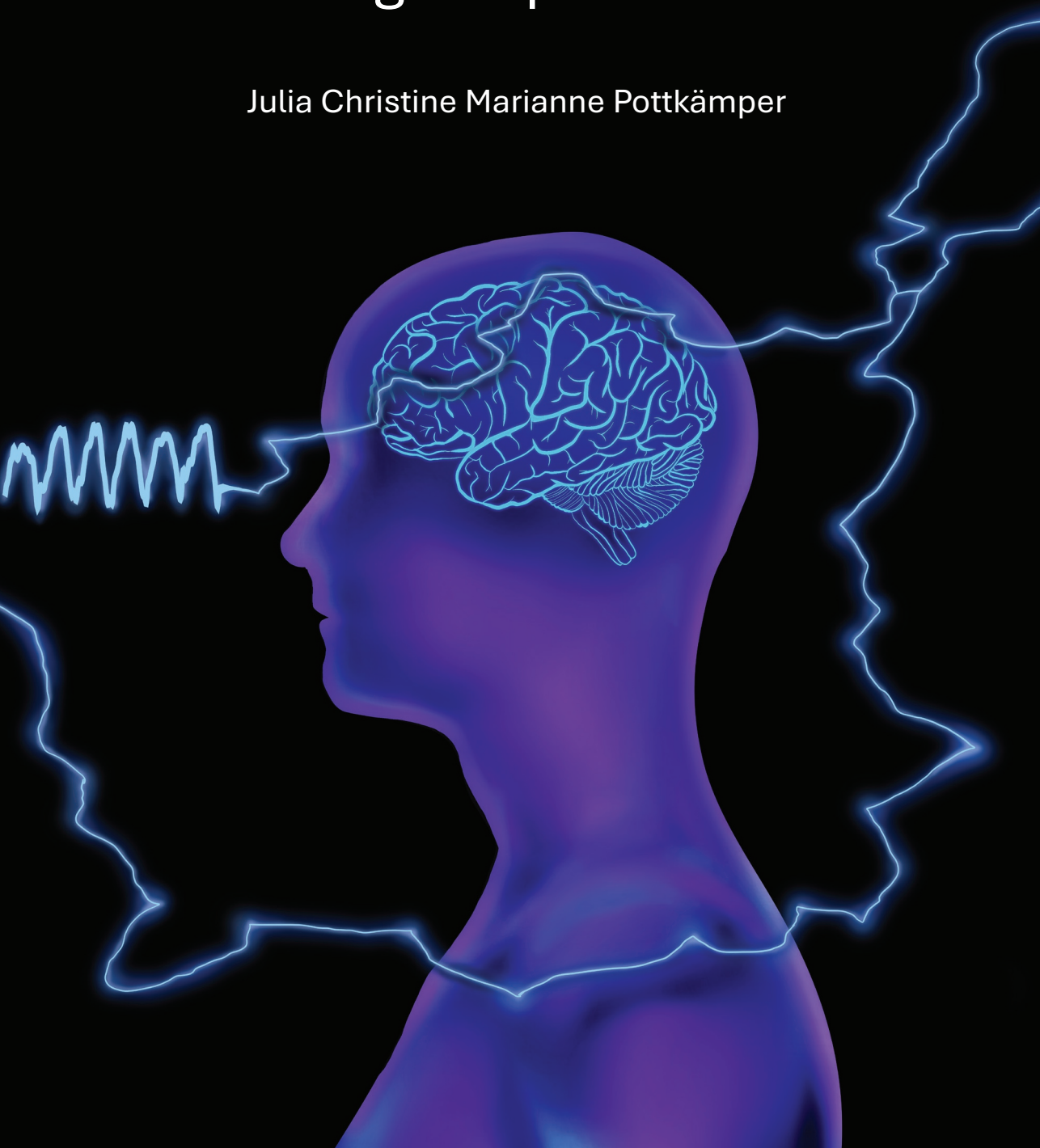
The end is just the beginning: Unraveling the postictal state

Julia Christine Marianne Pottkämper



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PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit
Twente, op gezag van de rector magnificus,
prof.dr.ir. A. Veldkamp,
volgens besluit van het College voor
Promoties
in het openbaar te verdedigen
op vrijdag 16 februari 2024 om 14.45 uur

door

Julia Christine Marianne Pottkämper

geboren op 03 juli 1992 te Remscheid, Duitsland

Dit proefschrift is goedgekeurd door:

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Cover design: J.C.M. Pottkämper
Printed by: Proefschriftmaken | proefschriftmaken.nl
Lay-out: J.C.M. Pottkämper
Graphical abstracts and scientific illustrations: J.C.M. Pottkämper
ISBN (print): 978-90-365-5959-1
ISBN (digital): 978-90-365-5960-7
URL: https://doi.org/10.3990/1.9789036559607

This work has been funded by the Dutch National Epilepsy Fund (EpilepsieNL; grant number WAR 19-02). Financial support by Clinical Science Systems and the Dutch Association of Clinical Neurophysiology for the publication of this thesis is gratefully acknowledged.

PROMOTIECOMMISSIE

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“If I had a chance for another try, I wouldn’t change a thing, this made me all on who I am inside.”

Tom DeLonge

Content

Abbreviations

AUD	Auditory network
ASL	Arterial spin labeling
ATN	Attention network
BL	Bifrontotemporal
Ca^{2+}	Calcium
CEN	Central executive network
CI95	Bayesian credibility interval at 95%
COX-2	Cyclooxygenase-2
DMN	Default mode network
DTI	Diffusion tensor imaging
ECT	Electroconvulsive therapy
EEG	Electroencephalography
GTCS	Generalized tonic-clonic seizures
ICA	Independent component analysis
IQR	Interquartile range
LUL	Left unilateral
MDD	Major depressive disorder
MDE	Major depressive episode
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
PGES	Postictal generalized EEG suppression
PSI	Postictal suppression index
rs-fMRI	Resting-state functional MRI
ROT	Reorientation time
RUL	Right unilateral
SN	Salience network
SPECT	Single-photon emission computed tomography
SUDEP	Sudden unexpected death in epilepsy
SYNAPSE	StudY of effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT
T_1W	T1-weighted
tBSI	Temporal brain symmetry index
UL	Unilateral

Chapter 1

Introduction

"After having completed the electroconvulsive therapy (ECT)-course, I lost most of my memories of the year 2019. I cannot remember much of that time. I cannot remember my way home anymore."

"Immediately after my ECT-session, I feel nauseous. I have headaches that develop hours after my ECT-session. I am very tired."

"My partner told me that every time when I wake up after ECT, I do not know where I am, who I am, or how I got here. I am confused and restless. As I awake, I do not recognize the SYNAPSE researchers, I certainly know from before."

These are paraphrased comments from postictal ECT patients who participated in the SYNAPSE trial, which highlight the variety and severity of postictal impairments. Even though these symptoms may bother or frighten ECT patients, they are generally transient and are often in exchange for relieving their severe depressive symptoms. In epilepsy patients, though, no such ultimate positive antidepressive results of seizures are present.

1.1 Background

Epilepsy is a highly prevalent neurological disease, characterized by an elevated susceptibility to recurrent spontaneous seizures, affecting more than 50 million individuals worldwide (1-3). Around 10% of global population experiences at least one epileptic seizure during their lifetime (3). Seizures are defined as the "transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (2). These seizures may arise spontaneously or be triggered by various factors such as stroboscopic light, electrolyte disturbances (i.e., hypo- and hypercalcemia, hypo- and hypernatremia, and hypomagnesaemia), stress, sleep deprivation, fever and other infectious diseases, over- and dehydration, brain tumors, use or withdrawal of several (pharmacological) drugs and alcohol, and exposure to electricity (4-8).

Seizures manifest in four distinct phases: prodromal (i.e., confusion, irritability, mood disturbances), early ictal ('aura'), ictal (i.e., the seizure), and postictal (i.e., following the seizure; Figure 1.1) (9-11).

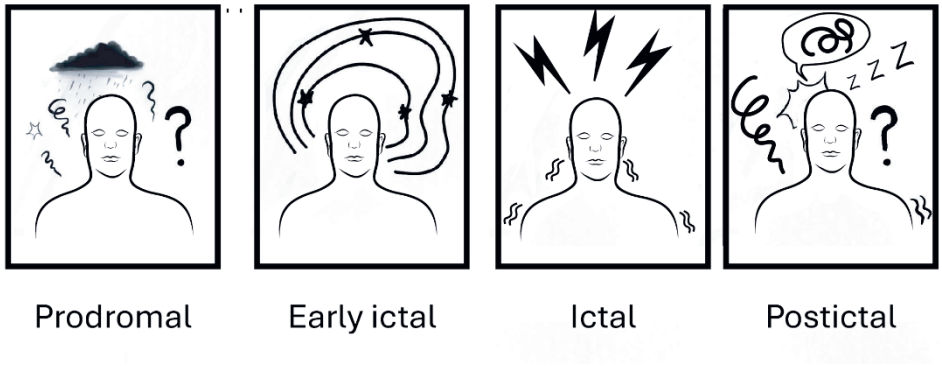


Figure 1.1 Four phases of seizures: The prodromal, early ictal, ictal, and postictal phase.

1.2 The postictal state

Following seizures, patients may experience various postictal manifestations encompassing unresponsiveness, impaired cognition, headache, nausea, myalgia, delirium, psychiatric-, or neurologic symptoms (12-14). The duration and severity of these postictal manifestations exhibit considerable variability, primarily contingent upon the seizure type and duration, with generalized tonic-clonic seizures correlating with more pronounced symptoms (15, 16). The burden of epilepsy for patients and their relatives escalates as postictal symptoms interfere with daily life (17). Notably, approximately one-third of all epilepsy patients may not achieve seizure freedom with presently available therapies (i.e., pharmacological antiepileptic drugs), thereby elevating their susceptibility to postictal complications (1, 18).

1.3 Knowledge gap

The postictal state, identified as a marginalized aspect in seizure management, has received limited attention (14). Over the past five decades, the literature pertaining to the postictal state constitutes approximately 1.2 % (1.904 publications) of the total epilepsy publications (136.528 publications; see Figure 1.2) available on PubMed. A systematic literature review has revealed substantial underreporting of postictal symptoms across numerous studies (unpublished data). The unpredictability of seizures poses a considerable challenge to clinical research, hindering the systematic exploration of the postictal state in clinical trials. The absence of patients at the hospital during seizures further complicates matters, precluding the systematic application of postictal electroencephalography (EEG), magnetic resonance imaging (MRI), or clinical measures.

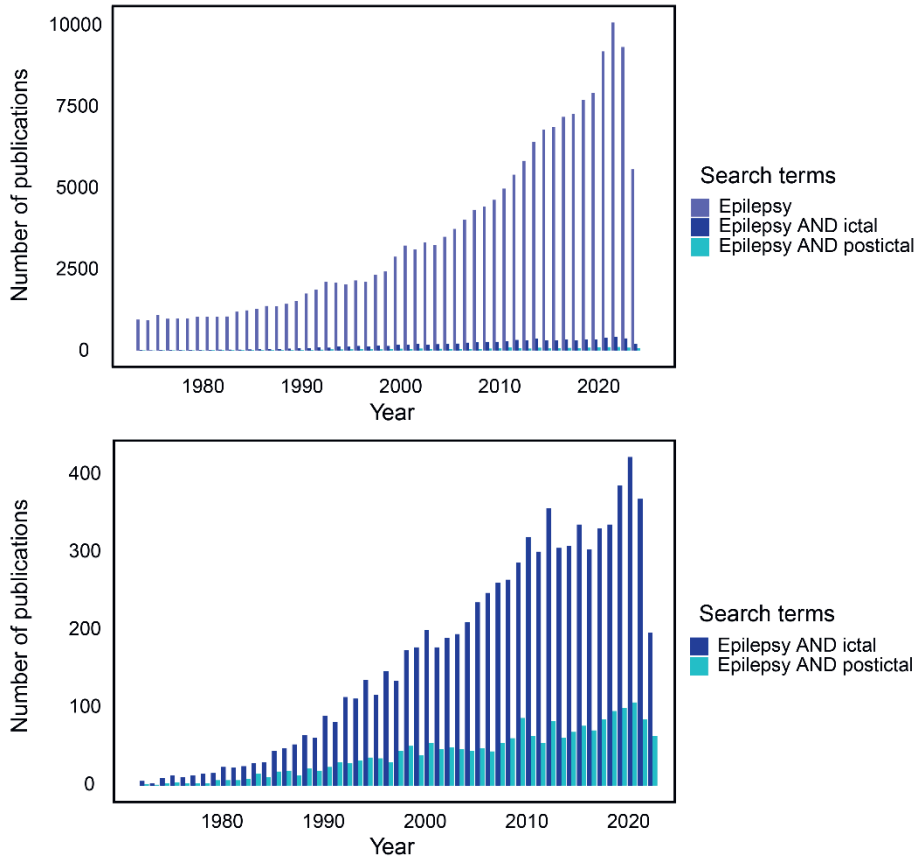


Figure 1.2 PubMed results between 1973 and 2023 for the search terms epilepsy, ictal, and postictal, highlighting the scarcity of postictal research.

1.4 Electroconvulsive therapy

In clinical practice, we know a treatment that uses electricity to elicit seizure activity and that may circumvent this problem: electroconvulsive therapy (ECT). Introduced in the late 1930s, ECT serves as a treatment for severe psychiatric disorders, particularly treatment-resistant major depressive disorder (MDD) (19, 20). Nowadays, this procedure is performed under general anesthesia and involves proper muscle relaxation (21). Electric currents are applied via plate electrodes on the scalp to intentionally elicit a short-lasting generalized tonic-clonic seizure (22). The location of the used plate electrodes may vary, mainly depending on clinical indication (i.e., severity of depression) and burden of possible side effects (Figure 1.3) (21, 23). Right (and occasionally left) unilateral electrode placement according to d'Elia is mostly chosen at the first treatment session to reduce cognitive side

effects (24). If insufficiently effective, switching from unilateral to bifrontotemporal electrode placement after six sessions is advised. In case of life-threatening depressive symptoms (i.e., high risk for suicide, severe dehydration or starvation, or catatonia) or significant somatic comorbidity, starting ECT with bifrontotemporal electrode placement is preferred (21, 24).

After ECT-induced seizures, patients experience similar (mostly transient) postictal symptoms compared to epilepsy patients such as headache, nausea, myalgia, memory disturbances, delirium, and other cognitive impairments (25-31). In approximately 25% of the patients, postictal symptoms after ECT warrants medical intervention (i.e., administration of benzodiazepines or propofol), due to severe motor restlessness or confusion (31). Although ECT is often very effective in treating depressive disorders in 60-80% of patients, the side effects may constitute a limitation on the clinical applicability of ECT and may contribute to the stigma of the treatment (32). However, ECT may give clinicians and researchers the opportunity to study the postictal state systematically in a well-controlled environment.

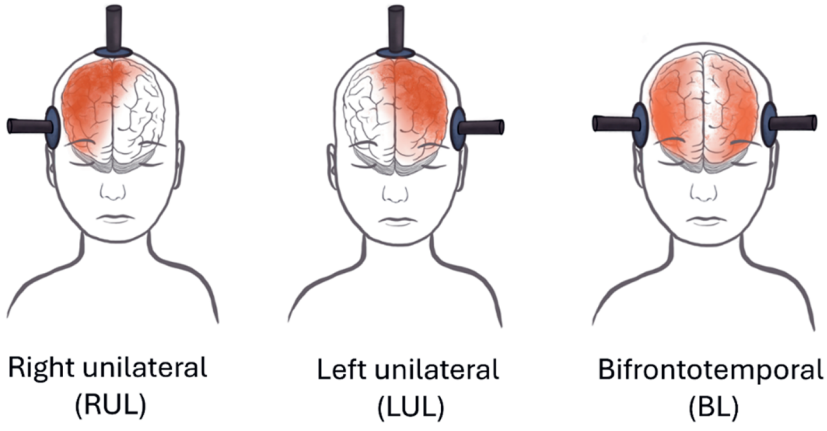


Figure 1.3 Electrode placement in electroconvulsive therapy (ECT). The conventional electrode placements in clinical practice are right unilateral (RUL), left unilateral (LUL), and bifrontotemporal (BL). Red color indicates how the electrical field of the ECT-stimulus is supposed to spread in the brain under the electrodes (33, 34).

1.5 Tentative pathophysiological mechanism of the postictal state

Effective treatment of postictal manifestation is not yet available. This is related to insufficient knowledge about underlying pathophysiological mechanisms (12, 15, 16, 35). Vasoconstriction-mediated cerebral hypoperfusion and hypoxia is the most scientifically supported hypothesis, although other mechanisms have been proposed (Figure 1.4) (15, 16). In this hypothesis, cyclooxygenase-2 (COX-2) and L-type Ca^{2+}-channels are the key molecular targets in mediating postictal hypoperfusion/hypoxia. COX-2 is a postsynaptic enzyme, which enables catalyzation of vasoactive prostanoids that modulate the vessel diameter leading to vasoconstriction. Therefore, COX-2 antagonists may reduce postictal vasoconstriction and hypoperfusion. Downstream of COX-2 are L-type Ca^{2+}-channels located on the smooth muscle of arterioles. Blocking of those Ca^{2+}-channels may also prevent postictal vasoconstriction. Pre-seizure administration of acetaminophen, a selective COX-2 antagonist, or nifedipine, a Ca^{2+}-channel antagonist, blocked postictal hypoxia in experimental animal models. Nifedipine, but not acetaminophen, was also effective if given *after* the seizure (16).

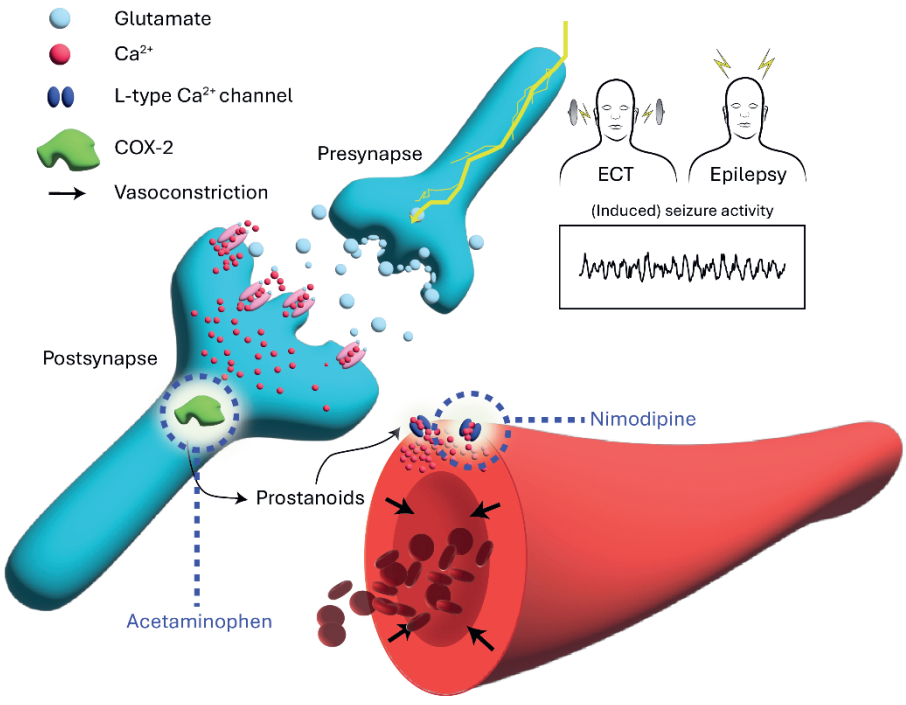


Figure 1.4 Supposed postictal pathophysiological mechanism involving cyclooxygenase-2 (COX-2), which is a critical enzyme in regulating mediating postictal hypoperfusion and hypoxia. Acetaminophen pre-treatment or nimodipine pre- or post-treatment reduced postictal hypoxia in rats. Acetaminophen is a COX-2 inhibitor, which enables catalyzation of vasoactive prostanoids that modulate the vessel diameter leading to vasoconstriction. Nimodipine is a L-type Ca^{2+}-channel inhibitor, which channels are located on smooth muscles of arterioles and their blockage may prevent vasoconstriction. ECT = electroconvulsive therapy, Ca^{2+} = calcium.

1.6 Outline of the dissertation

In this dissertation, we use ECT-induced seizures to systematically study the dynamics of the postictal state with EEG, MRI, and clinical measures, and test novel treatments that hold potential to alleviate postictal symptoms.

In **chapter 2**, we present a review of the literature on current knowledge of the postictal state regarding EEG, MRI, and clinical features, as well as underlying pathophysiological mechanisms, and provide a new integrated definition of the postictal state.

In **chapter 3**, we describe comparisons of spontaneous and ECT-induced seizures to substantiate that ECT comprises a valuable human model to study the postictal state.

In **chapter 4 – 7**, we present results of the StudY of effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT (SYNAPSE). SYNAPSE was a prospective clinical trial with three-condition randomized cross-over design, investigating two promising drugs (i.e., acetaminophen and nimodipine) to alleviate postictal symptoms.

In **chapter 4**, we study the relation between postictal EEG recovery, clinical reorientation, and seizure duration.

In **chapter 5**, we investigate cerebral perfusion in the postictal state with arterial spin labeling magnetic resonance imaging (ASL-MRI). These measurements are controlled for test-retest effects with ASL-MRI measurements of healthy controls. ASL-MRI is a non-invasive neuroimaging measure to quantify perfusion without the use of an exogenous tracer.

Changes in postictal resting-state brain networks, estimated with functional MRI and controlled for test-retest effects, are presented in **chapter 6**.

In **chapter 7**, we present the final results of the SYNAPSE trial on the effects of pre-ECT treatment with nimodipine or acetaminophen on postictal EEG recovery, clinical reorientation, and cerebral perfusion. In advance, we hypothesized that these interventions would improve postictal recovery.

In **chapter 8**, we provide a summary of all previous chapters. We discuss our findings in **chapter 9** and place them in the broader context of the field, with methodological considerations, and future perspectives.

Chapter 2

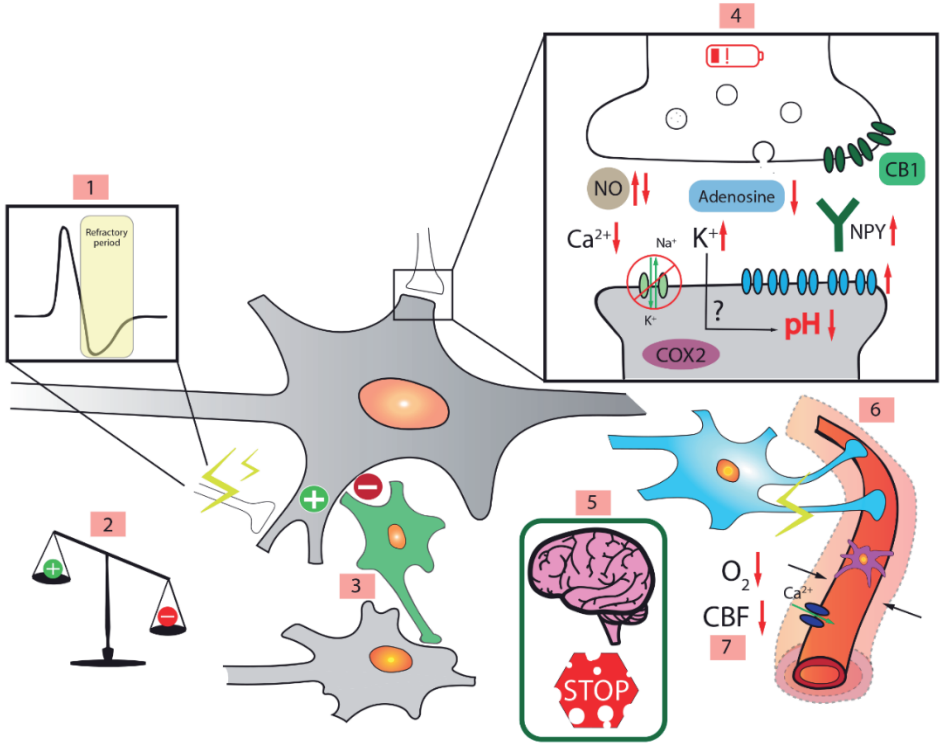
The postictal state – What do we know?

Clinical manifestations, pathophysiology, and treatment

Pottkämper, J. C. M., Hofmeijer, J., van Waarde, J. A., and van Putten, M. J. A. M.

Epilepsia 2020; 61(6): 1045-1061.

Graphical abstract



Legend

1. Active inhibition
2. Excitation-inhibition imbalance
3. Inhibitory interneurons (green)
4. Intra- and extracellular mechanisms: neuronal exhaustion (red battery), neurotransmitter depletion, increased extracellular potassium, decreased extracellular calcium, increased/decreased nitric oxide (NO), cyclooxygenase 2 (COX2) activity, lower pH, lower adenosine, Na^+/K^+-ATPase pump, neuropeptide Y (NPY), increased opioid receptors, CB1 and CB2 (cannabinoid receptor 1 and 2 as representation of endocannabinoids)
5. Blood-Brain Barrier damage (CBF = cerebral blood flow)
6. Neurovascular decoupling (purple pericyte, blue astrocyte)
7. Hypoperfusion/Hypoxia (L-type calcium channel; red arrows pointing down/up represent decrease/increase).

⊕ represents excitation, ⊖ inhibition

Abstract

This narrative review provides a broad and comprehensive overview of the most important discoveries on the postictal state over the past decades as well as recent developments. After a description and definition of the postictal state, postictal symptoms, their clinical manifestations, and related findings will be discussed. Moreover, pathophysiological advances will be reviewed, followed by current treatment options.

Key points

- The postictal state shows a rich phenomenology of neurological deficits and/or psychiatric symptoms, varying in severity and duration
- We define the postictal state as "a temporary brain condition following seizures a) manifesting neurological deficits and/or psychiatric symptoms, b) often accompanied by EEG slowing or suppression, c) lasting minutes to days"
- Pathophysiological mechanisms are being elucidated, but mostly limited to pre-clinical models
- Current treatment options consist mainly of symptom suppression and are not strongly established in clinical trials

2.1 Introduction

Patients with epilepsy not only have seizures, but also experience an aftermath of seizures: the postictal state. This includes a variety of sensory, cognitive, and motor deficits such as unresponsiveness, headaches, and memory impairments (12-14, 36, 37). Furthermore, psychiatric symptoms may occur, including postictal depression and psychosis (14, 38, 39). Symptoms can vary in severity and may last from minutes to hours or even days, depending on age, type of seizures, and underlying brain disease (13). A recent systematic review of 45 studies identified postictal clinical symptoms and characteristics in various epilepsy types (13). Postictal unresponsiveness was most common with a mean frequency of approximately 96%. Postictal headaches, migraines, and psychosis had a mean frequency of 33%, 16%, and 4%, respectively. The extent and intensity of the postictal state affects patients' quality of life substantially and correlates strongly with patients' rating of seizure severity, but has received little attention in epilepsy treatment (14, 40).

