseline, showing dominant frequencies in the alpha band. B, Seizure activity with a decline of dominant frequency in the theta band is preceded in ECT patient by the ECT stimulus artifact (red circle). C, Postictal suppression follows. D, Return of EEG activity with frequencies 1-12 Hz at $t = 18$ min (EPL2) and 1-15 Hz at $t = 18$ min (ECT1). The red arrow indicates movement artifacts in the immediate postictal state

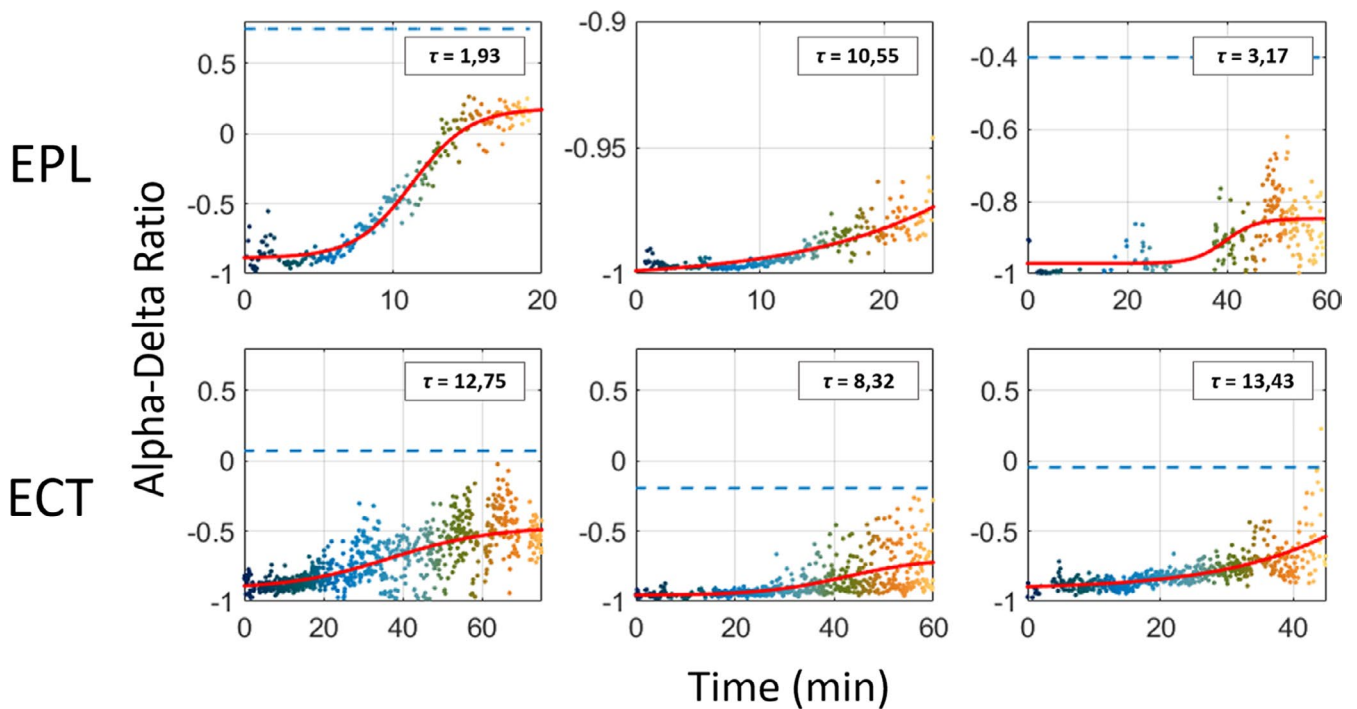


FIGURE 4 Postictal alpha-delta ratio. The top row shows patients ECT1, ECT2, and ECT3. The bottom row shows patients EPL1, EPL2, and EPL3. A negative value indicates relatively more delta than alpha activity. The red line indicates the curve fit with a sigmoid function. The blue line indicates baseline alpha-delta ratio values (assessed before the seizure). τ indicates speed of EEG recovery in minutes. Note that the y-axis for patient EPL2 was modified to illustrate the trend of increasing alpha-delta ratios (baseline value ($= -0.2$) outreached figure borders). Dot color was chosen for visual presentation only

delta activity was present at the end of recordings, while ratios partially recovered toward baseline at $t = 75$ minutes, $t = 60$ minutes, and $t = 40$ minutes (patients ECT1, ECT2, and ECT3, respectively). In epileptic seizures, recovery to

baseline was not observed ($t = 18$ minutes, $t = 28$ minutes, for patients EPL1, EPL 2, respectively).

Severity of clinical postictal symptoms seems to relate to longer postictal recovery, as quantified with the time constant τ .

Patient ECT1 was severely confused, restless, and unapproachable, with a postictal EEG recovery time constant $\tau = 12.75$ minutes. Patient ECT2 reported a headache and was slightly confused, corresponding with $\tau = 8.32$ minutes. Patient ECT3 had the longest speed of EEG recovery ($\tau = 13.43$ minutes), but was quickly awake, showed no signs of confusion, and had an increased need for sleep. In epilepsy patient EPL2, postictal sleep was reported, corresponding with $\tau = 10.55$ minutes. Patient EPL3 had muscle ache and fatigue, with $\tau = 3.17$ minutes. Postictal symptom reports were not available for patient EPL1.