In contrast to the ictal state, an operational definition for the postictal state is not straightforward due to the challenges of identifying exact onset and termination points (38). Although postictal symptoms have first been described in 1849 by Todd, a clear definition is still lacking (41). In Figure 2.1, a timescale of the postictal state is presented. The duration of the postictal state differs in terms of clinical manifestation; T1 (purple) represents the short duration of seconds to minutes; T2 (green) includes hours, reflecting physical and cognitive symptoms; T3 (blue) represents days to weeks, in which psychiatric symptoms as postictal psychosis may occur. If postictal symptoms span a broader timescale, this will be indicated as T1-T2, T2-T3, or T1-T3. This framework will be used throughout the review. Conceptually, the postictal state can be defined as a transient abnormal brain condition with neurologic deficits or psychiatric symptoms during the period following an epileptic seizure, which is reflected in the electroencephalogram (EEG) as suppression of physiological rhythms (T1-T2; Figure 2.1) (38). On a fundamental level, one could define the postictal state as desynchronization of neuronal networks, for instance resulting from disbalance in transmembrane ionic gradients (T1). Another definition of the postictal state that appears in the literature is "a manifestation of seizure-induced reversible alterations in neuronal function, but not structure" (T1) (42). Based on these considerations, we suggest the following definition for the postictal state: "A temporary brain condition following seizures a) manifesting neurological deficits and/or psychiatric symptoms, b) often accompanied by EEG slowing or suppression, c) lasting minutes to days" (T1-T3). In this narrative review, we identified articles that mentioned the postictal state, and ordered the results in five sections: 1) clinical manifestations, 2) EEG characteristics, 3) neuroimaging and biochemistry, 4) pathophysiological mechanisms, and 5) treatment options.

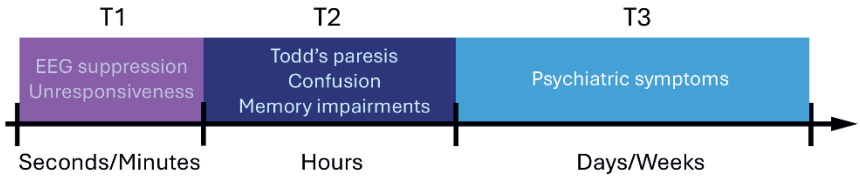


Figure 2.1 Timescales of the postictal state. The duration of the postictal state differs in terms of clinical manifestation; T1 (purple) represents the short duration of seconds to minutes; T2 (green) includes hours, reflecting physical and cognitive symptoms; T3 (blue) represents days to weeks, in which psychiatric symptoms as postictal psychosis may occur. If postictal symptoms span a broader timescale, this will be indicated as T1-T2, T2-T3, or T1-T3. This framework will be used throughout this review.

2.2 Search strategy and selection criteria

We searched PubMed, MEDLINE, and the Cochrane databases for English articles between January 1849 and December 2019. We searched for symptomatology and treatment strategies. The key terms used were 'postictal*' in combination with 'psychiatry', 'EEG', 'behaviour', 'neuroscience', 'MRI', 'epilepsy', and 'neurological deficits'. Articles were reviewed that mentioned the postictal state in the title or abstract and included human data. We excluded articles that did not focus on epilepsy, stroke-related seizures, and study protocols.

2.3 Clinical manifestations

The postictal state shows a rich phenomenology of neurological deficits and/or psychiatric symptoms, summarized in Table 2.1.

2.3.1 Altered consciousness

Altered states of consciousness range from unresponsiveness to postictal coma, which is a common finding after generalized tonic-clonic seizures (T1) (43, 44). Recovery of consciousness may, in some cases, reveal neurological lateralized deficits, including paresis (45). After awakening from coma, memory is often temporarily impaired (T2).

2.3.2 Cognitive dysfunction

Cognitive functions that decline most after seizures are alertness and short-term memory (T2) (36). Sixty-six out of 100 refractory focal epilepsy patients showed postictal memory impairments depending on the location of seizure foci (46). Visual memory impairments occur if seizure foci are in the nondominant hemisphere, whereas verbal memory is impaired if seizure foci are located in the dominant hemisphere. Furthermore, patients may experience clouded thinking,

impaired attention and concentration, and decreased verbal skills (14). In right TLE, a decline in visual attention and spatial orientation was reported, while verbal memory was impaired in left TLE (36). The more seizures a patient experiences, the larger the likelihood of severe postictal cognitive impairment.

2.3.3 Autonomic dysregulation

Coughing and spitting can occur after temporal lobe seizures, presumably reflecting ictal-induced autonomic dysfunction, or in some instances, aspiration during the seizure (T1) (47). Also, postictal hypersalivation, nose rubbing, cardiovascular dysfunction (arrhythmia, brady- and tachycardia), myocardial infarction, neurogenic pulmonary edema, and transient systemic hypo- and hypertension have been reported (T1-T3) (48). Postictal hyperthermia resulting from ictal muscle activity was found to be related to seizure duration in several patients (48). Neurogenic edema is an uncommon complication in the postictal state, too, resulting from changes in the alveolar capillary endothelium, that typically resolves within 24 hours (49).

2.3.4 Headache

Postictal headache occurs in approximately 66% of patients (13, 50). It ranges from moderate to severe in intensity, frequently with migrainous features, and durations from minutes to hours (T1-T2) (51). Postictal headache is reported more often in patients with generalized-tonic clonic, focal seizures with impaired awareness, or repetitive or prolonged seizures. Gender and family history of migraines or headaches do not seem to be risk factors for postictal headache (45, 51).

2.3.5 Changes in mood and affect

Postictal depressive and anxiety symptoms may occur for more than 24 hours and within 5 days postictally (T3) (37). In a sample of focal epilepsy patients, 18 out of 100 patients showed postictal depressive symptoms, characterized by anhedonia, helplessness, self-deprecation, or suicidal thoughts (46). Postictal anxiety may include constant worrying, agoraphobia, and unpleasant feelings due to increased self-awareness (i.e., self-consciousness) and is often accompanied by a depressive disorder (52). In a small (N = 5) retrospective sample, postictal mania was associated with symptoms of elevated and euphoric mood, distractibility, hyperactivity, disinhibition, pressured speech, decreased need for sleep, flight of ideas, grandiosity, and hyperreligiosity (53). Postictal hypomania is also common (T1-T2) (37).

2.3.6 Postictal paresis

Todd's paresis is a specific example of a severe postictal motor impairment, which can be misdiagnosed as ischemic stroke (T2) (16). Diagnostic tools with high specificity or sensitivity to differentiate between Todd's paresis, transient ischemic attacks, or stroke (mimics) are currently lacking (54, 55). Careful clinical assessment including physical and neurological evaluation and brain imaging is

advised (55). Todd's paresis can develop after focal and generalized seizures involving the (contralateral) sensorimotor cortex and can even present bilaterally (56). In a sample of 229 patients with focal to bilateral tonic-clonic seizures, approximately 6% developed Todd's paresis (57). There is a high risk that Todd's paresis may not be discovered, if not specifically sought for by clinicians, leading to an underestimation of prevalence (45).

2.3.7 Visual and auditory disturbances

Postictal blindness (amaurosis) is reported in two thirds of patients with childhood occipital epilepsy of Gastaut, with occipital or occipitotemporal seizure foci (T1-T2) (58, 59). Older patients may have postictal visual loss as well, if seizures started in occipital areas (58). Postictal palinacousis is the phenomenon of preservation of an external auditory stimulus after its cessation, as for example a fragment of a previously heard sentence, manifesting in an auditory illusion (60). In the few cases of palinacousis, none of the patients had electrographic seizures during the event.

2.3.8 Language dysfunction

Postictal speech disturbances can be indicative of seizure location and seizure spread and often involve postictal dysphasia (T1) (36, 61). Approximately 38% of patients experience language impairments (13). Most postictal speech disturbances occur in patients with TLE of the dominant hemisphere or if seizures spread to the dominant temporal lobe (61). Postictal language delay with paraphasia was found to be longest if seizure onset is located in the nondominant temporal lobe and spreads to the contralateral dominant temporal lobe (61).

2.3.9 Sleep

If seizures occur during sleep, postictal phenomena may range from confusion on awakening to disturbances in sleep patterns (T2-T3) (62). This introduces challenges for the differential diagnoses of sleep disorders as parasomnia, too. For instance, sleep disturbances may affect memory consolidation and attention, but this may also be directly related to the postictal state (62). Sleep apnea may also occur after nocturnal seizures, introducing a risk for sudden unexpected death in epilepsy (SUDEP) (63). Postictal sleep may also be a symptom suggested to be related to activation of cerebral inhibitory systems to terminate seizures (44). Postictal sleep has been reported in approximately 6 up to 45% of patients (13, 50).

2.3.10 Psychiatric symptoms and syndromes

Postictal psychiatric symptoms include delirium, changes in perception (e.g., hallucinations), thoughts (e.g., incoherence, delusions), and motor disturbances (e.g., catatonia; T2-T3) (25, 50, 64, 65). Postictal delirium may transit to a postictal psychosis, including violent behaviour (14, 25, 66). In some patients, violent, bizarre, or sexual inappropriate behaviour occurs (67, 68). Two meta-analyses showed that the estimated prevalence of postictal psychosis ranges between 2-4 %, independent of type of epilepsy (13, 67). Diagnostic criteria include return of

normal mental function within one week and duration of one day to three months (14, 69). However, no clear definition of postictal psychosis is provided in the literature. It remains also unclear whether the psychosis is part of the ictal period alone or represents an underlying psychiatric illness, which makes its diagnosis and treatment challenging, but diagnostic criteria designed by Logsdail and Toone may be used (12, 70). In a study with 100 epilepsy patients, approximately half of those patients presenting with isolated psychotic symptoms also had a history of psychiatric disorders as depression, anxiety, and attention deficit disorders (46). Psychic auras and grandiose and religious delusions occurred frequently in a sample of thirty TLE patients, compared to interictal and chronic psychosis (71). Postictal Cotard and Capgras delusion have been reported in case studies (72). Affective symptoms may occur during postictal psychosis, including the Cotard and Capgras delusion, which may lead to the discussion whether the patient suffers a postictal mood disorder or psychotic disturbance (73). A higher incidence of violent behaviour was established in postictal compared to interictal psychosis with risk for suicidal attempts and acting violently (66, 68). There are conflicting viewpoints on which seizure type puts patients most at risk for a postictal psychosis. Patients with generalized seizures were more likely to develop postictal psychosis than patients with focal impaired awareness seizures, but others suggested the opposite relationship (69, 74). In which way genetic predispositions play a role in postictal psychosis is uncertain (68). Catatonia has been reported rarely in the postictal state, as it seems to be more commonly associated with the ictal state (75, 76).

2.3.11 Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP is defined as an unidentifiable cause of death, which is non-accidental and non-suicidal, excluding status epilepticus as possible cause, occurring during or immediately after a seizure (T1) (77). Epilepsy patients are twenty times more likely than the general population to die unexpectedly, but the risk of SUDEP varies widely within the epilepsy population (78). The most important risk factor for SUDEP is a high frequency of generalized tonic-clonic seizures (16). The MORTality in Epilepsy Monitoring Unit Study identified postictal respiratory depression and cardiac dysfunction occurring after generalized tonic-clonic seizures as critical factors in SUDEP (79). Postictal generalized EEG suppression (PGES) has been observed in all monitored SUDEP cases. This could be referred to as an early postictal neurovegetative breakdown (79). Respiratory and cardiac dysfunction has also been observed and related to SUDEP in a small sample of forty-two patients (80). Other recent work on 69 patients with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures also suggests an association between the occurrence of potentially high-risk cardiac arrhythmias and longer ictal/postictal hypoxemia (81).

Postictal hypoxemia and PGES seem to be risk factors for SUDEP (T1) (82). Recent work on peri-ictal central apnea and SUDEP in 218 patients established that post-convulsive central apnea was associated with longer oxygen saturation recovery

times to mild hypoxemia but not with total hypoxemia duration (83). Whether prolonged ictal central apnea and post-convulsive central apnea can serve as potential biomarkers for an increased risk of SUDEP needs to be validated in larger studies. The relation between PGES and SUDEP remains controversial and poorly understood. Asadollahi and colleagues found that the risk of SUDEP increased by 1.7% for each one second increase in duration of PGES after generalized convulsive seizures (N = 67) (77). Contrary to this finding, SUDEP patients may have shorter duration of PGES after generalized convulsive seizures (84). PGES and postictal hypoxemia showed a strong correlation (N = 73), which may indicate its involvement in SUDEP (82). In a study with N = 59 patients, longer PGES (i.e., > 20 seconds) was no reliable predictor of SUDEP (85). However, antiepileptic drug reduction and PGES during sleep may be associated with a higher risk of SUDEP (85). Limited sample sizes in aforementioned studies have to be considered.

There have been a few breakthroughs pointing to a key mechanism relating to SUDEP (16, 86, 87). It is proposed that spreading depolarization propagating to brainstem cardiorespiratory centres has an active role in the postictal cardiorespiratory collapse, based on animal models of human SUDEP (86).

2.3.12 Social and economic impact

Patients' health and well-being are severely affected by postictal symptoms (T3) (88). Higher mortality and morbidity in patients suffering from epilepsy in childhood as well as higher age are well-known clinical characteristics (89-92). Postictal aspiration remains a common threat after generalized seizures that needs to be dealt with immediately by administering oxygen, if patients are supervised in a hospital setting (T1) (45). Caregivers and loved ones are also affected by these circumstances, as patients depend on their immediate help. In the aftermath of seizures, patients can deal with injuries as burns, fractures, and tongue biting. Patients, caregivers, and their loved ones may be confronted with an increased burden of homicide and suicidal behavior (66, 69). Postictal cognitive and behavioral impairment may also lead to lowered self-esteem, increased stigma, as employment difficulties (93).

Table 2.1 Clinical manifestation of the postictal state

Category	Signs and symptoms
Altered consciousness	Unresponsiveness Confusion Coma Delirium*
Cognitive dysfunction	Declined alertness and short-term memory Visual and spatial memory impairments Delirium*
Autonomic dysregulation	Coughing Spitting Hypersalivation Nose rubbing Hyperthermia Cardiovascular dysfunction (arrhythmia, brady- and tachycardia, hypo- and hypertension) Myocardial infarction Neurogenic pulmonary edema Dysregulated breathing patterns
Headache	Migraines Fatigue
Changes in mood and affect	Depressive mood and affect state disturbances
Postictal paresis	Todd's paresis
Visual and auditory disturbances	Blindness/visual loss Hallucinations Palinacousis
Language dysfunction	Speech and language disturbances Dysphasia
Sleep	Sleep disturbances
Psychiatric symptoms and syndromes	Delirium* Postictal psychosis (perception and thought disturbances) Motor disturbances (catatonia)
SUDEP	Unidentifiable non-accidental and non-suicidal cause of death
Social and economic impact	Higher mortality and morbidity Lowered self-esteem and increased stigma Unemployment

*Delirium is a syndrome in which consciousness, cognitive functions and psychiatric symptoms (e.g., hallucinations, delusions, mood disturbances) may occur.

2.4 Electroencephalography (EEG) characteristics of the postictal state

The most common EEG characteristics during the postictal state are suppression and slowing of brain rhythms (94). Postictal EEG suppression is defined as abnormal slow-wave activity or suppression with amplitudes less than 10 μV within 30 seconds of seizure cessation, lasting more than 2 seconds (T1) (38, 39, 77). It has been found in 84% of seizures in 94% of epilepsy patients (95, 96). Different definitions of postictal EEG suppression have been proposed, as - for example - EEG attenuation of more than 2 seconds (77). The underlying mechanism of postictal EEG suppression remains unknown (97). It may be related to anoxia, acute hypercapnia, or cortical spreading depression (97).

As recovery of the EEG advances, initial delta slowing (< 4 Hz) transitions to theta frequencies (4-7 Hz) before returning to baseline background activity (T1) (38, 94). Examples are shown in Figures 2 and 3. Delta slowing can be considered as the most important postictal EEG change as it occurs after up to 81% of the seizures. This phenomenon is sometimes accompanied by intermittent epileptiform discharges (i.e., postictal spikes) (94).

Postictal EEG changes can last up to 24 hours (T1-T2) (36). Recovery to baseline EEG also depends on the use of antiepileptic drugs. For example, patients treated with levetiracetam demonstrate quicker recovery of postictal slowing to baseline compared to placebo (36, 88).

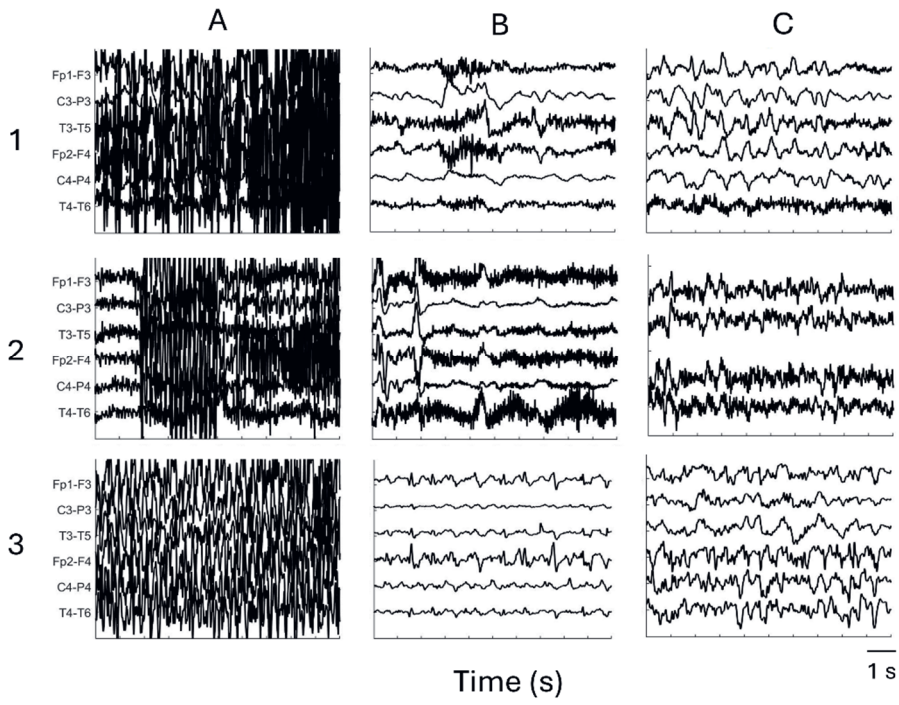


Figure 2.2 Examples of EEG recordings, showing (A) seizure activity, (B) postictal suppression or slowing, and (C) return of background activity. Patient 1 was 88 years old and had a generalized seizure which was followed by EEG suppression after approximately 3 minutes postictally, and postictal slowing occurring approximately 25 minutes postictally. Row 2 represents data from a 77-year-old patient with a generalized seizure. Postictal suppression occurred after approximately 1 minute after seizure activity, with postictal slowing after 9 minutes postictally. Noisy frontal channels excluded to maintain visibility of the EEG. The last patient (3) was 65 years old. After the seizure, EEG shows sporadic spikes over the frontal regions with suppressed activity (3B; t = 25 min) and subsequent appearance of rhythms in the delta and theta band. with postictal suppression 25 minutes postictally and slowing approximately 1-hour postictally (3C). Filter settings 0.5-35 Hz. Vertical scale bar: 50 μV.

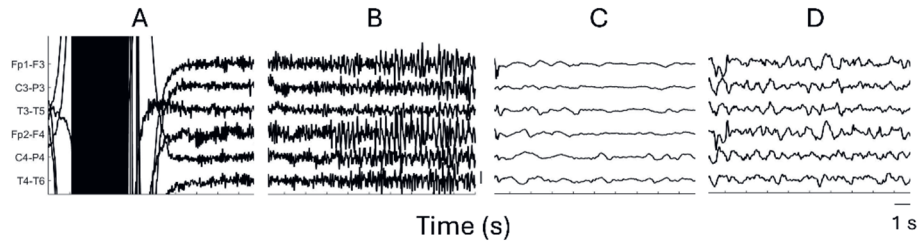


Figure 2.3 Electroencephalographic activity during and after electroconvulsive therapy (ECT). (A) Artifact resulting from the ECT stimulus with (B) subsequent seizure activity; (C) EEG suppression 80 seconds postictally; (D) EEG slowing 22 minutes after seizure activity. Note the similarities between ECT-evoked seizures and spontaneous epileptic seizures, shown in Figure 2.2. Filter settings 1-35 Hz. Vertical scale bar: 50 μV.

2.4.1 Spatial characteristics

The spatial extent of the postictal suppression depends on the seizure type. In patients with TLE, postictal slowing may develop on the site ipsilateral to seizure onset. In generalized tonic-clonic seizures, postictal suppression involves both hemispheres (36).

In TLE patients, increased seizure severity was associated with global postictal elevation of relative spectral delta power in several brain areas (39). Furthermore, a regional decrease in delta power was established in ipsilateral temporal regions but increased in frontal regions. Postictal delta activity in frontal-parietal regions has been related to seizure-induced behavioural manifestations (e.g., impairments in responsiveness and consciousness) (39). A combination of EEG attenuation and delta slowing may result in more severe postictal clinical disturbances, rather than one of these EEG changes in isolation (94).

2.4.2 Clinical correlates

High frequency gamma activity (> 25 Hz) during postictal EEG attenuation of lower frequencies may be associated with clinical features as postictal immobility (T1) (95). These findings hint on ongoing brain activity from subcortical structures that cannot be discovered with standard scalp EEG alone. Furthermore, postictal EEG suppression has been related to a higher risk of developing postictal psychosis (74).

2.5 Duration of the postictal state

2.5.1 Myoclonic and atonic seizures

Defining the duration of the postictal state after myoclonic seizures is challenging. Myoclonic seizures involve brief, clustered muscle jerks, often occurring while falling asleep (38). Defining offsets for myoclonic seizures is difficult, as it is unclear whether, and if so, how these individual short-lasting muscle jerks should be clustered. Atonic seizures present with short duration and decreased muscle tone. Reports about the postictal state in atonic seizures have been scarce. Until now, no indication has been provided about the duration of the postictal state in these seizure types. Postictal states are more likely to occur if seizures last longer, and patients with very brief absence seizures (< 15s) generally do not have a postictal state (T1) (38). Absence epilepsy mostly lacks a postictal state, as background EEG before and after seizures is normal and postictal hypoxia does not seem to occur, providing diagnostic value (98, 99).

2.5.2 Focal with impaired awareness seizures

As early as in the year 1983, Theodore and colleagues investigated the duration of the postictal state in focal impaired awareness seizures from clinical characteristics as postictal confusion and speech disturbances (100). Mean postictal duration was 89 seconds, with a maximum of 767 seconds, based on immediate responsiveness (T1). Baker et al. showed that the revised version of the Liverpool Seizure Severity Scale could reliably identify seizure severity, focusing among others on postictal symptoms and duration of the postictal state (50). In a sample of 97 epilepsy patients, time to full recovery was more than 60 minutes for almost 40% of patients (T1).

2.5.3 Focal to bilateral tonic-clonic seizures

In contrast, Kaibara and Blume assessed duration by focusing on EEG features, either delta or theta slowing, attenuation, or spike activation (101). They showed that mean duration of postictal scalp EEG changes after focal seizures was 275 seconds, ranging from 7 seconds to more than 40 min (T1) (94, 101). Others reported postictal periods of 45 minutes after generalized convulsions, defining postictal duration as recovery of consciousness and motor function (102). The postictal state ranged from 2 minutes to 2 months based on symptom presentation, i.e., postictal headache or confusion and postictal psychosis, respectively (T1-T3) (13).

There have been controversial findings for postictal duration and age. If epilepsy onset occurred after the age of 18 and if seizures started in the dominant hemisphere, patients were more likely to have longer postictal duration (T1) (58). A recent study retrospectively investigated factors associated with postictal duration after generalized seizures, with longer periods for elderly patients, longer seizure duration, and higher functional dependence (T2) (102). In contrast, Arkilo, Wang, and Thiele found that children needed on average more time to return to

background EEG (120 minutes) than adults (84 minutes; T2) (103). Furthermore, postictal slowing was shorter for frontal lobe seizures than temporal lobe seizures (T2) (103).

The various differences in definitions for the postictal state further illustrate the demand for adapting the definition for an accurate estimation of its duration (13). A definition solely based on responsiveness or recovery of motor function questions the validity of results (100, 102). We, and others, argue that the widely used criteria based on clinical observation alone are too crude to provide an accurate measure of the full postictal state (38, 44).

2.6 Differentiation between the ictal, interictal, and postictal state

Differentiation between the ictal, interictal, and postictal state remains challenging (104). Depending on the type of the seizure, the transition from ictal to postictal state is more or less apparent from clinical observation. Recovery of language or motor function may reliably determine the end of the ictal state. This remains challenging, however, as during the postictal state, clinical symptoms may improve but in some, electrographic seizures persist (2, 38). Marking the end of a seizure based on clinical manifestations can be therefore difficult (2). Continuous EEG recordings may have additional value in determining the postictal state, as this helps to identify that the ictal EEG characteristics have vanished (95). Quantitative EEG measures may aid in determining boundaries of the postictal state. In particular in the treatment of a non-convulsive status, continuous EEG monitoring is nearly mandatory to assess transition to the postictal state and if treatment is satisfactory (44).

Pragmatically, patients should show recovery of neurological deficits within 30 to 60 minutes (T1); otherwise, a non-convulsive status must be considered (44). Recently, various EEG criteria for nonconvulsive status epilepticus were reported as the “Salzburg consensus criteria” (105).

However, some EEG signals are associated both with seizures and the postictal state, such as rhythmic slowing in the theta and delta frequency range or periodic discharges (T1-T2) (94). Distinguishing clinically between postictal activity and nonconvulsive status epilepticus can be difficult, because clinical signs are often subtle and nonspecific and can occur both ictally and postictally (106). Further, in some critically ill patients, the transition from the ictal to the postictal state is more gradual, and patients can even enter a state known as the “ictal-interictal-continuum” (107). If the EEG shows focal or generalized periodic discharges with a frequency lower than 2.5 Hz or intermittent bursts of generalized spike-waves, postictal activity or nonconvulsive status epilepticus is not obvious, and evaluating the clinical response to anti-epileptic medication is generally advised (104). Despite these limitations, EEG remains the most valuable tool for differentiating between the ictal and postictal state (38).

2.7 Neuroimaging and biochemistry

2.7.1 Neuroimaging

Functional magnetic resonance imaging (fMRI) and single photon emission computed tomography (SPECT) have identified various changes in the postictal state (Table 2.2). The extent and duration of postictal EEG suppression (T1) in the delta frequency range was correlated with hippocampal atrophy in TLE patients: postictal delta power was lower on the right side if hippocampal atrophy on the ipsilateral site was also worse (108). Deactivation of the default mode network (DMN) may persist after a seizure in epileptic patients (T1-T2) (109). Cortical areas that were found to generate slow waves partly overlap with regions involved in the DMN.

2.7.2 SPECT

Neuroimaging studies have also identified significant changes in cerebral blood flow during the postictal state (42, 110-112). In one study, ictal hyperperfusion was followed by postictal hypoperfusion (T1) (42). Ictal hyperperfusion has been related to increased glucose and oxygen demand, which sometimes also manifested postictally, leading to contradicting findings (106, 113). In a patient with epilepsy after encephalitis and postictal psychosis, hyperperfusion in the right temporal lobe and left basal ganglia manifested, indicating the possible relevance of increased cerebral blood flow in postictal psychosis (T2) (114).

2.7.3 Diffusion-weighted imaging

With diffusion-weighted imaging (DWI), decreased diffusion in grey and increased diffusion in white matter was found in focal status epilepticus patients, presumably reflecting cell swelling of cortical neurons at seizure foci (T2) (42). In a case study, decreased diffusion was located around seizure foci in the gray matter, with facilitated diffusion in the underlying white matter (115). Another study in epilepsy patients showed postictal decreased cerebral blood flow in regions as hippocampus, parahippocampal gyrus and cortex (116).

2.7.4 Arterial spin labeling

Arterial spin labeling (ASL) MRI provides reliable information about postictal brain perfusion and may serve as reliable tool to identify seizure onset zones prior to surgery (15, 110). Increased ipsilateral blood flow relative to seizure onset may be found immediately after seizures terminate, which drops below baseline levels up to 1 hour after seizure termination (T1; Figure 2.4) (15, 42). Another study showed that perfusion decreased postictally in the hippocampus but in turn showed a reversed (hyper-) perfusion pattern in the parahippocapmal gyrus, probably reflecting increased metabolism to restore neuronal excitability (T1-T2) (117). In a recent study using ASL-MRI in twenty-one patients with idiopathic generalized epilepsy, increased cerebral blood flow in the left parahippocampal gyrus, bilateral fusiform gyri, and left middle temporal gyrus was observed postictally, highlighting

cortical hemodynamic abnormality (T3) (118). In twenty-one TLE patients, using ASL, postictal hypoperfusion in the lateral temporal lobe manifested prominently, while sparing the mesial temporal lobe (T2) (110). Two patients showed postictal hyperperfusion, which might be explained by the delayed scanning time and complexity of brain network distortion (110).

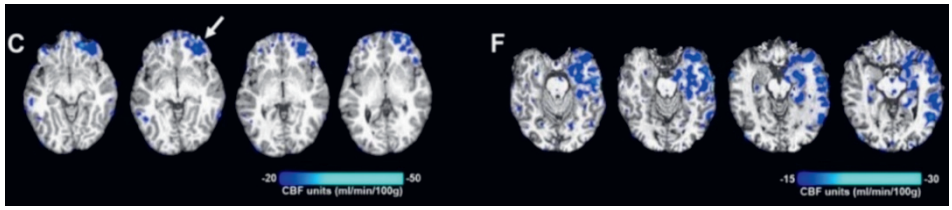


Figure 2.4 Subtraction cerebral blood flow (CBF) maps taken with ASL-MRI in a patient with frontal lobe epilepsy (C) and temporal lobe epilepsy (F). The four CBF maps show the transition from interictal to postictal state. Both patients show left hypoperfusion relative to seizure onset (left frontal with > 20 mL/100g/min, and left temporal with > 15 mL/100g/min, respectively). Figure taken from Farrell et al. 2016.

2.7.5 Biochemistry

Increased blood levels of ammonia have been observed in epilepsy patients who did not regain complete consciousness after seizure termination (T1-T2) (119). However, the level of consciousness was not recorded during the postictal state continuously but initially after the seizure and after one to two hours. Whether the distinction in ammonia levels can be explained by regaining consciousness or prolonged postictal impairment is unclear, as no postictal measurements were performed. It seems that hyperammonaemia can occur in generalized tonic-clonic but not focal seizures (45).

Similarly, increased levels of the hormone prolactin in serum have been observed after seizures, which may be due to disruption of hypothalamic function (T1) (120). However, baseline prolactin levels are ambiguous as baseline levels are influenced by a multitude of factors (i.e., sex, type of epilepsy, stress) (45). Seizures may also influence the release of gonadotropin-releasing hormone that in turn regulates gonadal sex hormones (120). Increased levels of serum creatine kinase have been found in patients with focal and tonic-clonic seizures (T3) (121). Literature on cerebrospinal fluid lactate is scarce, but shows indication of postictal increases across seizure types (45). Most likely, all these biochemical changes seem epiphenomena, and are probably not involved in termination of seizures or neuronal dysfunction in the post-ictal state. Studies on postictal biochemistry are scarce and mostly inconclusive.

Table 2.2 Summary of neuroimaging studies of the postictal state (2001-2019).

Result	Technique	Population	Reference
Hippocampal atrophy	T1 and T2-weighted MR images	Intractable focal epilepsy with impaired awareness	Olejniczak et al. 2001
Deactivation default mode network	SPECT	Epilepsy with spontaneous secondarily generalized tonic-clonic seizures	Blumenfeld et al. 2009
Dysregulated cerebral blood flow			
Hypoperfusion (lateral temporal lobe, hippocampus)	SPECT, ASL - MRI, PWI, CT	Temporal Lobe Epilepsy, Focal Epilepsy	Koepp et al. 2010, Farrell et al. 2016, Gaxiola-Valdez et al. 2017, Li et al. 2019
Hyperperfusion (parahippocampal gyrus)	PWI	(Extra-) Temporal Lobe Epilepsy	Leonhardt et al. 2005
Hyperperfusion (right temporal lobe, basal ganglia)	SPECT	Epilepsy after encephalitis (during postictal psychosis)	Yasumoto et al. 2015
Hyperperfusion (left parahippocampal gyrus, bilateral fusiform gyri, left middle temporal gyrus)	ASL	Idiopathic epilepsy	Chen et al. 2016
Dysregulated diffusion			
Decreased diffusion around seizure foci Increased diffusion in underlying white matter	DWI	Focal status epilepticus	Koepp et al. 2010

Note: ASL-MRI, Arterial spin labeling magnetic resonance imaging; CT, computed tomography; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; SPECT, single photon emission computed tomography

2.8 Pathophysiological mechanisms

The processes that are involved in the transition from the ictal to the interictal state are only partially understood. Many candidate biophysical mechanisms may terminate seizures and initiate the postictal state, summarized in Figure 2.5 and Table 2.3 (14, 42, 122, 123). T1-T3 codes are used to point at the postictal time period in which mechanisms are supposed to occur.

2.8.1 Neuronal exhaustion (T1)

Almost two decades ago, neuronal exhaustion was dismissed as candidate mechanism for seizure termination and the beginning of the postictal state, since neurons preserved their ability to generate action potentials after repeated intracellular stimulation at the start of the postictal state (14).

2.8.2 Neurotransmitter depletion (T1)

Direct evidence for neurotransmitter depletion is lacking (14). However, vagus nerve stimulation seems to be effective in treating postictal symptoms. It may be speculated that vagus nerve stimulation increases arousal via the locus coeruleus, reducing postictal drowsiness (124, 125). This also suggests that neurotransmitter pathways are still intact if they are amenable to stimulation (126). Also, glutamate depletion might occur during seizures, which may continue into the interictal or postictal state (127).

2.8.3 Active inhibition and changes in ion homeostasis (T1)

Postictal symptoms may also result from active inhibition of neuronal function (14). This hypothesis is based on the observed association between postictal refractoriness and increased seizure thresholds (128). Postictal refractoriness may result from selective neuronal hyperpolarization that inhibits activity for several minutes or longer (14). Shunting inhibition may be involved in this process by reducing effective neuronal coupling (127). Decreased extracellular Ca^{2+} may be involved in inhibiting synaptic transmission (127). Network inhibition of subcortical structures may be involved in impaired consciousness after temporal lobe seizures by sending inhibitory output to neocortical neurons (39, 43). Another candidate mechanism is an increased concentration of extracellular potassium following seizures, that may cause a depolarization block and suppression of neural activity (14). Other mechanisms involved in the postictal state may be important for seizure termination. Intracellular acidification (lower pH), supposedly resulting from increased extracellular potassium, seem to aid in seizure termination by reducing excitability (127). Endocannabinoids activate CB1 receptors on presynaptic receptors, resulting in a reduction of neurotransmitter release (129). Activation of receptors on excitatory presynaptic terminals will result in a decrease of glutamate release (127, 130, 131). Neuropeptide Y has endogenous anticonvulsant effects, with high postictal expression levels hours after seizures.

2.8.4 Opioid receptors (T2)

Another, more controversial, candidate mechanism relates to opiates and opioid receptors in the postictal state.(14) Increased levels of opioid receptors have been established after seizures that last for several hours (37, 58). An opiate antagonist was shown to reverse unconsciousness after seizures in rats. In contrast, however, no change in seizure duration was discovered after administering an opiate antagonist following electroconvulsive therapy in depressed patients, questioning its role in the human postictal state (14).

2.8.5 Adenosine and nitric oxide (T1)

Adenosine and nitric oxide also seem to play a role in the pathophysiology of the postictal state. Increased levels of adenosine were observed *in vivo* during and up to 18 minutes after seizures, indicating a potential role in terminating seizures and postictal refractoriness (132). Nitric oxide may be involved in regulating postictal cerebral blood flow (14).

2.8.6 Hypoperfusion and hypoxia (T2)

Recently, Farrell and colleagues showed in a study in rodents and humans that postictal behavioural symptoms result from hypoperfusion and hypoxia (15, 16). After both spontaneous and electrically induced seizures in rats, local blood flow and brain tissue oxygen concentrations in the hippocampus decreased dramatically for more than one hour, mediated by local vasoconstriction (15). Hypoperfusion and hypoxia were positively correlated with seizure duration and severity, both in animals and humans (15). Postictal perfusion with ASL-MRI in epilepsy patients with focal seizures also showed a decreased cerebral blood flow in the affected region. In agreement with this mechanism, caffeine, which is a well-known vasoconstrictor, has been shown to aggravate postictal hypoxia in rodents (133). This mechanism possibly acts via antagonistic effects on adenosine receptors.

Farrell and colleagues also propose that cyclooxygenase-2 (COX-2) and L-type Ca^{2+}-channels are involved in the induction of postictal hypoperfusion and hypoxia (16). They showed that by administering COX-2 and L-type Ca^{2+}-channel antagonists prior to seizure onset, postictal hypoperfusion and hypoxia were reduced in rodents (15, 16). These experimental findings provide new insights in the mechanisms that are related to postictal phenomena.

Contradicting Farrell's hypothesis, Prager et al. support the view that neurovascular decoupling without hypoxia may be the main mechanism responsible for microvascular dysfunction in epilepsy (134). They tested their hypothesis by investigating changes in capillary neurovascular coupling in hippocampal slices of rats during recurrent seizures induced by 4-aminopyridine or low-Mg^{2+} conditions. They observed, despite normoxic conditions, that neurovascular decoupling and blood-brain barrier (BBB) dysfunction occurred, in small cortical arterioles, accompanied by perivascular cellular injury and pericyte

dysfunction. Their results may exclude hypoxia as a mechanism involved in postictal hypoperfusion in epilepsy, as hypoxia may not be necessary for pericyte dysfunction. Kovács and colleagues also report that postictal phenomena may be related to hypometabolism that results from neurovascular decoupling following seizures, highlighting the role of neurovascular coupling (135).

Experimental differences between Prager et al. and Farrell et al. are of interest here: Prager et al. used hippocampal slices to measure oxygen saturation, whereas Farrell et al. implanted oxygen-measuring probes in brains of freely moving rats (15, 134). Further, Prager et al. induced seizures with low Mg^{2+} or 4-aminopyridine, while Farrell et al. studied rats with spontaneous seizures or after kindling. These differences may have contributed to the discrepancy in findings, where the *in vivo* results of Farrell et al. may provide stronger evidence than the *in vitro* results of Prager et al.

2.8.7 Neurovascular decoupling (T1-T2)

Another possible mechanism is neurovascular decoupling, defined as a mismatch between neuronal energy demand (metabolism) and circulation (cerebral perfusion) (106). It remains unclear whether, and how, neurovascular decoupling takes place. During seizures, there is an increased metabolic demand, which ceases afterwards (117). However, if seizures persist, as occurs in status epilepticus, there is a continuous demand for increased energy, which cannot be matched with the blood flow (106). This progress leads to a decoupling of blood flow and metabolism, which in turn may result in hypoxia and glycolysis. The ensuing neuronal injury can be explained in terms of Na^+/K^+-ATPase pump failure from an ATP deficiency, but may also result from glutamate release and inflammatory responses (106).

In line with the hypothesis that hypoxia may exist in the postictal state is the selective sensitivity of inhibitory interneurons to hypoxia (136). These building blocks of cortical networks are responsible for organized gamma activity patterns (30-100 Hz), associated with cognition and memory, and known to show extreme sensitivity to oxidative and metabolic stress (136). Abnormal activity of interneurons may compromise information processing and may explain cognitive symptoms in a postictal hypoxic state (136).

2.8.8 BBB and perivascular inflammation (T1)

BBB dysfunction and subsequent perivascular inflammation after traumatic brain injury or stroke has been suggested to be involved in epileptogenesis (134, 137). MRI detected perivascular neuroinflammation and BBB disruption in animals as well as in epilepsy patients (137). BBB disruption after seizures may be involved in the postictal state on short timescales but this is presently unknown.

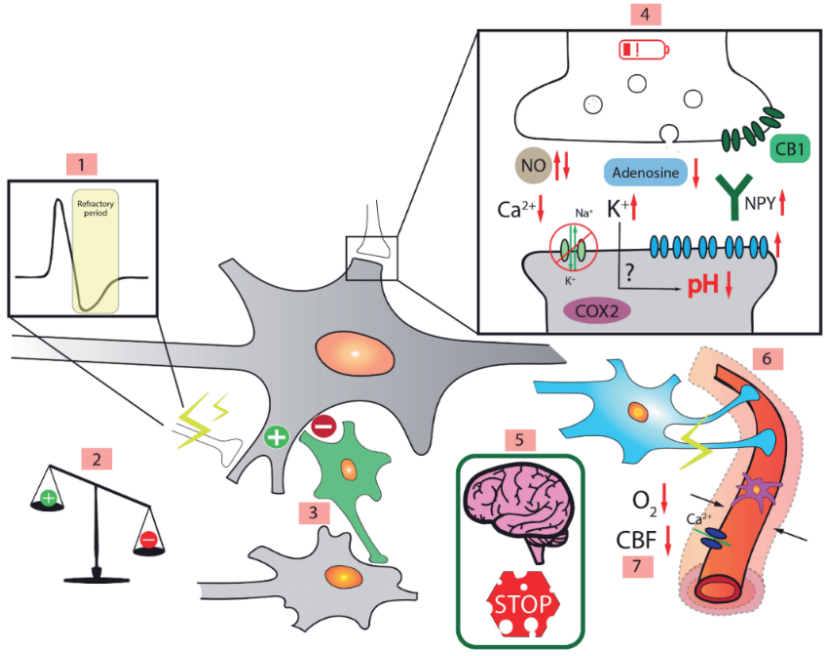


Figure 2.5 Schematic representation of pathophysiological mechanisms proposed to contribute to the postictal state. 1. Active inhibition. 2. Excitation-inhibition imbalance. 3. Inhibitory interneurons (green). 4. Intra- and extracellular mechanisms: neuronal exhaustion (red battery), neurotransmitter depletion, increased extracellular potassium, decreased extracellular Ca^{2+}, endocannabinoids binding to CB1 receptors, increased/decreased nitric oxide (NO), cyclooxygenase 2 (COX2) activity, lower pH, lower adenosine, Na^{+}/K^{+}-ATPase pump, neuropeptide Y (NPY), increased opioid receptors. 5. Blood-Brain Barrier damage. 6. Neurovascular decoupling (purple pericyte, blue astrocyte). 7. Hypoperfusion/Hypoxia (L-type Ca^{2+}-channel). ⊕ represents excitation, ⊖ inhibition. Black arrows indicate a direct influence or vasoconstriction, red arrows indicate an increase or decrease in activity or concentration, and green arrows show influx/efflux. Abbreviations: CBF (cerebral blood flow), CB1 and CB2 (cannabinoid receptor 1 and 2 as representation of endocannabinoids).

Table 2.3 Overview of proposed pathophysiological mechanisms involved in the postictal state.

Mechanism	Likelihood[a]	Reference
Neuronal exhaustion	Dismissed	Fisher & Schachter, 2000
Excitation-inhibition imbalance	Dismissed	Koepp et al., 2010
Changes in opiate receptors	Unlikely	Fisher & Schachter, 2000; Kanner et al., 2010; Theodore, 2010
Neurotransmitter depletion	Probable	Fisher & Schachter, 2000
Neuronal (active) inhibition	Probable	Löscher & Köhling, 2010; Rupprecht et al., 2010
Increased extracellular potassium	Probable	Fisher & Schachter, 2000
Decreased extracellular $Ca^{2+}$and intracellular acidification	Probable	Lado & Moshé, 2008
Changes in adenosine and nitric oxide concentrations	Probable	Fisher & Schachter, 2000
Neurovascular decoupling	Probable	Kovács et al., 2018
Dysfunction of inhibitory interneurons	Probable	Kann et al., 2014; Englot et al. 2010
Blood brain barrier dysfunction and inflammation	Probable	Gorter et al., 2019
Hypoperfusion and hypoxia	Likely	Farrell et al., 2016; Farrell et al., 2017

[a] Likelihood in this table describes the probability of a described mechanism being likely involved in the postictal state based on literature review. Dismissed means that a theory has been proven unlikely from experimental evidence, or lack of direct evidence. A mechanism is referred to as unlikely if there is no evidence in humans but only in animals. Probable means that a certain mechanism is likely to a certain extent, underlined by experimental evidence, but needs to be proven in future studies as there may be contradicting findings. Likely will describe a mechanism that has strong experimental evidence in support of this hypothesis.

2.9 Treatment options

Current treatment of the postictal state consists primarily of symptom suppression and prevention of complications (Table 4) (12).

2.9.1 Symptom suppression

Antiepileptic drugs (AEDs) may attenuate or shorten the postictal state, however only one study found levetiracetam to be effective (138). AEDs can alleviate postictal psychotic symptoms, but in turn may have anxiety and depressive mood-promoting side-effects (12). A few cases reports suggest that vagus nerve stimulation has a positive effect on the duration and symptoms of the postictal phase, independent of the effects of seizure frequency (126).

2.9.2 Prevention of complications

Administration of oxygen in the postictal state may counteract hypoxia (77). Paracetamol can limit postictal headaches (51). For most patients with mild and short-lasting postictal delirium no specific treatment is needed. However, if delirium is prolonged into postictal delirium or postictal psychosis, patients can be treated with antipsychotic drugs, (e.g., quetiapine, haloperidol) or benzodiazepines (e.g., midazolam, lorazepam), especially in case of uncontrolled behaviour and/or severe agitation (12, 102). These interventions are acceptable in these circumstances, even though some antipsychotic drugs carry an additional risk of seizure induction (139).

2.9.3 Future developments

If hypoxia caused by vasoconstriction, mediated via COX-2, is a prominent pathophysiological mechanism, as was shown in animal studies, COX-2 inhibitors and Ca^{2+}-antagonists are candidate drugs to reduce the duration and intensity of the postictal state (15). This is currently investigated in a clinical trial with randomized cross-over design, using electroconvulsive therapy (ECT)-induced seizures as a human model to study the postictal state (Figure 2.3) (35).

Table 2.4 Treatment strategies targeting postictal symptoms.

Treatment strategy	Current status of development	Reference
Vasoconstrictive-mediating drugs		
Acetaminophen	Animals	Farrell et al. 2016
Celecoxib		
Nimodipine	Human ongoing trial	NCT04028596[a]
Oxygen treatment	Hypothesis, not yet tested	Asadollahi et al. 2018
Psychotropic medication		
Quetiapine		Krauss & Theodore et al. 2010
Haloperidol	Humans, current treatment option	
Lorazepam		
Midazolam		Ohira et al. 2019
Antiepileptic drugs		
Levetiracetam	Human trials	Schmidt 2010
Vagus nerve stimulation	Human trials	Vonck et al. 2010
Drugs targeting BBB[b] dysfunction	Hypothesis not yet tested	Gorter et al. 2019

[a] ClinicalTrials.gov ID [b] BBB = Blood brain barrier

2.10 Conclusion

In this narrative literature review, a comprehensive overview of the postictal state is presented regarding its clinical manifestations, EEG characteristics, pathophysiological mechanisms, and treatment options. Several key outstanding questions need to be answered. Which metrics can best quantify the postictal state? Which pathophysiological mechanisms contribute most to postictal symptoms? Are there multiple mechanisms interacting, or is there one mechanism responsible for a variety of symptoms? How can we best treat the postictal state?

We propose to define the postictal state as:

"a temporary brain condition following seizures

a) manifesting neurological deficits and/or psychiatric symptoms,

b) often accompanied by EEG slowing or suppression,

c) lasting minutes to days".

Clinical assessment of the postictal state is not always reliable. Arterial spin labeling and EEG can assist in objective assessment of postictal hypoperfusion or suppression of neuronal activity. Further, assessment of hypoperfusion in the postictal state may serve as reliable tool to identify the seizure onset zone.

Postictal symptoms and their duration are highly variable and affect multiple brain areas. Several pathophysiological mechanisms may be involved. Postictal hypoxia, resulting from vasoconstriction, or spreading depression are novel candidate mechanisms, likely involved in SUDEP, too. If treatment of presumed postictal vasoconstriction has clinical benefit is currently studied in the SYNAPSE study (35).

Chapter 3

Seizures induced in electroconvulsive therapy as a human epilepsy model

A comparative case study

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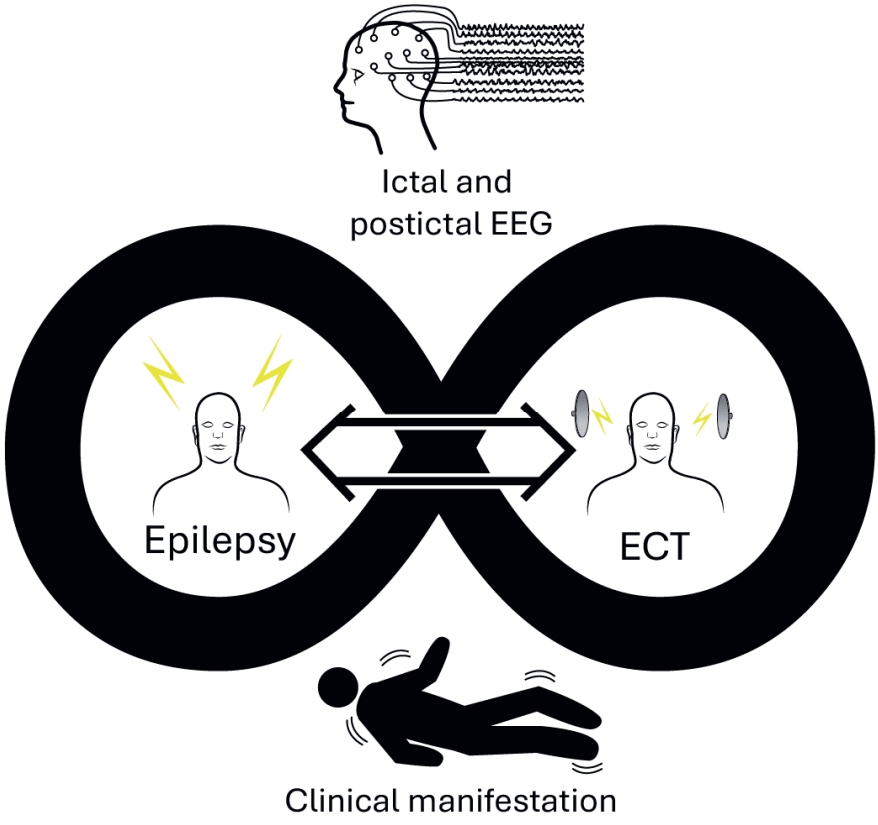
Epilepsia Open 2021; 6(4): 672-684.

Graphical abstract



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 temporary sedation 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.

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

3.1 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 (140-143). Zebrafish and Drosophila models have proven useful for low-cost drug testing in genetic epilepsies (140). Advantages of animal models include the possibility of invasive measurement techniques (e.g., hippocampal electrodes measuring pO_2 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 (144, 145). Another major disadvantage is that animal models cannot fully represent the structure and function of the human brain, hampering translation to patients with epilepsy (15, 134, 142, 146, 147). A human model of epileptic seizures may facilitate standardized investigation of ictal and postictal features and enhance translation from models to patients (88, 148, 149).

Since decades, 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 (150, 151). In extraordinary cases, ECT may be used to terminate intractable epileptic seizures (152). Using short electrical stimuli applied between two electrodes at the patients' head, under anaesthesia with proper muscle relaxation, seizure activity is elicited for 30 - 60 seconds (153). 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 an 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 (154). 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 afterwards (155-157). With the current use of sedation 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 administrating the

muscle relaxant (158). Postictal confusion, unresponsiveness, headaches, muscle pain, and cognitive impairments are frequently reported after generalized seizures in epilepsy and after ECT-induced seizures (13, 29, 66, 150, 159-162). 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 (156, 162, 163). 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 (164-168). Ictal hyperperfusion of the brain and postictal hypoperfusion have been established in both epilepsy and ECT patients (15, 151, 169, 170). Investigating tonic-clonic seizures is of increased value because clinical manifestation (i.e., tonic and clonic phase), electroencephalographic characteristics (i.e., generalized EEG spike wave complexes and postictal suppression), and neuroimaging findings (i.e., 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 an unique opportunity to systematically study ictal and postictal characteristics in humans, including treatments to ameliorate postictal symptoms in randomized controlled trial designs.

3.2 Methods

3.2.1 Study design

In this comparative case study, we included three patients with severe depressive disorder treated with ECT-sessions 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 centre Kempenhaeghe, Heeze, The Netherlands.

3.2.2 Patients

Inclusion criteria of ECT patients were a regular indication for ECT (i.e., treatment-resistant depressive episode), having no contraindications for EEG (i.e., sensitive scalp), and the ability to give informed consent. Criteria for including epilepsy patient data were seizure type (i.e., 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.

3.2.3 ECT procedure

ECT 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 (24, 171). ECT stimuli 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% O_2 starting before administration of anaesthetic (etomidate 0.2-0.3 mg/kg) and ventilation was continued with positive pressure during anaesthesia 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.