4 | DISCUSSION

In this comparative case study, we show that ictal and postictal EEG characteristics of spontaneous generalized epileptic seizures and ECT-induced seizures are essentially similar. Both visual examination and quantitative analyses of the EEG show striking similarities. Dominant ictal frequency follows the same decreasing trend while approaching seizure termination in both groups, which is in line with previous research.^{43,45} In both groups, postictal suppression is followed by a gradual postictal recovery. Clinical manifestation of the ictal state, with tonic-clonic jerks, as well as postictal symptoms showing unconsciousness, confusion, memory deficits, and headaches, shows similarities as well.¹⁹⁻²¹ Therefore, systematically attained ictal and postictal characteristics from ECT-induced generalized seizures may be translated to spontaneous seizures in epilepsy.

In epileptic as well as ECT-induced seizures, seizure onset zones differed. These deviations in ECT-induced seizures are partially explained by differences in stimulation technique (RUL vs BL electrode placement) and anatomical differences between patients.⁴⁶ Another explanation for the differences in seizure onset zones is that certain brain regions do not seem to be involved in seizures of epilepsy and ECT patients. This questions the use of the term “generalization” as parts of the brain may be spared.^{15,47} ECT-induced and epileptic seizures both seem to involve focal brain regions reflecting seizure onset and propagation in selective networks during generalized tonic-clonic seizures.^{15,48}

Postictal recovery is characterized by postictal EEG suppression followed by slow-wave activity. Subsequent normalization of EEG rhythms was indicated by a change in temporospectral features and evolution in alpha-delta ratio in ECT patients and in epilepsy patients. The speed of EEG recovery, indicated by τ , was faster after epileptic seizures than after ECT-induced seizures. Still, alpha-delta ratio did not recover to baseline in our epilepsy patients, while the ECT patients reached baseline to some extent at the end of recordings. This discrepancy may be related to the short length of EEG recordings in the epilepsy group, underestimating their recovery. Comparison of late postictal states was not

possible due to insufficient duration of postictal recordings from epileptic patients, emphasizing practical challenges of EEG research in epilepsy patients. If features of the postictal EEG correlate with the duration or clinical symptoms of the postictal state, this would be helpful to develop biomarkers to assess candidate treatments of the postictal state.

Another explanation for the apparent slow recovery following ECT-induced seizures may be related to anesthetic effects, which were absent in tonic-clonic seizures. EEG alpha and delta activity are both influenced by anesthetic drugs^{49,50} and may degrade at different speed in patients, thereby affecting and possibly prolonging postictal recovery after ECT-induced seizures.

Interictal slowing has been described in recurrent seizures, both in ECT and in epilepsy patients. In dated ECT literature, increasingly slow activity (ie, <8.5 Hz) in interictal EEGs has been described during the ECT course. This slowing was distributed diffusely, but predominantly frontal, and built up during the ECT course. After the last ECT session, the slowing gradually diminished, mostly disappearing within one month.^{45,51} Both severity and persistence of EEG-slowing were proportional to the number of administered ECT sessions.⁵¹ This interictal EEG-slowing has also been described in patients with recurrent spontaneous seizures.⁵²

Our study has certain limitations. First, findings may be limited by not matching epilepsy and ECT patients based on sex or age. However, effects of sex and age on seizure expression or EEG features are probably limited.^{48,53} Second, even though artifact rejection was performed, movement may still exert influence on our quantitative analyses. Third, additional medication, such as benzodiazepines, antiepileptics, and antidepressants, differed between the epilepsy and ECT patients, which may have influenced EEG characteristics and interpretation of our results.^{54,55} Fourth, the small number of seizures we included in this study is a major limitation, which may not represent both populations accurately. Fifth, anesthetic recovery may influence EEG characteristics, which needs to be acknowledged when examining postictal symptoms. When testing treatments to alleviate postictal symptoms with this ECT model, drug interactions (ie, anesthesia and concomitant psychopharmacological drugs) need to be considered. For example, previous research has shown that ketamine prolongs postictal generalized EEG suppression.³² Treatment of transient postictal symptoms in the early postictal state as prolonged unconsciousness and minor disorientation may not be interpreted reliably due to remaining anesthetic effects. The fact that we could find only three patients (representing 0.4% of suspected patients admitted in a period of thirteen years) with reasonably adequate ictal and postictal EEG registrations in epileptic generalized tonic-clonic seizures in our database highlights the limitation of capturing these seizures in daily practice. This finding further substantiates the importance of

a human epilepsy model. Moreover, standard EEG registration in epilepsy patients often does not include the postictal state (substantially) beyond the seizure itself. With human models, standardized investigation of postictal treatment may be feasible as well.

It is obvious that epileptic and ECT-induced seizures do not have the same seizure onset mechanisms. In ECT, an external electric force intentionally elicits seizure activity, primarily starting in the frontal lobes.³⁷ However, our EEG analyses reveal that ECT-induced generalized tonic-clonic seizures show many similarities to such seizures in patients with epilepsy, regardless of the seizure onset zone. This indicates that features that derive from systematic analysis of ECT-induced seizures and postictal states may be translated to seizures in patients with epilepsy.

In conclusion, we present ECT-induced seizures as a human seizure model that is suitable for systematic analysis of ictal and postictal characteristics in patients and for testing of treatments to ameliorate postictal symptoms.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Julia C. M. Pottkämper  <https://orcid.org/0000-0001-8049-9865>

Joey P. A. J. Verdijk  <https://orcid.org/0000-0001-5415-3940>

Jeannette Hofmeijer  <https://orcid.org/0000-0002-7593-5674>

Jeroen A. van Waarde  <https://orcid.org/0000-0001-6792-5727>

Michel J. A. M. van Putten  <https://orcid.org/0000-0001-8319-3626>

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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