3.2.4 EEG recordings

In ECT patients, continuous EEG was recorded before and during the ECT-session, continued up to approximately 1 h after the treatment. EEG electrodes were attached at the clinical neurophysiology department. A total of six seizures was 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 afterwards at the psychiatric department. A detailed overview of EEG acquisition methodology is presented in Table 3.1.

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, The Netherlands) and a full-band DC-coupled amplifier (TMSi, Oldenzaal, The Netherlands). 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., Eaton, OH, USA). A Schwarzer Ahns amplifier (Natus, Munich, Germany) or 32-channel acquisition amplifier (Brain quick SD, Micromed, Mogliano Veneto, Italy) were used. All EEGs were acquired with BrainRT software (OSC, Rumst, Belgium) and sampled at 250 Hz.

In all patients, baseline resting-state EEG consisted of 1 min 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 3.1 Patient characteristics and EEG acquisition methodology

Patient ID	ECT1	ECT2	EPL1	EPL2	EPL3
Age	45	40	77	14	30
Sex	Female	Male	Female	Female	Male
Clinical condition	MDD	MDD	Seizures induced by hypocalcaemia	Epilepsy with generalized tonic-clonic seizures	Epilepsy with gneralized tonic-clonic seizures
# Previous seizures (type of ECT course)	53 (maintenance)	9 (index)	NK	NK	NK
# Seizures analysed	1	1	1	1	1
ECT electrodes (charge, in mC)	BL (252)	RUL (327.6)	NA	NA	NA
Anaesthesia (mg)	Etomidate (30)	Etomidate (24)	NA	NA	NA
Muscle relaxant (mg)	Succinylcholine (100)	Succinylcholine (125)	NA	NA	NA
Additional postictal medication (mg)	Lorazepam and ondansetron (1, 4)	Ondansetron and propofol (4, 50)	NA	NA	NA
Postictal clinical symptoms	Severe confusion, restlessness, unapproachable	Headache, slightly confused	NA	Sleep	Muscle ache, fatigue
EEG acquisition					
Methods	Titanium nitride electro-cap with international 10-20 placement				Silver/silver chloride cup electrodes with international 10-20 placement
Software; amplifier	BrainRT[3]; Schwarzer Ahns amplifier[4] (sampling frequency: 250 Hz; impedances < 5 kΩ)				BrainRT[3]; 32-channel acquisition amplifier[5] (sampling frequency: 250 Hz; impedances < 5 kΩ)
Acquisition center	Medisch Spectrum Twente				Epilepsy centre Kempenhaeghe

ECT = electroconvulsive therapy; EPL = epilepsy; EEG = electroencephalography; mC = milliCoulomb; BL = bifrontotemporal; RUL = unilateral; ECT = electroconvulsive therapy; NA = not applicable; NK = not known; MDD = major depressive disorder; [1] Clinical Science Systems, The Netherlands; [2] TMSi, Oldenzaal, The Netherlands; [3] OSG, Rumst, Belgium; [4] Natus, Munich, Germany; [5] Brain quick SD, Micromed, Mogliano Veneto, Italy

3.2.5 EEG preprocessing

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

3.2.6 Qualitative EEG 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 (172). 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 arhythmic polyspike activity, and Phase III refers to rhythmic spike or polyspike wave activity (2.5 – 3.5 Hz) (173). In our qualitative analysis, Phase I up to Phase III were investigated. Ictal amplitude of waves was defined as trend (i.e., increase or decrease) including absolute peak-to-through value in a channel or region in which the pattern was most readily appreciated (i.e., frontal, central, temporal, parietal; Phase II & III). Ictal frequency of waves was characterised as the typical, minimum, or maximum frequency rate or range in the majority of the epoch (e.g., 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) (172). 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 μV (77). Recovery was defined as the first occurrence of slow waves (i.e., 0.5 - 4 Hz) in the postictal state.

3.2.7 Quantitative EEG analyses

Quantitative analyses refer to transforming the data using computerized programs (i.e., 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 analysed and averaged across all channels (i.e., 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 (122). 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

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

with α in the frequency range 8 – 13 Hz and δ in the frequency range 0.5 – 4 Hz. 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

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

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 perfect 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 (174).

3.2.8 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.

3.3 Results

3.3.1 Patient characteristics

Patient characteristics are given in Table 3.1. 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 (i.e., hypocalcaemia-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 3.2).

3.3.2 EEG evolution

Figure 3.1 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 µV) 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.

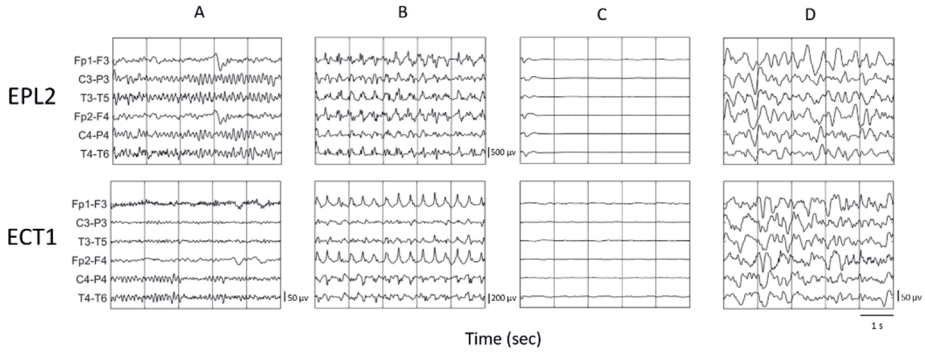


Figure 3.1 EEG epochs from patient EPL2 with spontaneous seizures (top row) and ECT-induced seizure of patient ECT1 (bottom row). (A) Baseline (eyes closed). (B) Seizure activity is followed by postictal suppression (1C *t* = 32 s postictal, 2C *t* = 3 s postictal), and postictal slowing (1D, 2D *t* = 25 min postictal). Filter settings 1-25 Hz. Epoch length 5 s. Vertical scale bar: 50 µV for (A), (C), and (D); 500 µV for 1B; 200 µV for 2B.

3.3.3 Qualitative EEG 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 3.2.

Table 3.2 Qualitative ictal and postictal characteristics in ECT and epilepsy patients

ECT patients									
Patient ID	Duration ECT stimulus (electrode placement*)	Δ ECT stimulus - start seizure	Seizure duration Phase I – III^	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
ECT1	3.7 s (BL)	1.5 s	74 s	Both hemis-pheres involved simultane-ously	Bilateral rhythmic peak synchronization preceded spike waves; peak wave complexes 20 s after start seizure	Increasing amplitude (bilateral frontal and central regions: 150 - 400 µV; left occipital and parietal regions: 70 - 250 µV; right occipital: 70 - 120 µV; temporal: 80 - 210µV)	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 right hemis-phere; after 19 s involve-ment left hemis-phere	Frontal right 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 µV; right occipital and parietal: 80 - 170 µV) followed by increasing left amplitude (frontal and central: 160 - 320 µV; occipital and parietal: 80 - 170 µV); bilateral temporal increase (100 - 290µV)	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 - left hemis-phere; after 1 s involve-ment right hemis-phere	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 µV) declined to 80 µV 12 s after start seizure; increased bilateral occipital amplitude (100 - 230 µV); bilateral temporal increase (80 - 190 µV)	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

* Electrode placement is bifrontotemporal (BL) or right unilateral (RUL); ^Phase I, II, and III refer to a classification scheme provided by Brumback et al.(173)

Epilepsy patients									
Patient ID	Duration ECT stimulus (electrode placement*)	Δ ECT stimulus - start seizure	Seizure duration Phase I – III^	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 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 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 - 1000µV) 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 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 end of seizure; delta activity remained until the end of the recording (postictal sleep)

* Electrode placement is bifrontotemporal (BL) or right unilateral (RUL); ^Phase I, II, and III refer to a classification scheme provided by Brumback et al.(173)

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 (i.e., 72 - 78 s for ECT-induced seizures, 73 – 136 s 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 min in ECT-induced seizures and 0.6 – 2.5 min in epileptic seizures (min-max). Recovery towards alpha activity was comparable between populations with 40 – 410 s and 57 – 150 s (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 (i.e., postictal 10 - 20 min) towards baseline frequencies (i.e., theta and alpha) in the late postictal state (postictal 60 min).

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 were 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).

3.3.4 Quantitative EEG analyses

Quantitative ictal and postictal EEG characteristics are summarized in Figure 3.2.

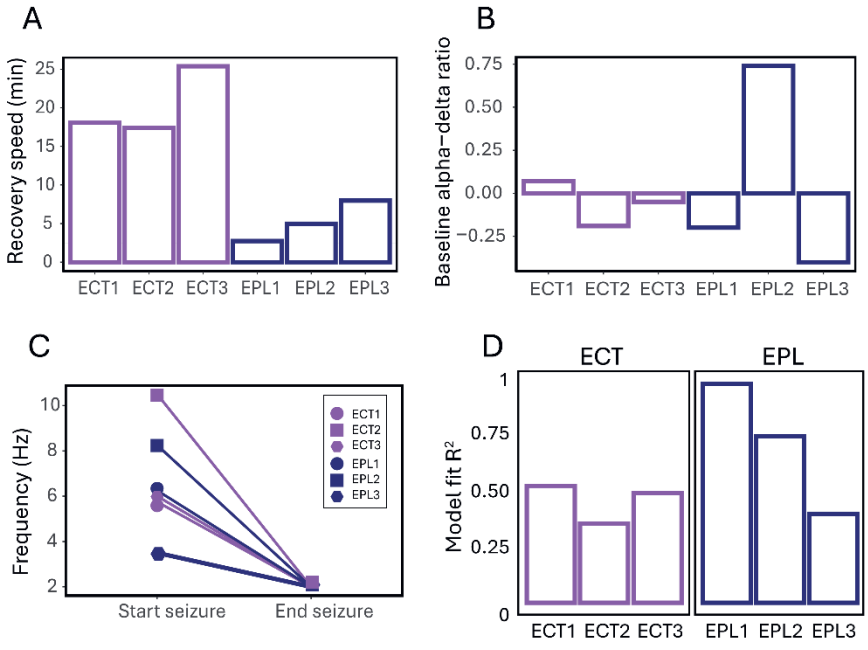


Figure 3.2 Postictal time constants, baseline alpha delta ratio, dominant ictal frequency, and model fit. (A) Postictal recovery speed in minutes (τ) for each patient. (B) Baseline alpha-delta ratios. (C) Dominant ictal frequency at the start and end of the seizure. Each line corresponds to one patient. (D) R^2 values representing the fit of the sigmoid model to the data, grouped by ECT patients (ECT) and epilepsy patients (EPL).

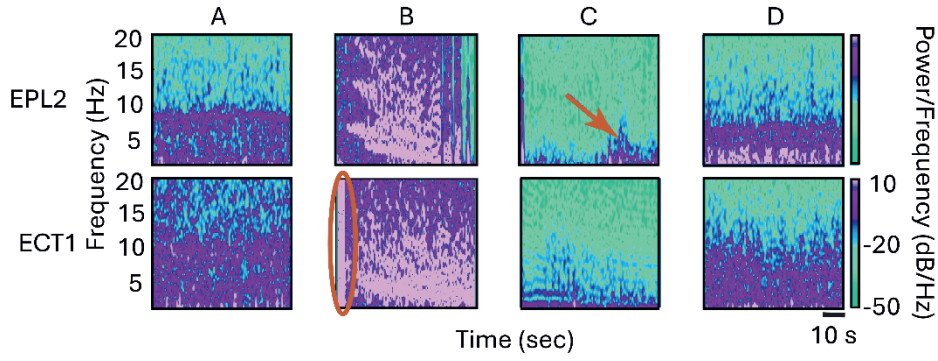


Figure 3.3 Spectrograms of an epileptic generalized seizure (patient EPL2) and an ECT-induced seizure (patient ECT1). A) Baseline, showing dominant frequencies in the alpha band. B) Seizure activity with decline of dominant frequency in the theta band and is preceded in ECT-patient by the ECT-stimulus 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). Epoch length 60 s. The red arrow indicates movement artifacts in the immediate postictal state. Time-frequency representations of the other four patients are presented in the supplementary material (Figure S3.1).

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 min and 2 – 15 Hz in patient ECT2 at t = 60 min.

Postictal evolution of alpha-delta ratio showed a similar trend in ECT-induced and epileptic seizures (Figure 3.4). In both groups, a steady increase from predominant delta towards alpha frequency occurred. Speed of postictal EEG recovery was faster in epilepsy patients than ECT patients (τ min-max: 1.93 – 10.55 min in epilepsy patients, 8.32 – 13.43 min in ECT patients). In ECT-induced seizures, predominant delta activity was present at the end of recordings, while ratios partially recovered towards baseline at t = 75 min, t = 60 min, and t = 40 min (patients ECT1, ECT2 and ECT3, respectively). In epileptic seizures, recovery to baseline was not observed (t = 18 min, t = 28 min, for patients EPL1, EPL 2, respectively).

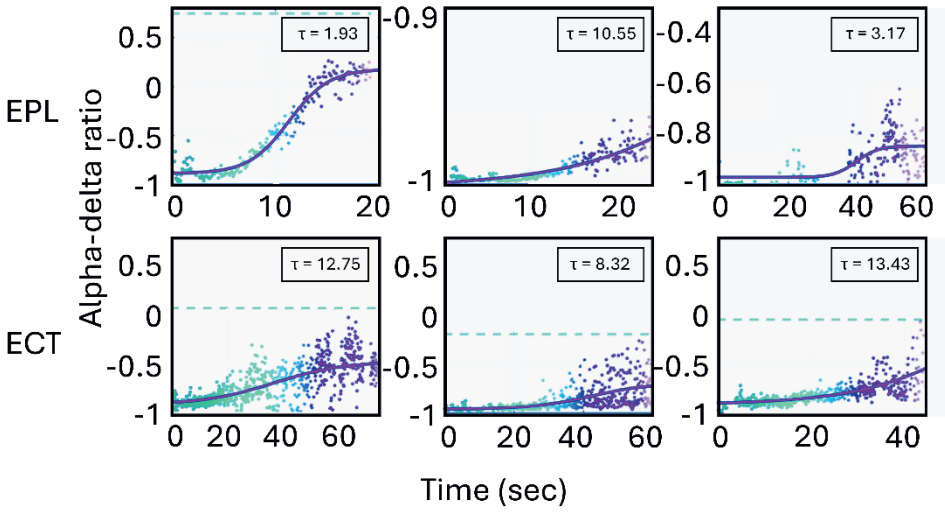


Figure 3.4 Postictal alpha-delta ratio. The top row shows patients ECT1, ECT2, and ECT3. The bottom row shows patients EPL1, EPL2, and EPL3. A negative value indicates relatively more delta than alpha activity. The red line indicates the curve fit with a sigmoid function. The blue line indicates baseline 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.

Severity of clinical postictal symptoms seem 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 τ = 12.75 min. Patient ECT2 reported a headache and was slightly confused, corresponding with τ = 8.32 min. Patient ECT3 had the longest speed of EEG recovery (τ = 13.43 min), 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 τ = 10.55 min. Patient EPL3 had muscle ache and fatigue, with τ = 3.17 min. Postictal symptom reports were not available for patient EPL1.

3.4 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 (122, 175). 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, show similarities as well (155-157). 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 (33). 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 (109, 151). 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 (151, 176).

Postictal recovery is characterized by postictal EEG suppression followed by slow wave activity. Subsequent normalization of EEG rhythms was indicated by a change in temporo-spectral 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 anaesthetic effects, which were absent in tonic-clonic seizures. EEG alpha and delta activity are both influenced by anaesthetic drugs and may degrade at different speed in patients, thereby affecting and possibly prolonging postictal recovery after ECT-induced seizures (177, 178).

Interictal slowing has been described in recurrent seizures, both in ECT and in epilepsy patients. In dated ECT literature, increasingly slow activity (i.e., < 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 (175, 179). Both severity and persistence of EEG-slowing were proportional to the number of administered ECT-sessions (179). This interictal EEG-slowing has also been described in patients with recurrent spontaneous seizures (180).

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 (176, 181). Second, even though artifact rejection was performed, movement may still exert influence on our quantitative analyses. Third, additional medication, as benzodiazepines, antiepileptics and antidepressants, differed between the epilepsy and ECT patients, which may have influenced EEG characteristics and interpretation of our results (182, 183). 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 (i.e., anesthesia, concomitant psychopharmacological drugs) need to be considered. For example, previous research has shown that ketamine prolongs postictal generalized EEG suppression (165). 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 (170). 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 which 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.

3.5 Supplementary material

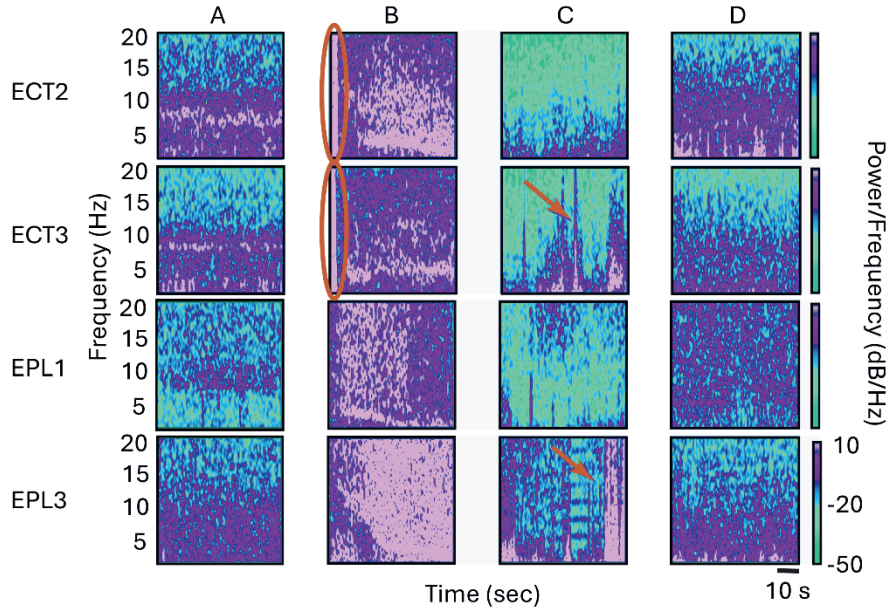


Figure S3.1 Spectrograms of ECT-induced and epileptic generalized seizures. Rows 1-4 show patients ECT2, ECT3, EPL1, and EPL3, respectively. (A) Baseline, showing dominant frequencies in the alpha band and lower frequencies (0.5 – 5 Hz). Seizure activity (B) Decline of dominant frequency in the theta band and is preceded in both ECT patients by the ECT-stimulus artifact (red circles). (C) Postictal suppression follows. (D) Return of EEG activity with frequencies 1 - 18 Hz at t = 60 min (patient ECT2), 1 - 10 Hz at t = 45 min (patient ECT3), 1 - 20 Hz at t = 18 min (patient EPL1), and 1 – 15 Hz at t = 60 min (EPL3). Note the artifacts during postictal suppression (i.e., bursts of activity). The arrows in the immediate postictal state (C) indicate movement artifacts as well as artifacts due to removing ECT-electrodes. Epoch length was 60 s.

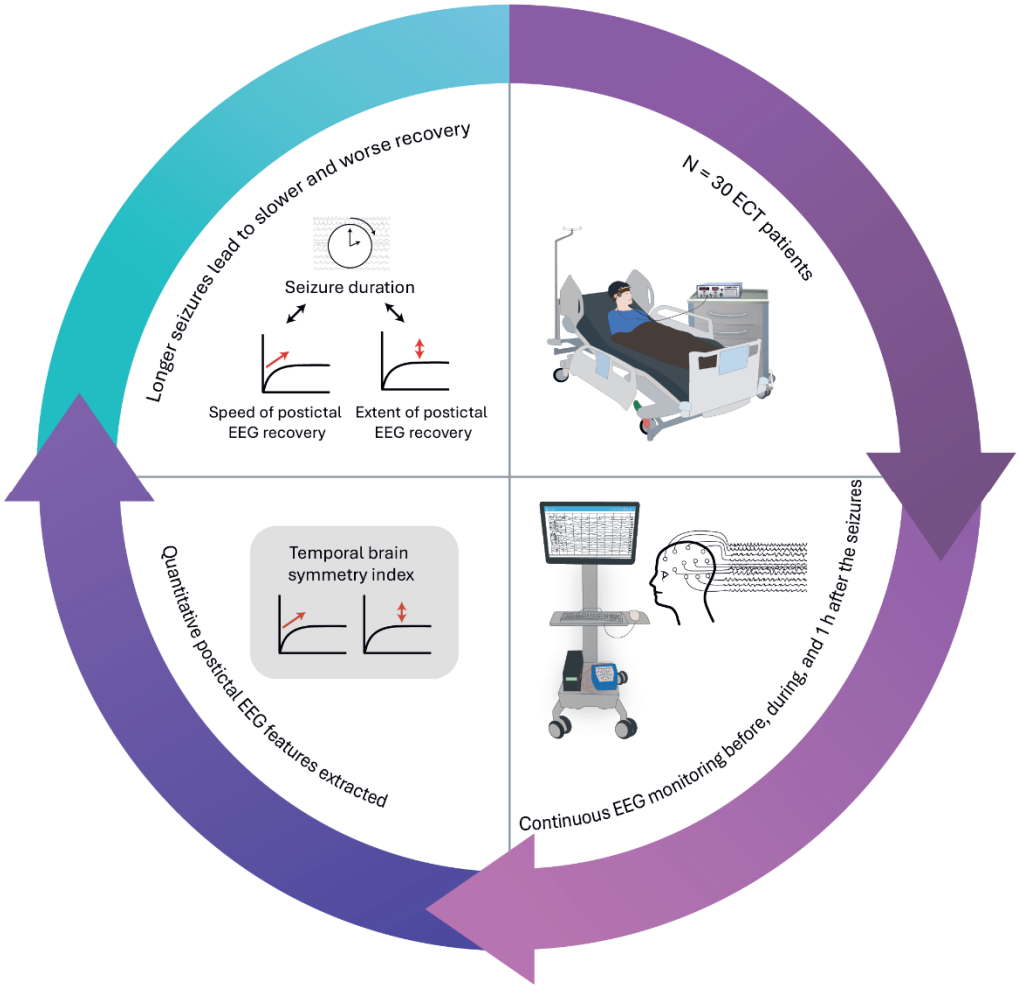
Chapter 4

Seizure duration predicts postictal EEG recovery after ECT-induced seizures

Pottkämper, J. C. M., Verdijk, J. P. A. J., Stuiver, S., Aalbregt, E., Schmettow, M., Hofmeijer, J., van Waarde, J. A., and van Putten, M. J. A. M.

Clinical Neurophysiology 2023; 148: 1-8

Graphical abstract



Abstract

Objective We aim to provide a quantitative description of the relation between seizure duration and the postictal state using features extracted from the postictal electroencephalogram (EEG).

Methods Thirty patients with major depressive disorder treated with electroconvulsive therapy (ECT) were studied with continuous EEG before, during, and after ECT-induced seizures. EEG recovery was quantified as the spectral difference between postictal and baseline EEG using the temporal brain symmetry index (BSI). The postictal temporal EEG evolution was modeled with a single exponential. The parameters of the model, including the time constant τ, describe the change and speed of postictal EEG recovery. The change from baseline EEG at t = 60 minutes post-seizure (ΔBSI) was calculated from the exponential fit. Postictal clinical reorientation time (ROT) was clinically established. A multivariate generalized multi-level Bayesian model was estimated with seizure duration and ROT as predictors of τ and ΔBSI.

Results EEG features of 290 seizures and postictal states were used for analyses. The model faithfully described the dynamics of the postictal EEG in nearly all patients. Seizure duration was associated with the recovery time constant, τ, and ΔBSI. ROT was associated with τ, but not with ΔBSI.

Conclusion Longer seizures are associated with slower postictal EEG recovery and more enduring EEG changes compared to baseline.

Significance Quantitative EEG allows objective assessment of the postictal state.

Key points

- Longer seizures increase the risk for postictal symptoms, however, their relationship is complex and research is scarce
- *Speed*, but not *extent*, of EEG recovery was associated with clinical reorientation, highlighting the clinical usefulness of this quantitative measure
- Longer seizures were associated with slower postictal EEG recovery and more deviation from baseline at one hour after the ECT-induced seizure
- More previous seizures were related to slower postictal EEG recovery, suggesting a cumulative effect of seizures
- Even though all patients recovered clinically at the end of our recordings, we were still able to observe clear EEG changes

4.1 Introduction

The postictal state after an epileptic seizure is characterized by neurological and psychiatric symptoms, such as impaired consciousness, headache, confusion, cognitive impairments, anxiety, and rarely psychosis (36, 38, 162). Not much is known about the underlying pathophysiology of these symptoms, although seizure terminating mechanisms such as enduring neuronal inhibition, disturbed excitation-inhibition balance within the brain, and changes in cerebral perfusion have been suggested (15, 162). A deeper insight into patient and seizure factors associated with postictal symptoms may contribute to identification of treatment targets. However, investigating the postictal state in epilepsy patients is challenging because seizures are unpredictable in nature (184, 185).

The relationship between seizure duration and postictal recovery is complex. In animals, prolonged seizures may manifest a variety of postictal cognitive and behavioral impairments, which probably generalizes to epilepsy patients (15, 36, 46, 186, 187). In patients, longer lasting generalized tonic-clonic seizures (i.e., duration up until 250 seconds) are associated with a clinically manifest postictal state, whereas the relatively short-term absence seizures are not (162, 188, 189). The extent of the tonic phase, but not total seizure duration, has been related to postictal generalized electroencephalographic (EEG) suppression, which in turn seems to be related to a more extensive clinical postictal state (190).

Most studies on the postictal state are hampered by ambiguous definitions of seizure and postictal state duration. Seizure duration is mostly defined based on the EEG, as the time interval between the onset of rhythmic brain activity and the end of ictal discharges or occurrence of postictal generalized EEG suppression. Clinical manifestations as tonic stiffening, self-reported aura, or epileptic motor activity play a supporting role (184, 191). Otherwise, postictal state duration is mostly defined based on clinical features alone, as the time between the end of the motor seizure and recovery of consciousness and motor function (102, 192). For more precise clinical quantification, the postictal state can be described by using questionnaires measuring the postictal reorientation time (ROT), a measure which is based on recovery of consciousness, motor function and the reorientation in time, place, and person (102, 193). However, all these clinical estimates are prone to subjectivity and lack of precision (194).

In this study, we use quantitative EEG features of the postictal state, in addition to the ROT, to study the relationship between seizure duration and postictal recovery. Since a systematic observation of ictal and postictal EEG is challenging in patients with epilepsy, we studied electroconvulsive therapy (ECT)-induced seizures (184). ECT is the most effective treatment for patients suffering from treatment-resistant depression. Findings from ECT-induced seizures can probably be extrapolated to seizures in epilepsy patients, as clinical and EEG manifestations are essentially similar (184). Recent EEG studies have shown that disruptions of background EEG rhythms can last up to 24 hours or longer after seizures, but the speed of recovery has not yet been quantified (36, 102, 162, 184). We hypothesized that seizure

duration is correlated with the speed of postictal EEG recovery and enduring postictal deviation from baseline, and that the postictal ROT is correlated with speed and extent of postictal EEG recovery.

4.2 Methods

4.2.1 Study design

This is an ad hoc analysis of EEG data of patients included in the StudY of effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT (SYNAPSE; NCT04028596) (35). SYNAPSE is an ongoing randomized cross-over trial with repeated measures of EEG and ROT in patients before, during, and until one hour after an ECT-induced seizure (35). In the current analyses, we included all available EEG measurements of the baseline, ictal and postictal state. Furthermore, prospectively collected clinical variables (age, sex), used electrode placement (i.e., right [RUL], left [LUL] unilateral, or bifrontotemporal [BL]), used charge to induce the seizure (in milliCoulombs [mC]), and the necessity to use medication directly after the seizure to treat severe postictal symptoms (e.g., severe motor restlessness, agitation, anxiety) were included.

4.2.2 Patients

Patients aged ≥ 18 years and treated with ECT for depressive episodes in Rijnstate Hospital, Arnhem, The Netherlands, with no contraindications for EEG and who were able to give oral and written informed consent, were included in our study.

4.2.3 ECT procedure

ECT was administered according to the Dutch treatment guidelines (21). Electrode placement included RUL according to d'Elia, LUL, and BL positioning (24). The Thymatron System IV device (Somatics Incorporation Lake Bluff, Illinois, USA) was used, delivering ECT stimuli with a constant-current (0.9 Ampère), bidirectional, square wave, and brief pulse (1 millisecond). Before administration of the anesthetic (i.e., etomidate 0.2-0.3 mg/kg body weight) and muscle relaxant (i.e., succinylcholine 0.5-1 mg/kg), patients were pre-oxygenated at 100% O_2. Ventilation was continued with positive pressure until resumption of spontaneous respiration after the procedure. If needed, additional pre- (e.g., methyl-atropine, flumazenil) and post-ECT medications (e.g., benzodiazepines, propofol) were provided at the discretion of the treating psychiatrist and anesthesiologist, and were registered accordingly. Concomitant medication use (e.g., antidepressants, antipsychotics, benzodiazepines, somatic medications) was kept constant during the ECT-course.

4.2.4 EEG recordings

Twenty silver/silver chloride cup electrodes were applied according to the International 10-20 system and fixated using EC2 paste. EEGs were recorded using

a NeuroCenter EEG recording system (Clinical Science Systems) and a full-band direct-coupled amplifier (TMSi). For pragmatic reasons, some EEG recordings were performed with a reduced montage with eleven electrodes. A reduced montage consisted of electrodes Fp2, Fp1, C3, C4, T3, T4, O2, O1, Fz, Cz, and Pz. For patients treated with BL ECT electrode placement, F7, F8, T3, and T4 were placed 10% above (F) or behind (T) the pre-defined position to make space for ECT electrodes. In case of RUL or LUL ECT electrode placement, left or right electrodes (i.e., for LUL: F7 and T3) and Cz were moved. Impedances were kept below 5 kΩ. EEGs were sampled at 256 Hz. Prior to each ECT-session, baseline resting-state EEGs of 5 min eyes closed were recorded, followed by continuous EEG registration during the seizure up until one hour of the postictal state.

4.2.5 EEG preprocessing

EEGs were manually inspected in a bipolar montage for artifacts. Channels with excessive noise, flatlines, or epochs with excessive (motion) artifacts were excluded from further analyses. EEGs were band-pass filtered between 1-25 Hz with a first order Butterworth filter and converted to a bipolar montage for post-processing. All EEG analyses and pre-processing steps were conducted with MATLAB R2010a (MathWorks, Natick, MA, USA). Only in one patient, EEGs had to be band-pass filtered from 3-13 Hz in order to make use of the available data, because of contamination with respiratory and muscle artifacts.

4.2.6 Clinical reorientation time

Clinical reorientation time was assessed using the ROT scale (193). This is a validated method to estimate recovery of cognitive function after ECT (194). In short, after the seizure, during the postictal state, patients were asked five questions every five minutes regarding their orientation in person (name, birthday), place (name of hospital), and time (age, day of week). The time in minutes between seizure onset and the moment that at least four of five questions were answered correctly for the first time (respective to baseline) was defined as the 'reorientation time'. ROT measures started at 5 minutes after the ECT-stimulus and continued up to 100 minutes. In case a patient was not reoriented within 100 minutes, the maximum time score (100 minutes) was given.

4.2.7 Seizure duration

To estimate the total seizure duration, the time interval in seconds between seizure onset and offset points was visually determined in the EEG. Seizure onset was defined as onset of rhythmicity or spike-wave complexes, including waveform repetition with relatively uniform morphology and duration. Seizure offset was defined as onset of postictal generalized EEG suppression, which was characterized by low amplitude in all channels (<10μV) of at least two seconds duration (77, 172, 184). If postictal generalized EEG suppression did not occur, seizure offset was determined based on the last occurring epileptiform spike-wave complex.

4.2.8 Speed and extent of postictal EEG recovery

To estimate *speed* and *extent* of postictal EEG recovery, we used the temporal Brain Symmetry Index (BSI) (195, 196). The BSI measures bilateral temporal evolution respective to a pre-defined baseline and not hemispheric asymmetry (196). In our study, the BSI was used as a metric of postictal EEG dynamics, referring to a pre-recorded baseline before the ECT-induced seizure to determine postictal EEG recovery.

Artifact-free 5 sec epochs were used for calculation of spectral characteristics. Welch's averaged periodogram method was used to estimate spectral density. Normalized absolute spectral differences between considered postictal epochs and baseline epoch (5 min eyes-closed) were calculated, using

$$BSI = 1 - \frac{1}{N}\sum_{i=1}^{N}\frac{1}{K}\sum_{j=1}^{K}\left\|\frac{S_{i,j}-S_{ref,i,j}}{S_{i,j}+S_{ref,i,j}}\right\| \qquad (1)$$

where $S_{i,j}$ were Fourier coefficients belonging to frequency i = 1, ..., *N* of bipolar derivations j = 1,2, ..., *K*. $S_{i,j}$ were postictal segments and $S_{ref,i,j}$ were baseline segments. Postictal segments started from seizure offset and ended at the end of the recording (range = 30 – 60 min). Values range between [0,1], with BSI = 0 indicating maximal difference with baseline EEG frequency characteristics and BSI = 1 perfect similarity with the baseline EEG.

To obtain a recovery curve that reflect the return of EEG activity, we subsequently fitted an exponential function

$$a_0 - a_1\, e^{-\frac{t}{\tau}} \qquad (2)$$

to the mean of BSI values per minute as a function of time, with parameters a_0 (asymptote), and a_1, and time constant τ. A cut-off of goodness-of-fit of 70% or higher was used to evaluate recovery curves as reliable.

We obtained two measures for the postictal EEG dynamics from the recovery curves (Figure 4.1). First, as a metric for *how fast* the EEG returns to its asymptotic or stationary value, we used the time constant τ. *Speed* of postictal EEG recovery is indicated by ~$(1/\tau)$. Second, to estimate the *extent* of postictal EEG recovery, we extrapolated the BSI value to 60 minutes using the postictal curves and considered the difference from baseline, ΔBSI. The ΔBSI has values between 0 and 1 where smaller ΔBSI values indicate more difference between the baseline and the postictal EEG at one hour postictal, reflecting enduring postictal EEG disturbance (i.e., less postictal recovery).

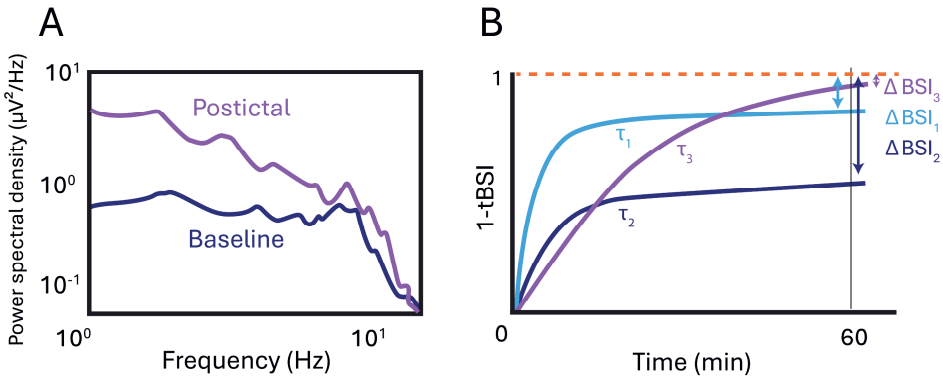


Figure 4.1 Schematic representation of power spectrum densities (A) and postictal electroencephalographic (EEG) recovery (B). Left panel: Example of baseline (blue) and postictal (purple) EEG power spectrum density. The baseline EEG has a peak frequency approximately 9 Hz. The postictal spectral density was obtained from an EEG segment recorded at 45 min after the seizure and shows a strong increase in the power of the frequencies between 1-8 Hz. Right panel: Recovery curves, using Eqn (2), for three hypothetical patients. The red-dashed line is the pre-ictal baseline. The light blue curve reflects the fastest evolution towards the asymptotic value (smallest τ_1), followed by the dark blue curve and purple curve, τ_2 and τ_3. The enduring postictal deviation from baseline (ΔBSI; brain symmetry index) reflects the *extent* of recovery, with patient 2 presenting more deviation (ΔBSI_2) from baseline compared to patient 1 (ΔBSI_1) at t = 60 min, which can be interpreted as less recovery to baseline. Patient 3 presents a slower recovery (larger τ_3), but with less deviation from baseline (ΔBSI_3) at t = 60 min.

4.2.9 Statistical analysis

Medians and interquartile ranges (IQR) are presented for continuous variables and numbers and percentages for categorical variables. Medians were chosen as the continuous variables were non-normally distributed. We developed a multivariate multilevel generalized linear model, using Bayesian methods (197, 198).

The multivariate multilevel generalized linear model was performed to account for within-subject correlation in longitudinal data analysis and non-normal distributions (199). The parameters τ and ΔBSI were treated as response variables. 'Number of previous seizures' (defined as N-1 with N the number of the ECT-sessions during the course in which the EEG measurement took place) and 'patient' were included as random effects to account for individual differences at baseline and allowing the model to estimate changes over time per patient. Because we could not *a priori* assume that the standard deviation of both response variables was constant over the treatment course, we chose a beta response distribution for τ and lognormal distribution for ΔBSI. This also accounts for the bounded range of both outcome variables that may further exhibit a non-symmetrical distribution. Default priors (i.e., weakly informative priors) were

chosen, as this was - to our knowledge - the first study to introduce postictal EEG recovery time constants and prior information on parameter estimates. The variables seizure duration, ROT, and number of previous seizures were included as fixed effects. To summarize our results (i.e., posterior distribution), we computed the 2.5%, 50%, and 97.5% quantiles, resulting in center estimates which represented the best guess for the true strength of the effect, and 95% credibility limits. Credibility intervals indicate how certain we can be about a center estimate. With narrow intervals, we are very certain that the true strength of the effect is close to center, whereas wide limits leave room for a much stronger or weaker true value. Due to the bounded response range, our model used the logarithm and logit links for linearization, which is a standard technique in generalized linear models (200). Note that for loglinear models the coefficients of the model are multiplicative, meaning that center estimates above (or below) 1 show a positive (or negative) association with the outcome. All statistical analyses were computed using R using the package brms (201, 202).

4.3 Results

4.3.1 Patient characteristics

Thirty patients with, in total, 305 EEGs were included in this study (median age 50 years; IQR = 22.5 years; range = 24 – 82 years; n = 14 [47%] male sex). Out of 30 patients, 21 (70%) were treated with BL electrode placement, seven with RUL and two with LUL. Only one patient started with RUL and changed to BL electrode placement during the ECT-course.

Fifteen EEG measurements (5% of all measurements) were excluded based on poor model fit, yielding an inclusion of 290 EEGs. Median length of postictal recordings was 59 minutes (IQR = 7.2; range = 24.9 – 90.3 min). Median seizure duration was 52 seconds (IQR = 27.7; range = 6.4 – 266 seconds). In 131 out of 290 postictal states (45%), medication was needed to treat (severe) postictal symptoms (i.e., agitation, confusion, or restlessness). Median delivered charge during the ECT-course was 303.4 mC (IQR = 276.2; range = 23.4 – 813 mC). Median number of ECT-sessions during the total treatment course was 12 (IQR = 27.7; range = 7 – 100). One patient was treated with maintenance ECT causing the outlier in total number of sessions (i.e., 100 ECT-sessions); without this patient the range of total was 7-25 ECT-sessions.

4.3.2 Speed and extent of postictal EEG recovery and clinical reorientation time

In our sample (N = 290), τ ranged from 0.5 to 138 min (median = 6.13 min, IQR = 8.78 min) and ΔBSI ranged from 0.03 to 0.98 (median = 0.29, IQR = 0.12). In Figure 2, we show EEG epochs and the recovery curve as a function of time for two patients. Patient P2 had a larger time constant (τ = 35.1 min), which means a slower postictal recovery period, than patient P17 (τ = 7.72 min).

Clinical reorientation time, measured with ROT, ranged from 5 to 100 min (median = 35 mins; IQR = 20 min). In 18 of 290 postictal states (6%), the ROT exceeded 100 minutes, which occurred in 7 patients. In 245 of 290 postictal states (84%, n = 16 patients), complete clinical reorientation was shown within our 60 minutes continuous EEG measurement. None of the patients reached EEG baseline levels (i.e., ΔBSI = 1) at the time that complete clinical reorientation was achieved. Figure 4.3 shows τ and ΔBSI values across the ECT-course plotted against seizure duration and ROT.

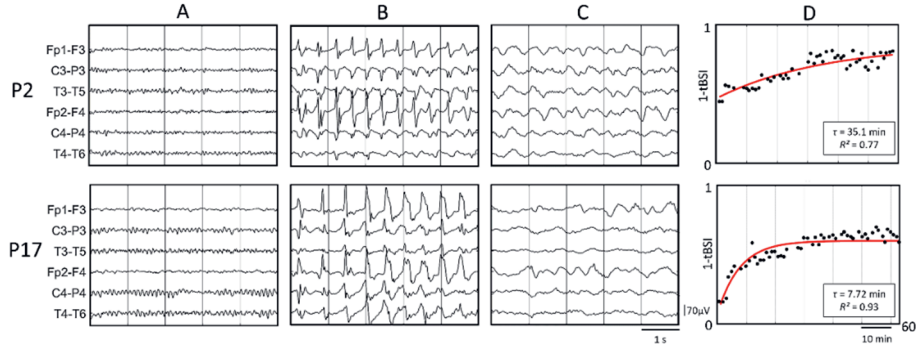


Figure 4.2 EEG epochs (panels A-C) and temporal brain symmetry index (panels D) as a function of time from patient P2 and P17. (A) Baseline, eyes closed. (B) Seizure activity. (C) Postictal slowing. (D) Evolution of the temporal brain symmetry index (BSI) for the first 60 minutes after the seizure. Goodness-of-fit indicated by R^2. Patient P2 had a larger time constant, τ, reflecting a slower postictal recovery than patient P17. Filter settings 1-25 Hz.

4.3.3 Seizure duration related to speed and extent of postictal EEG recovery

The results of the generalized mixed model relating seizure duration with τ and ΔBSI (including ROT and number of previous seizures as fixed effects) are presented in Figure 4.3.

The center estimate and 95% credibility limits (CI95) for seizure duration on τ and ΔBSI were only slightly larger than 1, but - given the tight CI95 around 1 – it confirmed a weak positive association (1.004 s [CI95 1.000, 1.009] and 1.003 s [CI95 1.001, 1.005], respectively). The effect of seizure duration on τ looks very small, but recall that this effect is in seconds. In order to illustrate the magnitude of the effect, we compared the predicted value of the shortest to the longest *speed* and *extent* of postictal EEG recovery. We calculated this by taking the multiplication factor to the power of the difference between the maximum and minimum seizure duration, $1.004\ s^{\ 266-6.4}$ = 2.82 for τ and $1.003\ s^{\ 266-6.4}$ = 2.18 for ΔBSI. This implies that the longest seizure with 266 seconds had an almost three times longer *speed* of EEG recovery and twice as much deviation in the postictal

EEG compared to the shortest seizure. Parameter estimates are presented in Table 4.1.

4.3.4 Clinical reorientation time related to speed of EEG recovery

A weak positive association of ROT with τ (1.005 min [CI95 1.000, 1.011]) was found, but not with ΔBSI (1.001 min [CI95 0.998, 1.004]). This effect could be illustrated as a 1.6-fold increase in *speed* of postictal EEG recovery compared to the shortest clinical reorientation time ($1.005\ min^{\ (100-5)} = 1.61$).

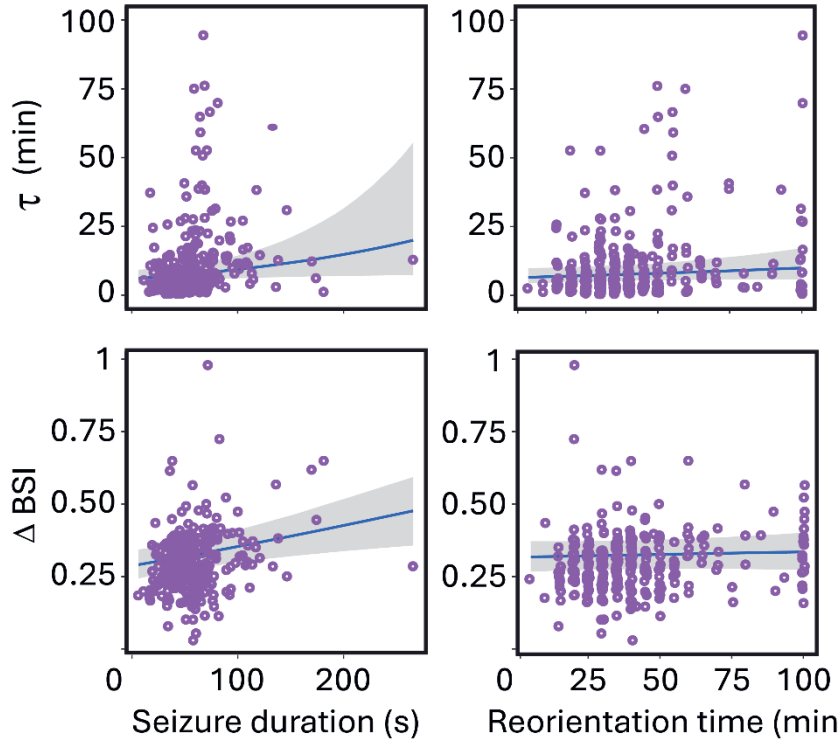


Figure 4.3 Time constant τ (reflecting the *speed* of postictal EEG recovery (~1/τ); upper panels) and ΔBSI (*extent* of postictal EEG recovery, brain symmetry index; lower panels) as a function of seizure duration and clinical reorientation time (ROT). τ was related to seizure duration and ROT. ΔBSI was related to seizure duration, but not ROT. Data are presented as averaged values per patient. Marginal effects (blue lines) were estimated from the model, representing how τ and ΔBSI are affected when seizure duration or ROT increase.

4.3.5 More previous seizures related to slower EEG recovery

The number of previous seizures showed a weak positive relationship with τ (1.029 [CI95 1.000, 1.064]) and no relationship with ΔBSI (1.000 [CI95 0.976, 1.027]; Figure 4.3). This implied that, the more previous seizures the patients had experienced during the ECT-course, the slower their EEGs progressed to baseline in the late postictal state. This effect could be illustrated as a factor 1.5-fold increase of τ, (i.e., slower speed of postictal EEG recovery) with 14 previous seizures compared to no previous seizures (i.e., $1.029^{(14-0)} = 1.49$).

Table 4.1 Parameter estimates with 95% credibility limits

Parameter	Center and 2.5% and 97.5% credibility interval limits	Interpretation
Intercept τ[a]	3.330 [2.127, 5.266]	
Seizure duration (s) – τ (min)	1.004 [1.000, 1.009]	Weakly positive association
Number of previous seizures – τ (min)	1.029 [1.000, 1.064]	Weakly positive association
ROT (min) – τ (min)	1.005 [1.000, 1.011]	Weakly positive association
Intercept ΔBSI[b]	0.368 [0.294, 0.462]	
Seizure duration (s) - ΔBSI	1.003 [1.001, 1.005]	Weakly positive association
Number of previous seizures - ΔBSI	1.000 [0.976, 1.027]	No association
ROT (min) - ΔBSI	1.001 [0.998, 1.004]	No association

[a]τ = Time constant indicative of *speed* of postictal EEG recovery
[b]ΔBSI = *Extent* of postictal EEG recovery measured as enduring postictal deviation from baseline (brain symmetry index)
ROT = Reorientation time

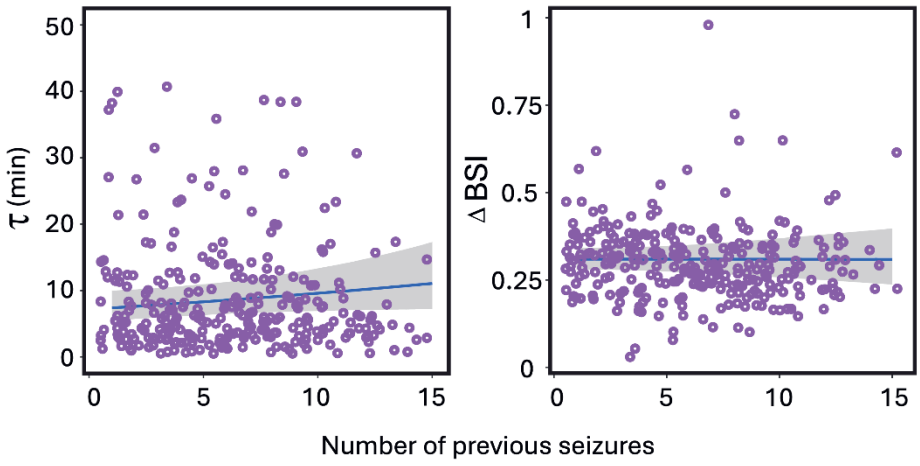


Figure 4.4 Time constant τ (reflecting the *speed* of postictal EEG recovery; left panel) and ΔBSI (*extent* of postictal EEG recovery, brain symmetry index; right panel) as a function of number of previous seizures in all patients (n = 30). τ but not ΔBSI was (weakly) related to the number of previous seizures. Blue lines represent marginal effects.

4.3.6 Sensitivity analyses

Because postictal use of benzodiazepines for agitation, as well as the chosen electrode placement and administered electrical charge (both determining the current flow through the patients' brains and - therefore - seizure onset zones), may have influenced the EEG recovery, sensitivity analyses were applied. The use of benzodiazepines, electrode placement, and electrical charge were included as fixed effects in the model, showing a positive trend of administration of benzodiazepines, i.e., probably positively influencing τ (1.390 [CI95 0.765, 2.468]) as well as ΔBSI (1.187 [CI95 0.871, 1.646]). These center estimates were larger than 1, but the wide ranges of CI95 prevented definite conclusions. Electrode placement (i.e., unilateral) had a strong negative association with τ (0.545 [CI95 0.319, 0.909]) and a probably weak negative association with ΔBSI (0.936 [CI95 0.714, 1.210]). However, for ΔBSI, CI95 were wide and upper limits beyond 1, preventing definite conclusions. In the sensitivity analyses, associations between seizure duration and ROT with τ remained (1.003 s [CI95 1.000, 1.008] and 1.005 min [CI95 1.000, 1.011], respectively). No associations were found between seizure duration and ROT with ΔBSI (0.997 s [CI95 0.995, 0.999] and 0.999 min [CI95 0.996, 1.002], respectively). The positive association with the number of previous seizures and τ remained (1.042 [CI95 1.005, 1.080]). Electrical charge did not have any associations with τ or ΔBSI (0.999 mC [CI95 0.998, 1.000] and 1.000 mC [CI95 0.999, 1.001], respectively).

4.4 Discussion

We report on a detailed assessment of the relation between seizure duration and postictal EEG recovery. The postictal EEG was quantified as the spectral difference from baseline EEG, where the temporal dynamics could satisfactory be modeled by a single exponential with time constant τ. We show that the *speed* ~(1/τ) and *extent* (ΔBSI) of postictal EEG recovery are related to seizure duration. Clinical reorientation time is associated with the speed, but not the extent, of postictal EEG recovery. During the ECT-course, the speed of postictal EEG recovery slows down, but the extent of the EEG recovery does not change, suggesting that having recently had more seizures affects the postictal EEG.

4.4.1 Longer seizure duration is associated with slower and less postictal EEG recovery

A key finding of this study is that a longer seizure duration leads to slower recovery of the EEG and more enduring deviation from baseline. This suggests that dynamic ictal processes are related to how fast and to which extent patients recover after seizures. Earlier work suggested that longer ECT-induced seizures increase the risk of severe postictal symptoms, such as postictal delirium or agitation (15, 25, 203, 204). Our results are in line with these findings: a longer ROT was associated with a larger τ, which was also correlated with longer seizures. The pathophysiological mechanisms are still unclear. Postictal clinical symptoms may be explained by prolonged cerebral hypoxia which may result from insufficient ventilation during seizures or cerebral vasoconstriction, or both (15, 205). However, whether cerebral hypoxia is important in ECT is debated, because only very short seizure durations (e.g., typically less than one minute) are elicited under optimal conditions (e.g., 100% oxygen saturation of the patient) and no signs of persistent brain damage after the procedure have been identified (8). Another recently developed hypothesis is based on brain clearance: the glymphatic system is partly responsible for cleansing excessive glutamate and K+ from the brain at seizure termination (206). This hypothesis may explain postictal generalized EEG suppression and subsequent recovery of slower and faster frequencies (206).

4.4.2 Clinical reorientation time versus postictal EEG recovery

The ROT was weakly positively associated with τ, but not with ΔBSI. This reflects that patients who needed a longer time to reach reorientation after their seizure showed slower speed of EEG recovery. In our sensitivity analyses, correcting for known clinical determinants of the ROT (i.e., postictal use of benzodiazepines, electrode placement, and applied electrical charge), independent associations between ROT and τ remained (i.e., 1.005 [CI95 1.000, 1.011], respectively)(193). This may imply that τ, as derived EEG parameter, may serve as an objective and reproducible variable in human studies of the postictal state.

In previous research, using bispectral index monitoring (BIS) with three EEG electrodes, longer ROT was found to correlate with longer duration of postictal EEG

suppression (207). If longer postictal EEG suppression is indicative of a longer postictal state, we may assume that also clinical postictal symptoms are more pronounced with extensive postictal suppression (207). In studies of epilepsy patients, though, seizure EEG characteristics did not influence postictal recovery of awareness (192, 208). However, in these studies, definition of recovery of awareness was based on any verbal communication or occurrence of motor function and therefore likely to present floor effects. Our study showed no association between the extent of postictal EEG recovery (i.e., ΔBSI) and clinical reorientation (i.e., ROT). This seems not in line with prolonged postictal symptoms related to extensive postictal EEG suppression, but studies are not comparable with respect of EEG recording and included patient groups. Further studies may examine different EEG electrode placement (e.g., related to frontal brain areas) and calculations of exponential recovery functions related to clinical measures of patients' postictal state.

In 245 of 290 postictal states (84%), our patients (n = 16; 53%) showed complete clinical reorientation within the 60 minutes postictal continuous EEG measurement. However, not a single patient had reached EEG baseline levels (i.e., ΔBSI = 1) at the time that complete clinical reorientation was achieved. This indicates that EEG recovery up until a certain point is sufficient for the basic cognitive functions assessed by the ROT, but that the ROT is not sensitive enough to capture complete electrophysiological restoration of brain functioning. This lack of sensitivity may be due to the very rough clinical ROT measurement we used, which measured only a very limited set of cognitive functions (i.e., orientation in time, place, and person) and only every five minutes. Moreover, at baseline before the consecutive ECT-session, some patients already showed difficulties to remember the day of the week. However, the cut-off for ROT allowed one lacking or wrong answer out of five questions, correcting for some variance. We conclude that although the patients' reorientation in time, place, and person is complete, we still may observe clear changes in the postictal EEG. This may reflect temporary dysfunction of other clinical readouts that are not 'captured' by the psychometric instrument ROT.

4.4.3 Repeated exposure to seizures is associated with slower speed of postictal EEG recovery

Patients with more previous seizures (i.e., who already had more ECT-sessions in the course of their treatment), appeared to have progressively slower speed of EEG recovery (i.e., a larger τ). It is well-known that progressive memory problems may occur in patients during the ECT-course (209, 210). We hypothesize that increasing cognitive problems may be associated with progressively slower EEG recovery, as this may imply that these patients may remain longer in the postictal state. Because in clinical practice patients are usually treated with ECT two to three times a week, their EEGs show slower recovery, and therefore may not recover completely from the postictal state of previous seizures. The extent of EEG recovery

was not associated with repeated exposure to seizures, which may mean that recovery to a 'baseline' does not define the extent of the postictal state entirely.

4.4.4 τ and ΔBSI as postictal EEG-features

This is the first study estimating speed and extent of postictal EEG recovery. We could estimate our EEG features τ and ΔBSI from the exponential recovery function in more than 95% of EEGs, which advocates for their feasibility and reproducibility to investigate the postictal state. Recovery curves could not be modeled in only some EEGs (5%) with our single exponential (cf Eqn. 2). This may imply that postictal EEG recovery does not always show a *gradual* development, but may occur in phases that cannot be captured by a single exponential. Thus, our method cannot be used for all ECT-induced or spontaneous seizures. In addition, baseline EEGs were collected during resting-state conditions, while patients were partly sleeping or drowsy during the postictal state, having significant influences on their EEGs. This results in a potential additional variation in the estimation of the ΔBSI.

4.4.5 Strengths and limitations

The strength of this study is the systematic, prospective collection of clinical and continuous EEG data before, during, and after seizures. Limitations include the following. The current study is part of an intervention trial investigating effects of vasodilatory treatments on the postictal state. Therefore, our study medication (i.e., acetaminophen or nifedipine or placebo) may have influenced postictal EEGs. However, since ECT-patients - as well as patients with epilepsy - usually use a variety of medications (including analgesics and antihypertensives), we may interpret our study treatment representative for current care. Furthermore, patients were supplemented with 100% O_2 and active ventilation (lowering CO_2 levels) which may have influenced the EEGs preictally. Also, administration of postictal benzodiazepines occurred in 45% of the postictal states and may also have influenced postictal EEGs. Our sensitivity analyses showed a positive trend of administration of benzodiazepines on τ and ΔBSI. However, wide ranges of CI95 prevent definite conclusions regarding this relationship. Propofol has been administered for one patient as post-ECT medication due to severe postictal agitation, which may have prolonged postictal EEG recovery (211).

We used Bayesian statistics for our analyses, because a frequentist approach might have had several practical and theoretical disadvantages. The frequentist approach would have dichotomized results into being 'significant' or 'non-significant', leading to the oversimplified and possible erroneous interpretation that non-significant results imply a 'negative trial' or showing an 'absence' of effect (212). The Bayesian approach has mainly been dictated by the complex requirements for an adequate model in the present study. For more information about Bayesian statistics and its advantages over the frequentist approach, we refer to other sources (212-214).

4.5 Conclusion

Slower postictal EEG recovery and more enduring deviation from baseline are associated with longer seizure duration in patients treated with ECT. More previous ECT-induced seizures contribute to slower postictal EEG recovery.

Chapter 5

Changes in postictal cerebral perfusion are related to the duration of ECT-induced seizures

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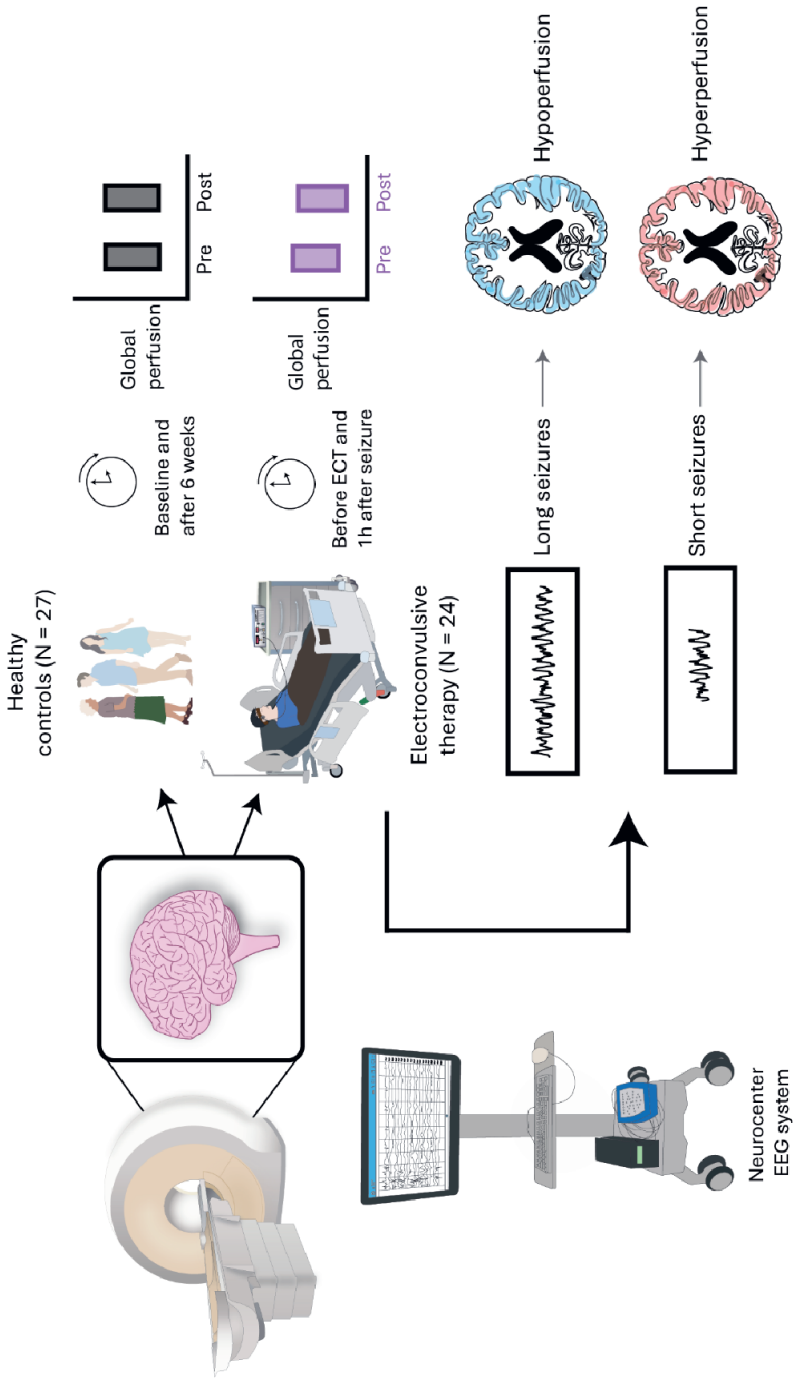
Epilepsia 2023

Graphical abstract



Abstract

Objective Postictal symptoms may result from cerebral hypoperfusion which is possibly a consequence of seizure-induced vasoconstriction. Longer seizures have previously been shown to cause more severe postictal hypoperfusion in rats and epilepsy patients. We studied cerebral perfusion after generalized seizures elicited by electroconvulsive therapy (ECT) and its relation to seizure duration.

Methods Patients with a major depressive episode who underwent ECT were included. During treatment, 21-channel continuous electroencephalogram (EEG) was recorded. Arterial spin labeling magnetic resonance imaging (ASL-MRI) scans were acquired before the ECT-course (baseline) and approximately one hour after an ECT-induced seizure (postictal) to quantify *global* and *regional* gray matter cerebral blood flow (CBF). Seizure duration was assessed from the period of epileptiform discharges on the EEG. Healthy controls were scanned twice to assess test-retest variability. We performed hypothesis-driven Bayesian analyses to study the relation between *global* and *regional* perfusion changes and seizure duration.

Results Twenty-four patients and twenty-seven healthy controls were included. Changes in postictal *global* and *regional* CBF were correlated with seizure duration. In patients with longer seizure durations, *global* decrease in CBF reached values up to 28 ml/100g/min. Regional reductions in CBF were most prominent in the inferior frontal gyrus, cingulate gyrus, and insula (up to ~35 ml/100g/min). In patients with shorter seizures *global* and *regional* perfusion increased (up to ~20 ml/100g/min). These perfusion changes were larger than changes observed in healthy controls, with a maximum median *global* CBF increase of 12 ml/100g/min and a maximum median *global* CBF decrease of 20 ml/100g/min.

Significance Seizure duration is a key factor determining postictal perfusion changes. In future studies, seizure duration needs to be considered as confounding factor due to its opposite effect on postictal perfusion.

Key points

- Electroconvulsive therapy-induced seizures lead to reductions in postictal *global* and *regional* cerebral blood flow, depending on seizure duration
- Longer seizures are associated with decreased postictal perfusion, while shorter seizures are associated with increased postictal perfusion one hour after ECT
- Investigating postictal perfusion after electroconvulsive therapy-induced seizures is feasible

5.1 Introduction

Following epileptic seizures, patients may display unresponsiveness, impaired cognition, headache, nausea, myalgia, delirium as well as psychiatric- or other neurologic manifestations (13, 162). These postictal symptoms may result from cerebral hypoperfusion as a consequence of seizure-induced vasoconstriction (15, 16). Postictal cerebral hypoperfusion has been observed up to an hour after seizures with widespread and regional perfusion and metabolic decreases. The brain regions involved may relate to the seizure onset zone (15, 109, 151, 215, 216). Increased postictal cerebral perfusion has been observed, too, but these studies were all hampered by small sample sizes and lack of correction for test-retest variability (15, 217-220). Seizure duration, seizure type, age, or timing of perfusion measurements may explain such divergent observations (15, 102, 112, 217-220).

Assessment of seizure duration and cerebral perfusion after spontaneous seizures is challenging. This has motivated us to study postictal perfusion in patients treated with electroconvulsive therapy (ECT)-induced seizures (170, 217). In ECT, mainly as treatment for severe depression, focal to bilateral tonic-clonic seizures are elicited by using an electrical stimulus, applied through two electrodes on a patient's head under anesthesia and with proper muscle relaxation (217, 221). Several characteristics of ECT-induced seizures, such as the type of ictal discharges and postictal electroencephalography (EEG) and clinical symptoms, appear similar to those of generalized seizures in epilepsy patients (184). This suggests that findings in studies that explore ECT-induced seizure characteristics, such as duration, and cerebral perfusion may be extrapolated to patients with epilepsy.

After ECT-induced seizures, previous studies showed divergent patterns of increased as well as decreased postictal cerebral perfusion in widespread bilateral cortical regions, in particular in specific frontal (i.e., inferior frontal gyrus, cingulate gyrus, insula) and subcortical regions (i.e., caudate, putamen, thalamus, midbrain, amygdala, hypothalamus, vermis) (170, 217, 219, 220). These opposite perfusion changes may be explained by differences in the timing of perfusion assessment. Perfusion measurements early in the postictal state (i.e., 10 – 30 min) mostly show increased cerebral perfusion, while later measurements (i.e., 45 – 60 min) may show decreased postictal perfusion. Measured after the complete ECT course (i.e., multiple induced seizures, mostly 10-20 sessions), increased cerebral perfusion in the thalamus was associated with worse cognitive impairment (222). Longer ECT-induced seizure duration was related to an increased risk of developing postictal delirium (25). To our knowledge, no studies examined the effect of seizure duration on global or regional cerebral perfusion after ECT-induced seizures.

In this study using arterial spin labeling magnetic resonance imaging (ASL-MRI) in patients with ECT-induced seizures, we investigated changes in postictal *global* and *regional* cerebral perfusion, compared to normal variation in healthy controls, and we relate changes in perfusion to seizure duration.

5.2 Methods

5.2.1 Study design

This study is an *post hoc* analysis of ASL-MRI data of patients included in the pre-registered prospective SYNAPSE study (NCT04028596), that had a randomized cross-over design to test vasodilatory drugs to reduce postictal symptoms (35). For the current analysis, we used ASL-MRI scans at baseline (< 1 week before start of the ECT-course) and 1 h after an ECT-induced seizure from each patient, but only in the control ('placebo') condition of SYNAPSE (i.e., a cup of water administered 2 h before ECT). To correct for normal variability over time and test-retest effects of the repeated ASL-MRI measurements, a group of healthy controls was included (ERB study number 2020-BC-12375), who were measured on the same MRI-scanner at two separate timepoints (i.e., baseline and after six weeks). Clinical variables (i.e., age, sex, regular smoking), electrode placement (i.e., unilateral [UL], or bifrontotemporal [BL]), number of ECT-session at ASL-MRI measurement (i.e., number of previous seizures before perfusion measurement), and applied charge to induce the seizure (in milliCoulombs [mC]) were registered.

5.2.2 Participants

We included 24 ECT patients and 27 healthy controls. Patients aged ≥ 18 years, diagnosed with (mostly pharmacotherapy-resistant) major depressive episode (established according to the Mini Neuropsychiatric Interview [MINI]), and treated with ECT in Rijnstate Hospital, Arnhem, The Netherlands, were included (223). Exclusion criteria were chronic use of acetaminophen, Ca^{2+}-antagonists, or non-steroid anti-inflammatory drugs, and contraindications for undergoing MRI or electroencephalogram (EEG). Healthy controls had no history of psychopathology (established with the MINI), had no contraindications for undergoing MRI, and were matched to patients on group-level based on age, sex, and level of education. All participants provided oral and written informed consent.

5.2.3 ECT procedure

ECT was administered according to the Dutch treatment guideline (21). Electrode placement was left to the discretion of the treating psychiatrist, and included unilateral (UL; according to d'Elia (24)) and bifrontotemporal (BL, also known as bitemporal) positioning. A Thymatron System IV device (Somatics Incorporation Lake Bluff, Illinois, USA) was used, delivering a constant-current (0.9 Ampère) with bidirectional square waves in brief pulses (1 ms). All patients were pre-oxygenated with 100% O_2 and most received etomidate as sedative and succinylcholine as muscle relaxant. Stimulus charge was determined based on either the half-age method (i.e., in case of BL electrode placement), or dosage-titration (i.e., with right or left UL electrode placement). In case of severe postictal confusion, midazolam 2-5 mg was provided intravenously (184). A detailed overview of the study protocol is given elsewhere (see Supplementary material **chapter 7**, 7.7) (35, 224).

5.2.4 Seizure duration based on electroencephalography

All patients were monitored with continuous EEG during the treatment and in the postictal state, until electrodes were removed MRI preparation. Prior to each ECT-session, twelve silver/silver chloride cup electrodes were applied according to the international 10-20 system. EEGs were recorded using a NeuroCenter EEG recording system (Clinical Science Systems) and a full-band DC-coupled amplifier (TMSi). Depending on ECT electrode placement, temporal or frontal electrodes were re-placed. For patients treated with BL ECT electrodes, the EEG-electrodes T3 and T4 were placed 10% behind the pre-defined position to ensure enough space for the ECT-electrodes. EEGs were sampled at 256 Hz and impedances were kept below 5 kΩ. Seizure duration was determined visually and defined as the time interval in seconds between the onset of rhythmicity or spike-wave complexes and the onset of postictal generalized suppression in all channels.

5.2.5 Clinical assessment of the postictal state

Reorientation time (ROT) was assessed by a questionnaire, consisting of 5 items concerning reproducing the patient's name, age, birthday, current location (i.e., the name of the hospital), and the day of the week, that patients were asked in a 5-minute interval (193). If a minimum of 4 out of 5 questions were answered correctly, compared to baseline answers, the score was indicated in minutes. Scores ranged from 5 to 100 minutes.

A visual analogue scale assessed subjective intensity of postictal headache, nausea, and myalgia on a scale from 0 (i.e., no pain) to 10 (i.e., worst pain) (225). These questions were asked at one hour postictally.

The postictal suppression index (PSI), estimated by the Thymatron device, was reported to indicate the amount of postictal suppression, based on two frontal EEG channels (226). The index is give in percentages, with 100 indicating perfect postictal suppression.

5.2.6 Magnetic resonance image acquisition and preprocessing

Resting-state ASL-MRI and T1-weighted (T1W) images in patients and healthy controls were acquired using the same 3T Philips Ingenia MRI scanner (Philips Healthcare, Best, The Netherlands) using a 15-channel head coil. ASL-MRI images were acquired with pseudo-continuous ASL (pCASL) labeling and a 3D gradient-and-spin-echo (GRASE) readout module. Scan parameters were as follows: labeling duration = 1800 ms, post label delay = 1900 ms, 4 background suppression pulses, repetition time (TR) = 4057 ms; echo time (TE) = 12 ms; flip angle = 90°; field of view (FOV) = 240 x 240 x 126 mm^3; matrix size = 64 x 60; voxel size = 3 x 3 x 6 mm^3; 21 transverse slices, and no slice gap. Labeling planes were placed perpendicular to the distal ascending portions of the internal carotid (227). The ASL-MRI data consisted of four label-control pairs. An M0 image was acquired for each participant using the imaging parameters identical to the ASL acquisition, without labeling and background suppression to calibrate the ASL signals. Total scan

duration was 5.5 min. T1W images were acquired with an isotropic voxel size of 1.1 mm; TR = 7.5 ms; TE = 4.6 ms; FOV = 256 x 238 mm^2, and 145 sagittal slices. All scan parameters were kept constant for patients and healthy controls.

FSL 6.0.3 (FMRIB Software Library, Functional Magnetic Resonance Imaging of the Brian Center, Department of Clinical Neurology, University of Oxford, Oxford, UK) and Permutation Analysis of Linear Models (PALM) in a Matlab R2022b environment (The MathWorks, Natick, MA, USA) were used for offline data processing (228). A mean perfusion image of the four subtraction images (control - label) was created. CBF was quantified using multicomponent modeling with Bayesian Inference for Arterial Spin labeling MRI (BASIL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BASIL) (229). CBF quantification was performed by kinetic model inversion, calibration with M0 scans, and registration with the function oxford_asl (230). CBF values were corrected for the four background suppression pulses (231). T1W images were preprocessed using a standardized pipeline (i.e., fsl_anat) involving brain extraction, cortical and subcortical segmentation, and registration to standard space (i.e., Montreal Neurological Institute [MNI]).(231) We derived individual gray matter (GM) probability maps (threshold > 0.2 probability for incorporating most gray matter voxels) that were binarized and then merged to create a binarized group-based GM mask. pCASL data were registered to standard space via the T1W image, which resulted in a CBF gray matter image with a 2 mm isotropic resolution. For each participant, we derived a GM partial volume corrected and smoothed CBF image. The GM partial volume images were multiplied with the group-based GM mask resulting in GM CBF images excluding white matter. *Global* CBF in GM was calculated by averaging CBF within each image. Subtraction (difference) images of baseline and postictal (or follow-up) images were calculated and used for voxel-wise analyses. A schematic overview of the preprocessing flow is presented in supplementary material Figure S1. Assuming that *regional* postictal perfusion decreases may be predominantly found in seizure onset zones, ten bilateral regions of interest were selected based on ictal ECT literature (i.e., inferior frontal gyrus, cingulate gyrus, insula, caudate, putamen, thalamus, midbrain, amygdala, hypothalamus, vermis) (170, 217, 219, 220). Bilateral regions-of-interest (ROIs) were defined based on anatomical locations of the Talairach Daemon Labels. Binary masks were created for all ROI's, multiplied with individual partial volume corrected GM CBF images. Mean *regional* perfusion was calculated for each ROI.

5.2.7 Statistical analysis

Clinical, demographic, and *global* and *regional* CBF data were analyzed with R version 4.2.3 (201). Medians and interquartile ranges (IQR) were reported for quantitative variables. Patients and healthy controls were compared with *t*-tests and chi-square tests for differences in age, sex, and level of education between groups. Pearson correlation coefficients between independent variables were investigated for multicollinearity. *P*-values < .05 were considered statistically significant.

For all analyses involving healthy controls we used Bayesian estimation analyses (BEST), while for between patient analyses, we used Bayesian regression models with R packages brms (232, 233). BEST is a Bayesian equivalent for a *t*-test using Markov Chain Monte Carlo simulation as part of the model. This analysis approaches the data structure most accurately without the restricting assumptions of traditional frequentist analyses (i.e., homogeneity of variances and normally distributed noise), generally provides more informative results about the samples, and provides quantitative certainty about the results (232, 233).

First, we investigated baseline CBF differences and average CBF changes over time (*global* and *regional*, ΔgCBF and ΔrCBF, respectively) in patients compared to healthy controls to account for test-retest effects with group by time interactions. Second, we examined whether *global* or *regional* postictal perfusion changes were related to seizure duration. To assess the possible influence of age on seizure duration (because elderly ECT-patients tend to show shorter seizures than younger patients) and baseline perfusion, a Bayesian regression model was implemented (234). Corrections for age (as this is a well-known confounder of perfusion differences), time interval between ECT-stimulus and ASL-MRI scan, number of previous ECT-induced seizures, electrode placement, and smoking were implemented (235). The association between ROT And ECT charge was investigated in a separate Bayesian regression model. In another regression model, ROT and PSI were investigated as fixed effects on perfusion outcomes, including age and seizure duration, to assess their influence on *global* and *regional* postictal perfusion changes. Independent variables were investigated to determine degree of multicollinearity.

5.2.7.1 Additional exploratory analyses

Voxel-wise analyses were performed to investigate whether other brain regions showed perfusion changes over time, controlling for normal variation in healthy controls. Three analyses were performed with gray matter CBF difference images using Permutation Analysis of Linear Models with threshold-free cluster enhancement to investigate 1) baseline perfusion differences between patients and healthy controls (corrected for age and sex), (2) differences in perfusion changes in patients versus healthy controls (corrected for sex and age), and 3) perfusion changes over time in patients corrected for covariates of no interest (i.e., age, sex, electrode placement, and time interval between ECT-stimulus and ASL-MRI scan) (236). Voxels were reported as significant, if these survived correction for multiple comparisons (family wise error rate [FWE]; $p < .05$).

5.2.7.2 Interpretation of Bayesian results

In Bayesian data analysis, a posterior distribution of parameters of interest is generated, which may be used to make decisions on whether the true parameters lie within a “region of practical equivalence” (ROPE) that is defined as an interval including zero (237). For this, a 95% highest density interval (HDI) is calculated from the posterior distribution, which covers 95% of the most credible values. We

defined the ROPE interval as (-0.1, 0.1), which may be interpreted as a practically negligible effect (238-240). If the HDI falls partly within the ROPE, we cannot conclude with certainty that there is an effect (i.e., *non-conclusive*). If the HDI falls outside the ROPE, we interpret the parameters values as *credible* effect. Thus, the ROPE may be viewed as a Bayesian alternative for a *p*-value, that can be used to accept or reject an explicitly formulated null hypothesis (i.e., interval -0.1, 0.1). Bayesian results will be presented as median parameter estimates of the posterior distribution together with its 95% credibility intervals (CI). The credibility interval is defined as the range containing 95% of probable parameter estimate values of the posterior distribution (233). The following settings were used in all Bayesian analyses: 8000 iterations, 4 chains, and default priors.

5.3 Results

Twenty-four patients were included in this study (median age 50 years [IQR = 22.5; range 24 – 82], 15 females [63%]). Fifteen patients were treated with BL (at the end of the ECT course), and nine exclusively with UL electrode placement (i.e., one patient received left UL electrode placement). Two patients were left-handed, one of which received left UL electrode placement. The other left-handed patient was treated with BL electrode placement. During the ECT course, median seizure duration on EEG was 56 seconds (IQR = 24.2; range 24.9 – 114). Median number of ECT-sessions in the course was 12 (IQR = 8, range 8 – 100), which lies within the normal range reported by others (150, 241).

Twenty-seven healthy controls were included to examine test-retest CBF variability with a median age of 55 years (IQR = 22.5, range 27 – 84), including 15 female participants (56%). Neither age (p = 0.954), sex (p = 0.826), level of education (p = 0.227), nor the number of smokers (p = 0.056) differed significantly between patients and healthy controls. Patient characteristics are presented in Table 5.1.

5.3.1 Clinical description of the postictal state

Eight out of 24 patients reported postictal headache, nausea, or myalgia after ECT, before entering the MRI scanner (see Table S1). Symptom severity scores ranged from 2 to 7. Headache was the most reported symptom (6 out of 8 patients), followed by nausea and myalgia. The two patients with the longest seizure duration (i.e., 101 and 114 s) both reported high scores (i.e., 7) of postictal headache. None of the patients showed signs of non-convulsive status epilepticus. Median reorientation time was 37.5 minutes (IQR = 21.3, range 20 – 100). The maximum ROT score (i.e., 100) was given to four out of 24 patients, indicating that they were still (somewhat) disoriented at the time of the ASL-scan acquisition. These patients had seizure durations of 34, 44, 59, and 79 seconds. Two of these patients reported postictal headache. The other patients who had lower ROT scores (max. 60 min) were adequate and reoriented. Median postictal suppression index was 85.2 % (IQR = 55.7, range 10 – 97.5). In 9 patients (38%), the postictal suppression index was not available.

Table 5.1 Characteristics of patients with cerebral perfusion measures after electroconvulsive therapy (ECT)-induced seizures, using arterial spin labeling magnetic resonance imaging (ASL-MRI)

Characteristic		**Patients (n = 24)**
Age in years, median (IQR; range)		56 (22.5; 24 – 82)
Female, n (%)		15 (63)
Number of smokers, n (%)		9 (38)
BL electrode placement at the end of the ECT-course, n (%)		15 (63)
Median delivered charge at ECT-session before ASL-MRI acquisition, in milliCoulombs (IQR; range)		303 (170.1; 125.6 – 659.7)
Median seizure duration on EEG, in seconds (IQR; range)		56 (24.2; 24.9 – 114)
Number of previous seizures (IQR; range)		4 (2 – 8; 4)
Reorientation time, in minutes (IQR; range)		37.5 (21.3; 20 – 100)
Timing postictal ASL-MRI scan during the ECT-course (%)		
	After ECT-session 2	3 (13)
	After ECT-session 3	6 (25)
	After ECT-session 4	5 (21)
	After ECT-session 5	3 (13)
	After ECT-session 6	1 (4)
	After ECT-session 7	2 (8)
	After ECT-session 8	4 (16)
Median interval between application of the ECT-stimulus and start postictal ASL-MRI sequence, in minutes (IQR; range)		66 (12.3; 53 – 90)
Concomitant psychopharmacological drug use, n (%)		
	Antidepressants	18 (75)
	Antipsychotics	17 (71)
	Antiepileptics	4 (17)
	Benzodiazepines	17 (71)
	Lithiumcarbonate	2 (8)
Number of patients needing medication for severe postictal symptoms after ECT*, n (%)		8 (33)

BL = bifrontotemporal; IQR = inter quartile range; EEG = electroencephalogram;
*Postictal medication consisted of a single dose of midazolam, ranging between 2-5 mg

5.3.2 Global CBF in patients controlled for test-retest variability

At baseline, the median gCBF in patients was 54.9 ml/100g/min (IQR = 21.9). After the seizure, patients had decreased as well as increased gCBF values compared to baseline (median gCBF 54.2 ml/100g/min, IQR = 25.1), which median did not differ from baseline (difference 2.0 ml/100g/min [CI95 -2.2, 6.3]; Figure 5.1). In patients, the maximum decrease of postictal gCBF appeared 28.3 ml/100/min, while the maximum postictal increase was 19.6 ml/100gmin. In healthy controls, median change in gCBF (i.e., ΔgCBF) was -3 ml/100g/min (range -20.7 – 12.6). Baseline gCBF did not differ between patients and healthy controls (-4.4 ml/100g/min [CI95 -13.2, 4.5]).

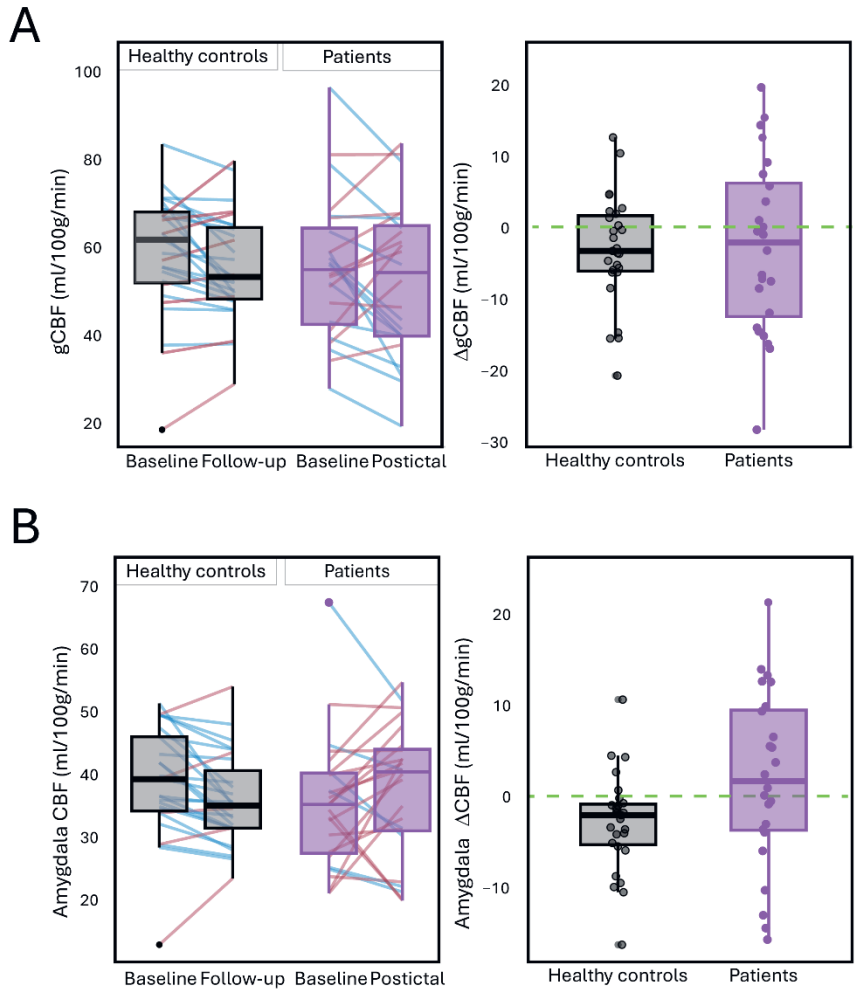


Figure 5.1 (A) *Global* cerebral blood flow (gCBF, left) and change in gCBF between baseline and postictal/follow-up (ΔgCBF, right) in electroconvulsive therapy patients (n = 24) and healthy controls (n = 27), essentially indicating that there was a negligible *global* CBF change between baseline and the postictal state when controlling for test-retest variation in healthy controls. ΔgCBF did not differ between groups (0.4 ml/100g/min [CI95 -5.7, 6.5]), but *global* CBF decreased in healthy controls over time (-2.9 ml/100g/min [CI95 -4.9, -0.8]). (B) *Regional* cerebral blood flow in the amygdala (left) and change in amygdala CBF between baseline and postictal/follow-up (ΔCBF, right) highlights a relative increase in postictal amygdala CBF in patients compared to a relative decrease in healthy controls at follow-up (-4.8 ml/100g/min [CI95 -9.5, -0.2]). However, this difference was largely attributable to changes in healthy controls rather than only to changes in patients, because the amygdala perfusion changed in healthy controls, but not in patients (-2.9 ml/100g/min [CI95 -4.9, -0.8] and 2.0 ml/100g/min [CI95 -2.2, 6.3], respectively). Blue lines indicate an individual decrease in CBF, red lines indicate an individual increase in *global* CBF respective to baseline. Green dashed lines indicate no change respective to baseline.

5.3.3 Regional CBF in patients controlled for test-retest variability

When comparing changes in *regional* CBF (i.e., ΔrCBF) in patients to those in healthy controls, only interaction effects were observed in the amygdala ΔCBF (-4.8 ml/100g/min [CI95 -9.5, -0.2], Figure 5.1), but not in any of the pre-specified regions (Figure S5.2, Table S5.2). This means that relative amygdala ΔCBF was increased in patients in the postictal state, while at follow-up in healthy controls, amygdala ΔCBF was decreased. This effect was largely driven by ΔCBF changes in healthy controls.

We found a negative relation between age and baseline perfusion for both patients and healthy controls (-0.6 ml/100g/min [CI95 -1, -0.2]), indicating that older participants had lower baseline perfusion values compared to younger participants, with a change of approximately 5 ml/100/min per decade (Figure S5.3).

5.3.4 Seizure duration in relation to CBF changes

All independent variables were investigated for possible correlations before analyses. A moderate negative correlation was found between seizure duration and age, meaning that older patients showed shorter seizures ($\rho = -0.6$, $p < 0.001$). This moderate correlation may prevent definitive conclusions about the individual contribution of seizure duration (or age) in the models. No relations between *global* and *regional* cerebral perfusion with either electrode placement, number of previous seizures, or smoking were established (see Table 5.2). This motivated to explore both the gCBF and rCBF analyses with, and without, age as a covariate to assess their relation with seizure duration.

Seizure duration was negatively related to ΔgCBF when including age (-0.4 ml/100g/min [CI95 -0.7, -0.2]) and when excluding age (-0.3 ml/100g/min [CI95 -0.6, -0.1]) in the models (Table 2, Figure 5.2B). Seizure duration was also negatively related to ΔrCBF in the cingulate gyrus (-0.5 ml/100g/min [CI95 -0.8, -0.2]), inferior frontal gyrus (-0.5 ml/100g/min [CI95 -0.9, -0.1]), and insula (-0.4 ml/100g/min [CI95 -0.7, -0.1]). ΔrCBF in the amygdala, caudate, and putamen showed inconclusive relationships with seizure duration (see Table 5.2). Seizure duration was not related to ΔrCBF in the hypothalamus, thalamus, midbrain, or vermis (Figure S4).

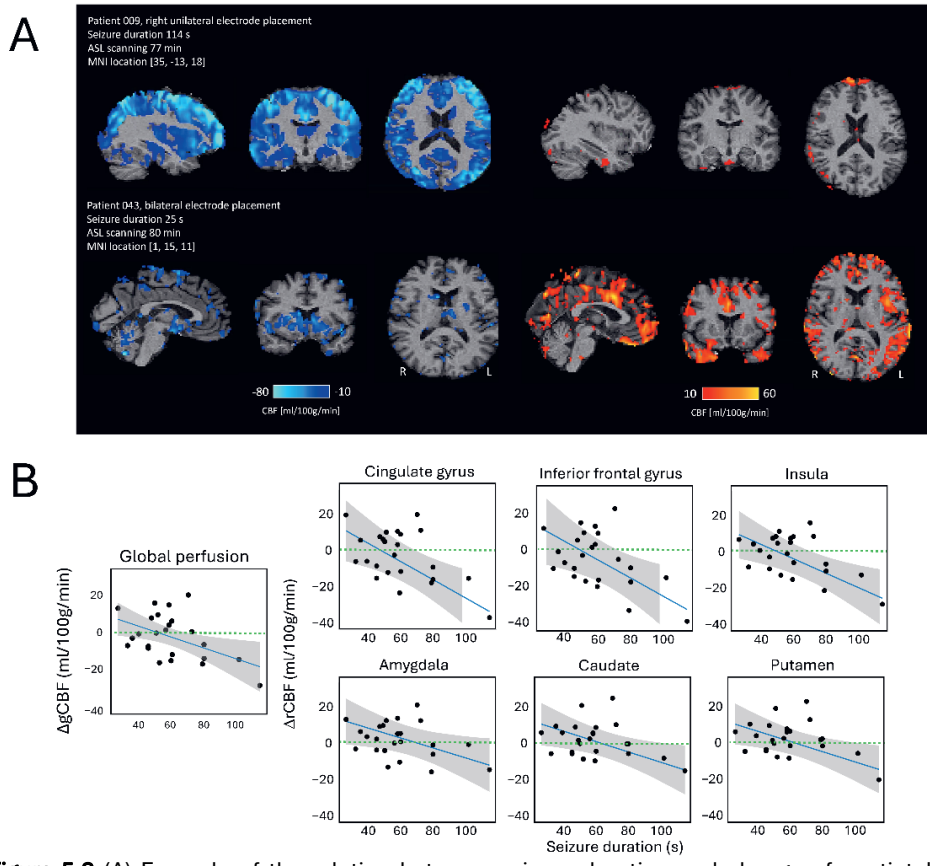


Figure 5.2 (A) Example of the relation between seizure duration and change of postictal cerebral blood flow (CBF) in a patient with the longest and in a patient with the shortest seizure. Subtraction CBF maps (postictal – baseline) of the patient with the longest seizure (patient 009; 114 s) and the patient with the shortest seizure (patient 043; 25 s), indicating profound and diffuse patterns of severe hypoperfusion (blue color) after the longest seizure, while for the shortest seizure hypoperfusion patterns were lower in magnitude and regionally restricted to midline and subcortical brain areas. The patient with the shortest seizure showed more widespread CBF increases (red color) compared to the patient with the longest seizure. Patient 009 was treated with right unilateral electrode placement, while patient 043 was treated with bifrontotemporal electrode placement. Voxel-wise CBF maps were superimposed onto the patient's T1W anatomical image. (B) Seizure duration was negatively related to both change in global and regional perfusion (ΔgCBF and ΔrCBF, respectively) in the cingulate gyrus, inferior frontal gyrus, and insula. The amygdala, caudate, and putamen showed a non-conclusive negative relation with seizure duration. Trend lines show the conditional effects of the Bayesian models. The dashed green lines indicate no change respective to baseline. CBF = cerebral blood flow; ΔgCBF = global perfusion change; ΔrCBF = regional perfusion change; ASL = arterial spin labeling; Δt = time interval in minutes between ECT stimulus and ASL acquisition; R = right; L = left.

Table 5.2 Summary of *global* and *regional* ΔCBF in relation with seizure duration, electrode placement, age, time to ASL acquisition, number of previous seizures, and smoking

	Global ΔCBF (ml/100g/min)		**ΔCBF amygdala (ml/100g/min)**		**ΔCBF caudate (ml/100g/min)**		**ΔCBF cingulate gyrus (ml/100g/min)**		**ΔCBF inferior frontal gyrus (ml/100g/min)**		**ΔCBF insula (ml/100g/min)**		**ΔCBF putamen (ml/100g/min)**	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	52.9	-3.7 – 110.2	51.3	1.8 – 100.4	64.2	20.0 – 109.1	57.7	-8.6 – 121.3	62.9	-7.6 – 136.1	56.7	6.5 – 107.5	61.1	17.1 – 104.5
Seizure duration (s)	-0.4	-0.7 – 0.1	-0.3	-0.5 – 0.0	-0.3	-0.5 – 0.1	-0.5	-0.8 – 0.2	-0.5	-0.9 – 0.1	-0.4	-0.7 – 0.1	-0.3	-0.5 – 0.1
Electrode placement (Bilateral)	-2.4	-12.7 – 7.8	-2.6	-11.6 – 6.4	-0.6	-9.0 – 7.4	-0.1	-11.8 – 11.5	-4.3	-17.5 – 9.0	-1.2	-10.2 – 8.0	0.3	-7.6 – 8.1
Age (years)	-0.3	-0.7 – 0.2	-0.2	-0.6 – 0.2	-0.3	-0.6 – 0.1	-0.3	-0.8 – 0.2	-0.2	-0.8 – 0.3	-0.2	-0.6 – 0.2	-0.3	-0.6 – 0.1
Time to ASL acquisition (min)	-0.1	-0.7 – 0.5	-0.3	-0.8 – 0.3	-0.3	-0.8 – 0.2	-0.2	-0.8 – 0.6	-0.2	-1.0 – 0.5	-0.3	-0.8 – 0.3	-0.3	-0.7 – 0.2
Number of previous seizures	-3.9	-10.3 – 2.5	-1.8	-7.3 – 3.8	-5.0	-10.0 – 0.2	-2.9	-10.1 – 4.6	-4.0	-12.2 – 4.0	-3.4	-9.1 – 2.2	-4.1	-9.1 – 0.8
Smoking	3.9	-6.6 – 14.3	1.0	-8.1 – 10.0	2.4	-5.8 – 10.6	7.2	-4.6 – 19.0	6.6	-6.4 – 20.0	6.4	-2.9 – 15.9	2.9	-4.9 – 11.1
ROPE interpretation	Credible		Inconclusive		Inconclusive		Credible		Credible		Credible		Inconclusive	

Note: ASL = Arterial Spin Labeling, CI = Credibility Interval, **Δ**CBF = change in Cerebral Blood Flow, ROPE = region of practical equivalence

Exemplary, in the patient with the longest seizure duration (i.e., 114 s), postictal *global* cerebral perfusion decreased with 28.3 ml/100g/min and regional cerebral perfusion in the inferior frontal gyrus decreased with 38.2 ml/100g/min. This corresponded to a 52% and 88% decrease in CBF compared to baseline, respectively. The patient with the shortest seizure (25 s) showed relatively small increases in postictal gCBF (15.4 ml/100g/min) and rCBF in the cingulate gyrus, inferior frontal gyrus, and insula (19.6 ml/100g/min, 16.0 ml/100g/min, and 11.4 ml/100g/min, respectively). Figure 5.2A illustrates this contrast in the two patients having the longest and shortest seizure duration. ROT was not associated with administered stimulus charge (2.20 mC [CI95 -0.03 4.38]). ROT and PSI were not associated with *global* or *regional* postictal perfusion (see Table S5.3).

5.3.5 Exploratory voxel-wise analyses in patients and healthy controls

Additional exploratory voxel-wise analyses were performed to investigate whether specific regions showed baseline perfusion differences between patients and healthy controls and whether perfusion changed over time between both groups. In patients, voxel-wise perfusion changes in the postictal state were explored. None of these analyses showed significant differences in any analyses across all gray matter voxels, after correction for multiple comparisons.

5.3.6 Sensitivity analyses

Eight patients (33%) received 2-5 mg midazolam IV after ECT and before the ASL-MRI acquisition because of severe postictal confusion. Studies on the influence of acute benzodiazepine administration have reported decreased CBF, cerebral metabolic rate, oxygen consumption, and intracranial pressure by enhancing the inhibitory effect of GABA-A receptors (242, 243). The use of benzodiazepines may be associated with increased risk for ischemic stroke (244). To verify whether our results were not driven by the administration of midazolam, we examined the groups of patients with or without postictal midazolam more closely and performed sensitivity analyses. The median postictal gCBF of patients who received postictal midazolam (n = 16) was 47.9 ml/100g/min (IQR = 26.3), while in the group without postictal midazolam (n = 8) median postictal gCBF was 57.5 ml/100g/min (IQR = 25.0). The median values for the selected ROIs are described in Supplementary Table S5.4 and Figure S5.5.

When excluding the group with postictal midazolam administration, the relation between ΔgCBF and seizure duration remained credible (-0.5 ml/100g/min [CI95 -0.7, -0.3]) as well as with ΔrCBF in the insula (-0.4 ml/100g/min [CI95 -0.8, -0.1], see Supplementary Table S5.5 and Figure S5.6). The ΔrCBF in the cingulate gyrus and inferior frontal gyrus showed a negative trend in the association with seizure duration (-0.6 ml/100g/min [CI95 -1.1, -0.1] and -0.6 ml/100g/min [CI95 -1.1, -0.1], respectively). The group by time interaction in the amygdala (controlled for test-retest effects) disappeared (-5.6 ml/100g/min [CI95 -11.6, 0.3]). These results, however, may be partly explained by the smaller sample size (n = 16).

5.4 Discussion

In this ASL-MRI study, seizure duration in patients after ECT-induced seizures was related to *global* and *regional* postictal perfusion changes. On group level, median *global* and *regional* CBF values did not differ between baseline and in the immediate postictal state, controlled for test-retest variability. However, seizure duration was related to changes in postictal perfusion, where longer seizures were associated with larger decreases of *global* and *regional* postictal perfusion and shorter seizures were associated with increases in postictal perfusion. In some patients, *regional* postictal perfusion was reduced to 50% of baseline values.

5.4.1 Global and regional perfusion in patients and healthy controls

Median gray matter perfusion at baseline in our patients was 54.9 ml/100g/min and 61.7 ml/100g/min in healthy controls, which both compare to values in the literature, reporting gray matter perfusion values of 40 to 52 ml/100g/min and 18.4 to 83.4 ml/100g/min, respectively (245, 246).

Also, in line with the literature, our CBF values decreased with age (approximately 5 ml/100g/min/decade; see Figure S5.3), which supports the reliability of our results (235, 247, 248). In our healthy controls, a median decrease of *global* perfusion was shown (i.e., -3 ml/100g/min [±7.8]), which may be interpreted as test-retest effect of two measurements taken on different time points. CBF values in patients above or below this 'normal' limit likely result from an effect of the ECT-induced seizures on perfusion in patients.

On group level, median *global* and *regional* CBF values did not differ between baseline and in the immediate postictal state, controlled for test-retest variability. This may be explained by the timing of the postictal scans (i.e., median 66 min), because postictal cerebral perfusion changes after ECT-induced seizures may be more pronounced shortly after the seizure. However, the most likely explanation is its relationship with seizure duration.

5.4.2 Seizure duration relates to ΔgCBF and ΔrCBF

While on group level, medians of global and regional perfusion measures in patients did not change in the postictal state compared to baseline, we did observe that a longer duration of ECT-induced seizures was associated with decreased postictal *global* perfusion up to a maximum of 28.3 ml/100g/min, while shorter seizures were associated with a relative increase in postictal perfusion. In addition, seizure duration was also negatively related to *regional* postictal perfusion in the cingulate gyrus, inferior frontal gyrus, and insula. These relations appeared independent of the patients' age, while age was also negatively related to seizure duration. Our findings are comparable with those of a study in epilepsy patients, which showed larger decreases in *regional* perfusion in the postictal state in patients having longer seizures (15). In ECT patients, longer seizure duration may result in more severe postictal clinical symptoms (249). Previous ECT studies have reported mixed patterns regarding *regional* perfusion changes, primarily reporting

decreases in frontal and temporal cortices (151, 216, 219, 220). In our sample, neither mean *global* nor *regional* perfusion changed on group level between baseline and the postictal state, which is most certainly explained by the influence of seizure duration on CBF changes. Another explanation for these null findings may be differences in time intervals between seizure activity and perfusion measurements. These new insights may promote future studies regarding more *regional* perfusion analyses, clinical consequences of (longer) seizure duration, or intervention studies regarding minimalization of seizure duration and postictal hypoperfusion to improve patient outcomes.

5.4.3 Pathophysiological considerations

The maximum decreases in *regional* CBF in the postictal state ranged from 9 to 38 ml/100g/min, corresponding to a maximum of 30-47% decrease from baseline. Similar changes during the postictal state were reported in patients with epilepsy, in a 4-aminopyridine (4-AP) seizure model in mice, and CT-perfusion measurements in adult patients with refractory epilepsy (15, 111, 112). Both Farrell et al. and Lim et al. showed that the early hypoperfusion (30 min post-seizure) was mainly induced by arteriolar constriction (15, 111). In the 4-AP mice model, hypoperfusion that persisted for over an hour resulted from increased capillary stalling induced by neutrophil adhesion to brain capillaries (111). Similar mechanisms may be involved in the postictal state in our patients, however, these mechanisms cannot explain the increased perfusion observed in patients with short seizures (cf Figure 4), of the order of 10 ml/100g/min, which suggests that other processes are involved, too. A candidate mechanism is increased activity of glia, to clear excessive extracellular potassium, which is known to be associated with *regional* CBF increases (250-253). The relative strength of these counteracting mechanisms and their temporal relation may then define the net effect.

5.4.4 Strengths and limitations

Strengths of our study include the prospective, systematic collection of clinical and ASL-MRI data shortly after ECT-induced seizures. Our methodology may enable studying postictal perfusion in a longitudinal fashion with repeated scans at regular time intervals. Further, the inclusion of healthy controls, to control for test-retest effects, using the same scanner and settings, appeared important. Limitations include the relatively small sample sizes of patients and healthy controls. Also, the influence of the anesthetic agent (i.e., etomidate) in patients could have caused reductions in CBF (243). However, this is unlikely as the half-life of etomidate is 2-4 minutes and the postictal scans were acquired after approximately 1 h. Midazolam administration may have partly influenced our results, because the relation between rCBF and the cingulate gyrus and inferior frontal gyrus disappeared, when excluding patients receiving postictal midazolam. However, these results may also be explained by the smaller sample size. Postictal hypoperfusion in some patients may have already returned to baseline before the ASL-MRI measurements, although the regression models showed no independent relation with this time interval. A significant limitation to the interpretation is the

potential cumulative effect of seizures on postictal perfusion changes, which may be addressed in future studies by scanning patients early in their ECT-course. In addition, the patients' baseline ASL-MRI scans may not have been optimal, as these were not acquired after a sham procedure in the operation room. Finally, we could not obtain full brain coverage in all patients, precluding some brain regions from voxel-wise analyses.

5.5 Conclusion

Changes in *global* and *regional* postictal perfusion were related to the duration of ECT-induced seizures. Longer seizures were associated with larger decreases of *global* and *regional* postictal perfusion, while shorter seizures were associated with increases in postictal perfusion. Future studies may replicate these findings in a larger sample, investigating patients earlier in their ECT-course.

5.6 Supplementary material

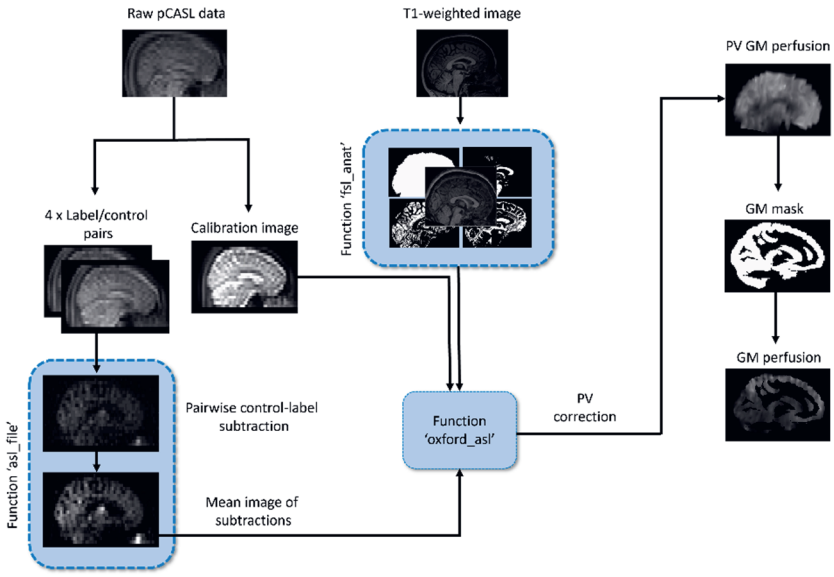


Figure S5.1 Schematic representation of the preprocessing of ASL-MRI and T1W image workflow. pCASL = pseudo continuous arterial spin labeling; CBF = cerebral blood flow; PV = partial volume; GM = gray matter

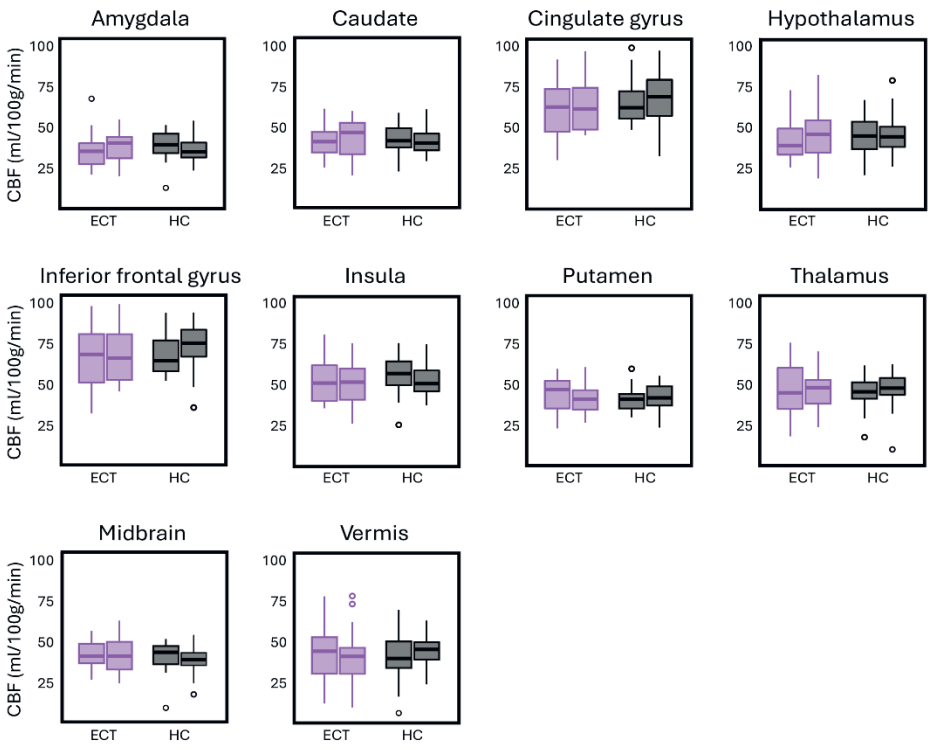


Figure S5.2 Cerebral blood flow (CBF) in ten pre-specified regions-of-interest at baseline and postictal/follow-up in electroconvulsive therapy patients (n=24) and healthy controls (n=27). No regions showed relevant perfusion changes in patients nor in healthy controls. Purple boxplots indicate the ECT group. Black boxplots indicate the healthy control group. Left boxplots of each group represent perfusion measured at baseline, while right boxplots represent postictal/follow-up perfusion. The points indicate outliers.

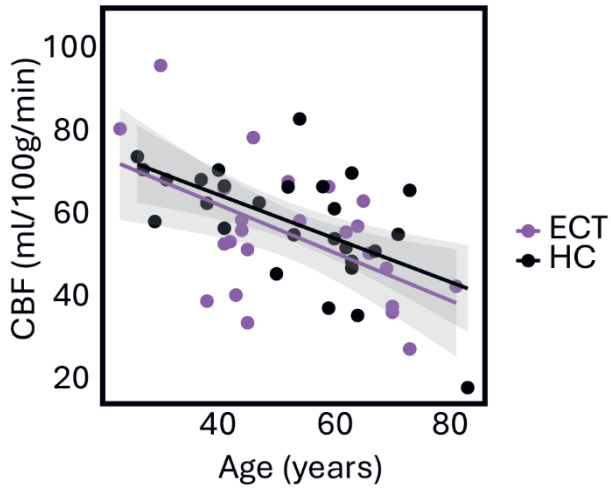


Figure S5.3 Age was negatively associated with baseline cerebral blood flow (CBF). Data of patients are represented in red, and healthy controls (HC) in blue.

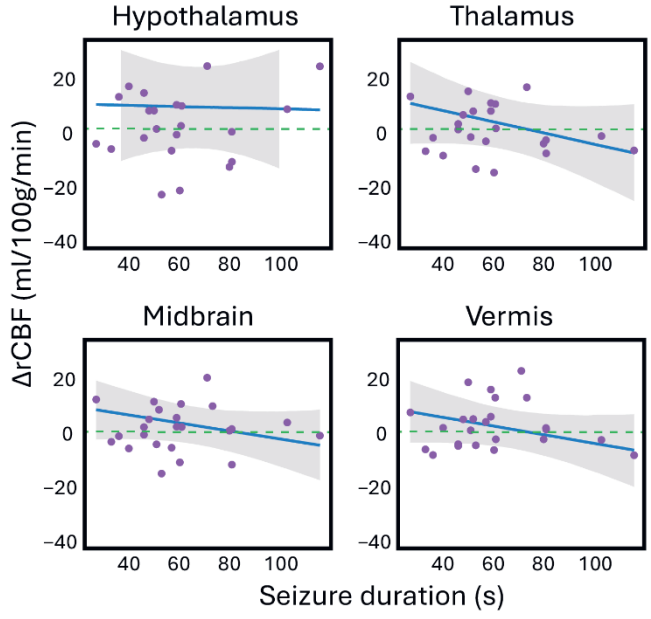


Figure S5.4 Change in *regional* cerebral blood flow (ΔCBF) in hypothalamus, thalamus, midbrain, and vermis. Seizure duration was not associated with ΔCBF in these regions. The dashed green lines indicate no change respective to baseline.

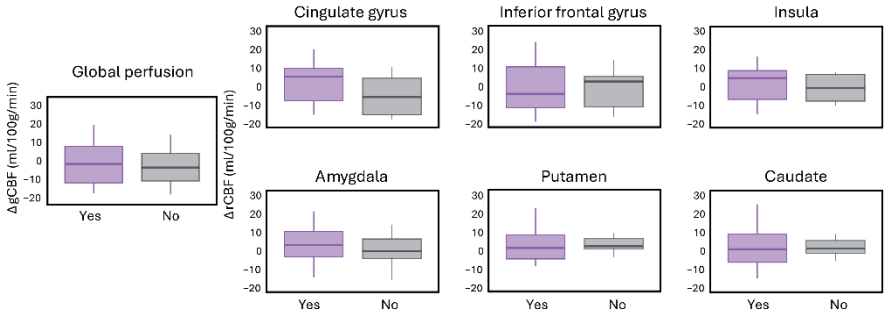


Figure S5.5 Global and regional perfusion changes (gCBF and rCBF, respectively) in patients who received postictal midazolam (red, Yes) and patients who did not (blue, No).

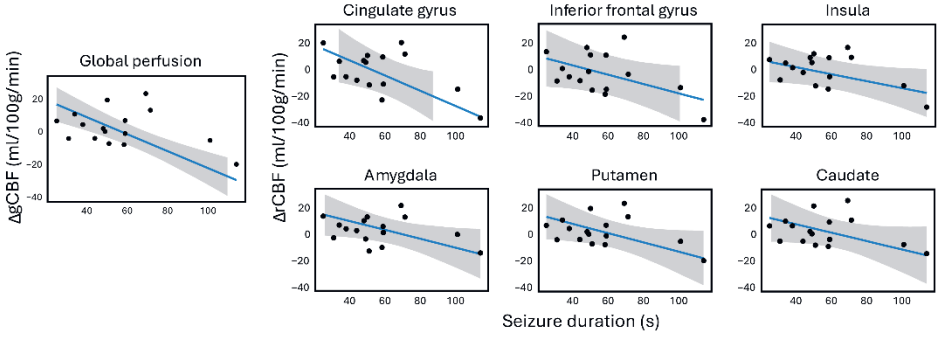


Figure S5.6 Relation between change in global and regional CBF (ΔgCBF and ΔrCBF, respectively) in relation to seizure duration in patients who did not receive postictal midazolam.

Table S5.1 Self-reported occurrence of postictal headache, nausea, and myalgia. Eight out of 24 patients reported at least one postictal symptom before entering the MRI-scanner. If postictal symptoms are experienced, headache is the most reported symptom.

Patient number	Headache	Nausea	Myalgia	Seizure duration (s)
#08	7			101
#09		7		114
#12		5		55
#13	3	2		50
#27	2			34
#28	7			59
#39	3		4	51
#41	6	4	4	48

Table S5.2. Summary of *regional* ΔCBF in relation with seizure duration, electrode placement, age, time to ASL acquisition, number of previous seizures, and smoking

	ΔCBF hypothalamus (ml/100g/min)		**ΔCBF thalamus (ml/100g/min)**		**ΔCBF midbrain (ml/100g/min)**		**ΔCBF vermis (ml/100g/min)**	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	52.0	-39.3 – 143.6	39.9	18.4 – 98.5	36.5	20.0 – 109.1	57.7	-8.6 – 121.3
Seizure duration (s)	-0.0	-0.5 – 0.5	-0.2	-0.5 – 0.1	-0.2	-0.5 – 0.1	-0.5	-0.8 - – 0.2
Electrode placement	-3.5	-20.2 – 13.3	-2.8	-13.3 – 7.8	-0.8	-9.0 – 7.4	-0.1	-11.8 – 11.5
Age (years)	-0.3	-1.0 – 0.4	-0.3	-0.8 – 0.1	-0.3	-0.6 – 0.1	-0.3	-0.8 – 0.2
Time to ASL acquisition (min)	-0.3	-1.3 – 0.7	0.0	-0.6 – 0.6	-0.0	-0.8 – 0.2	-0.2	-0.8 – 0.6
Number of previous seizures	-2.9	-13.4 – 7.4	-2.6	-9.1 – 3.9	-2.0	-10.0 – 0.2	-2.9	-10.1 – 4.6
Smoking	-4.6	-21.5 – 12.4	-0.2	-11.2 – 10.3	-4.2	-5.8 – 10.6	7.2	-4.6 – 19.0
ROPE interpretation	Credible		Inconclusive		Inconclusive		Credible	

Note: ASL = Arterial Spin Labeling, CI = Credibility Interval, ΔCBF = change in Cerebral Blood Flow, ROPE = region of practical equivalence

Table S5.3. Summary of *global* and *regional* ΔCBF with no relation to ROT or PSI

	Global ΔCBF (ml/100g/min)		**ΔCBF amygdala (ml/100g/min)**		**ΔCBF caudate (ml/100g/min)**		**ΔCBF cingulate gyrus (ml/100g/min)**		**ΔCBF inferior frontal gyrus (ml/100g/min)**		**ΔCBF insula (ml/100g/min)**		**ΔCBF putamen (ml/100g/min)**	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	42.4	-2.8 – 87.3	34.7	4.7 – 74.4	36.9	-1.1 – 75.9	58.6	7.7 – 107.9	46.0	-4.3 – 96.4	47.6	9.9 – 85.7	41.2	5.9 – 76.3
Seizure duration (s)	-0.4	-0.7 – 0.1	-0.2	-0.5 – 0.1	-0.3	-0.5 – 0.0	-0.5	-0.9 – -0.1	-0.5	-0.8 – -0.1	-0.4	-0.7 – 0.1	-0.3	-0.6 – -0.0
Age (years)	-0.4	-1.0 – 0.2	-0.4	-0.9 – 0.1	-0.4	-9.0 – 0.1	-0.6	-1.3 – 0.2	-0.5	-1.2 – 0.2	-0.6	-1.1 – -0.1	-0.5	-1.0 – -0.0
ROT	-0.2	-0.4 – 0.1	-0.1	-0.3 – 0.2	-0.1	-0.3 – 0.2	-0.2	-0.5 – 0.1	-0.2	-0.5 – 0.1	-0.1	-0.3 – 0.2	-0.0	-0.3 – 0.2
PSI	0.1	-0.1 – 0.3	1.0	-0.1 – 0.2	0.1	-0.1 – 0.2	0.1	-0.1 – 0.3	0.2	-0.1 – 0.4	0.1	-0.1 – 0.3	0.1	-0.1 – 0.2
ROPE interpretation ROT and PSI	Inconclusive		Inconclusive		Inconclusive		Inconclusive		Inconclusive		Inconclusive		Inconclusive	

Note: ASL = Arterial Spin Labeling, CI = Credibility Interval, **Δ**CBF = change in Cerebral Blood Flow, ROPE = region of practical equivalence

Table S5.3 (continued). Summary of *global* and *regional* ΔCBF with no relation to ROT or PSI

	ΔCBF hypothalamus (ml/100g/min)		**ΔCBF thalamus (ml/100g/min)**		**ΔCBF midbrain (ml/100g/min)**		**ΔCBF vermis (ml/100g/min)**	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	26.4	-46.2 – 10.2	33.6	22.7 – 88.2	17.8	-24.6 – 60.2	33.0	-2.0 – 67.9
Seizure duration (s)	0.2	-0.4 – 0.7	-0.2	-0.6 – 0.3	-0.1	-0.4 – 0.3	-0.2	-0.4 – 0.1
Age (years)	-0.4	-1.4 – 0.5	-0.4	-1.2 – 0.3	-03	-0.8 – 0.3	-0.4	-0.9 – 0.1
ROT	-0.1	-0.5 – 0.4	-0.1	-0.4 – 0.3	-0.1	-0.3 – 0.2	-0.1	-0.3 – 0.1
PSI	-0.1	-0.4– 0.2	0.0	-0.3 – 0.3	0.0	-0.2 – 0.2	0.1	-0.1 – 0.2
ROPE interpretation ROT and PSI	Inconclusive		Inconclusive		Inconclusive		Inconclusive	

Note: ASL = Arterial Spin Labeling, CI = Credibility Interval, **Δ**CBF = change in Cerebral Blood Flow, ROPE = region of practical equivalence

Table S5.4. Overview of median rCBF values of the selected ROIs in patients that received postictal midazolam (n = 16) and in those who did not (n = 8)

ROI	Median rCBF [ml/100g/min] (IQR)	
	Postictal midazolam administration (n = 16)	No midazolam (n = 8)
Cingulate gyrus	56.3 (20.6)	63.7 (18.2)
Inferior frontal gyrus	60.3 (25.2)	68.6 (19.3)
Insula	45.2 (20.1)	50.8 (14.3)
Amygdala	33.9 (14.7)	35.6 (8.1)
Putamen	40.8 (16.5)	41.7 (10.4)
Caudate	40.5 (19.9)	42.5 (11.1)

Table 5.5 Summary of *global* and *regional* ΔCBF in the group of patients who did not receive postictal midazolam

	Global ΔCBF (ml/100g/min)		**ΔCBF cingulate (ml/100g/min)**		**ΔCBF inferior frontal gyrus (ml/100g/min)**		**ΔCBF insula (ml/100g/min)**		**ΔCBF amygdala (ml/100g/min)**		**ΔCBF caudate (ml/100g/min)**		**ΔCBF putamen (ml/100g/min)**	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	68.6	27.0 – 111.5	66.4	-29=8.8 – 162.0	83.4	-21.6 – 184.3	72.5	5.3 – 140.6	66.6	4.2 – 131.0	73.3	3.4 – 131.9	71.2	-0.7 – 141.7
Seizure duration (s)	-0.5	-0.7 - - 0.3	-0.6	-1.1 - - 0.1	-0.6	-1.1 - - 0.1	-0.5	-0.8 – 0.1	-0.3	-0.7 - - 0.0	-0.4	-0.7 – 0.0	-0.3	-0.7 – 0.1
Electrode placement (Bilateral)	-2.6	-10.9 – 5.4	0.1	-18.8 – 19.4	-3.8	-23.6 – 16.0	0.0	-13.1 – 13.2	0.2	-12.2 – 12.7	-0.0	-13.6 – 13.5	-0.4	-14.3 – 14.2
Age (years)	-0.6	-1.0 - - 0.3	-0.6	-1.5 – 0.3	-0.6	-1.5 – 0.3	-0.5	-1.1 – 0.1	-0.5	-1.1 – 0.1	-0.4	-1.0 – 0.2	-0.5	-1.1 – 0.2
Time to ASL acquisition (min)	0.2	-0.3 – 0.6	0.1	-0.9 – 1.2	-0.0	-1.1 – 1.0	-0.0	-0.8 – 0.7	-0.1	-0.7 – 0.6	-0.2	-1.0 – 0.5	-0.2	-0.9 – 0.6
Number of previous seizures	-4.9	-9.6 - - 0.3	-4.6	-15.4 – 6.2	-5.5	-16.7 – 5.9	-5.6	-13.3 – 2.-	-4.2	-11.2 – 3.1	-4.6	-12.4 – 3.1	-6.4	-14.4 – 1.8
Smoking	-3.9	-13.6 – 5.4	3.4	-18.9 – 25.0	-1.5	-24.2 – 20.3	2.3	-12.8 – 17.7	-6.1	-20.6 – 8.3	0.2	-15.3 – 16.1	0.5	-15.0 – 16.6

Note: ASL = Arterial Spin Labeling, CI = Credibility Interval, **Δ**CBF = change in Cerebral Blood Flow;

Chapter 6

Decreased connectivity in the central executive and auditory network after electroconvulsive therapy-induced seizures: A postictal resting-state fMRI study

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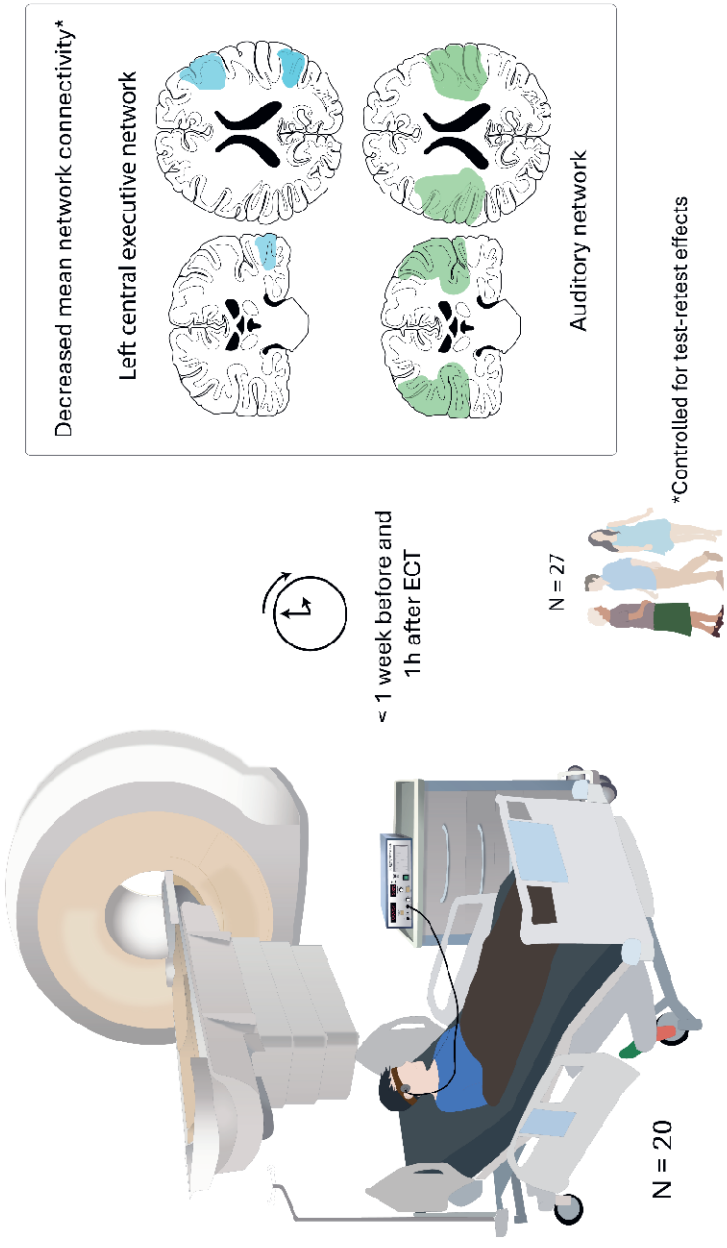
In preparation

Graphical abstract



Abstract

Background Seizures may induce postictal disruption of resting-state networks (RSNs), but investigation is challenging in epilepsy because of unpredictable seizures. Postictal RSNs can be investigated with electroconvulsive therapy (ECT). Changes in the default mode network (DMN), attention network (ATN), central executive network (CEN), and salience network (SN) have been suggested in people with altered consciousness, which is a key postictal symptom.

Objective We investigated how connectivity in brain-wide RSNs changed at one hour after induced seizures in patients receiving ECT.

Methods We collected resting-state functional magnetic resonance imaging (rs-fMRI) scans in 20 patients with a major depressive episode before and one hour after ECT. Also, we collected scans on two occasions in 27 healthy controls matched to patients in age, sex, and level of education, to account for test-retest effects. RSNs of interest and exploratory RSNs were extracted using a group-information guided independent component analysis. Changes in mean and voxel-wise RSN connectivity strength were compared between groups.

Results Group by time interaction analyses showed a postictal decrease in mean connectivity strength in the left CEN and the auditory network in patients, compared to healthy controls (-0.18 [CI95 -0.26, -0.10] and (-0.22 [CI95 -0.36, -0.07], respectively). Voxel-wise analyses revealed a connectivity reduction within the left CEN in patients compared to healthy controls.

Conclusion ECT-induced seizures were associated with a postictal decrease of connectivity strength in the left CEN and the auditory network. These network changes may underlie clinical features of the postictal state.

Key points

- Decreased connectivity in multiple resting-state networks (RSNs) has been established in disorders of consciousness, representing postictal symptoms
- We investigated postictal RSNs with group-information guided independent component analysis at one hour after the ECT-induced seizure
- Decreased connectivity in the left central executive and auditory network has been found, controlled for test-retest effects

6.1 Introduction

Postictal symptoms manifest as neurologic, psychiatric, and autonomous symptoms, often involving an impaired state of consciousness and add to the burden of epilepsy (14, 25, 38, 162). Neuroimaging studies of the postictal state in epilepsy patients are hampered by the unpredictable nature of epileptic seizures (38, 184). This is probably why little is known about which brain dynamics underlie these clinical symptoms. However, disrupted functional connectivity may be expected, because epilepsy is increasingly conceptualized as a brain network disorder (254). Functional connectivity in the brain can be investigated with functional magnetic resonance imaging (fMRI), which is able to extract so-called resting state networks (RSNs). Anatomically separate but functionally connected brain regions from such RSNs can be extracted with independent component analysis (ICA) (255, 256). RSNs serve as a proxy for synchronous neuronal activity intrinsically generated by the brain at rest (i.e., without a specific task), which allows to investigate the brain's functional architecture (255, 257).

Studies using fMRI in epilepsy research are scarce, however, the most common finding in patients who experienced generalized tonic-clonic seizures is a decrease in functional connectivity within the default mode network (DMN) and the attention network (ATN), also sometimes referred to as dorsal attention network, suggesting a reorganization of these networks in patients with recurrent seizures (258-263). In patients exposed to repeated seizures due to mesial temporal lobe epilepsy, it was hypothesized that accumulating white matter alterations disrupt connecting DMN nodes, which may result in decreased DMN connectivity (264). Otherwise, shorter seizures have been related to higher mean functional connectivity values in the medial prefrontal cortex, a key node in the DMN (258). Within-network connectivity of the ATN has been shown to decrease in refractory epilepsy (261).

Most previous studies have been performed in the interictal state (i.e., with unknown interval between the last seizure and MRI acquisition). Knowledge about the immediate postictal state is lacking. To date, only one study investigated rs-fMRI in rats within the first minutes postictally, finding widespread postictal cortical blood oxygenation level dependent (BOLD) decreases, mostly in the hippocampus (265). How long these effects persist and if these effects are also present in humans is unclear. Also, it remains unknown how these changes are related to postictal clinical manifestations.

After generalized seizures, patients often display unresponsiveness, sleepiness, and in severe cases confusion or postictal delirium, which can be defined as impaired states of consciousness (38, 162). In (other) delirious states, dysfunction of the DMN, ATN, salience network (SN), and central executive control network (CEN) have been hypothesized, but studies reported mixed results, varying from increased to decreased connectivity (266-268), increased connectivity of the DMN with frontal regions (i.e., posterior cingulate cortex and medial prefrontal cortex), and reduced connectivity between subcortical and cortical regions (i.e., striatum, temporal pole, orbitofrontal cortex) (268). A model of delirium has been proposed,

wherein subcortical regions have hyperconnectivity with the SN, leading to problems in its regulatory function (268). Taken together, these findings indicate that, in addition to the DMN and ATN, the SN and CEN may play a role in the postictal state as well.

We aimed to study changes in RSNs directly after the seizure. To achieve this, we acquired rs-fMRI scans at approximately one hour after electroconvulsive therapy (ECT)-induced seizures, to investigate postictal changes in functional connectivity in twelve large-scale canonical RSNs compared to baseline, controlled for test-retest effects in healthy controls. We hypothesized that the postictal state would be associated with functional connectivity changes in the ATN, DMN, CEN, and SN.

6.2 Methods

6.2.1 Study design

This is a *post hoc* analysis with rs-fMRI data of the prospective clinical trial with three-condition randomized cross-over design SYNAPSE, in which patients participated in two medications and one placebo condition (NCT04028596) (35). SYNAPSE was approved by the local medical-ethical authority, and the protocol and primary outcomes of this study can be found elsewhere (see Supplementary material **chapter 7**, 7.7) (35). For the current analyses, we used rs-fMRI scans at baseline (i.e., < 1 week before start of the ECT-course) and 1 h after the ECT-induced seizure in the placebo condition (i.e., 50cc water), as measure of the immediate postictal state. To interpret our results in patients, we controlled for test-retest effects using two separate rs-fMRI measures from healthy controls (i.e., baseline and follow-up), scanned with the same MRI device and software.

6.2.2 Participants

Patients aged ≥ 18 years, who were diagnosed with major depressive episode and treated with ECT at Rijnstate Hospital, Arnhem, The Netherlands, were included. Exclusion criteria were chronic use of acetaminophen, Ca^{2+}-antagonists, or non-steroid anti-inflammatory drugs, and contraindications for undergoing MRI (35). Healthy controls had no history of psychopathology, had no contraindications for undergoing MRI, and were matched to patients in age, sex, and level of education. All participants were Dutch speaking and gave oral and written informed consent.

6.2.3 ECT procedure

ECT was administered according to the Dutch treatment guideline. Electrode placement included unilateral (UL; according to d'Elia(24)) or bifrontotemporal (BL; also known as bitemporal). ECT was administered using a Thymatron System IV device (Somatics Incorporation Lake Bluff, Illinois, USA), delivering a stimulus with constant-current (0.9 Ampère) in bidirectional, square waves and in brief pulses (1 ms). Intravenously, patients received anesthesia (etomidate 0.2-0.3 mg/kg) and

proper muscle relaxation (succinylcholine 0.5-1 mg/kg), and were pre-oxygenated (100% O_2, positive pressure) until resumption of spontaneous respiration. In case of severe postictal confusion or restlessness, 2.5-5 mg midazolam was administered intravenously. Pre- and post-ECT medication was kept constant in the context of current care and left to the discretion of the treating psychiatrist (e.g., antidepressant, antipsychotic, analgesic) (184).

6.2.4 Electroencephalography

Ictal electroencephalography (EEG) was used to determined seizure duration. Twelve silver/silver chloride cup electrodes were applied according to the international 10-20 system. EEGs were recorded using a NeuroCenter EEG recording system (Clinical Science Systems) with a full-band DC-coupled amplifier (TMSi). Seizure duration was determined visually and defined as the time interval in seconds between the onset of rhythmicity or spike-wave complexes and the onset of postictal generalized suppression in all channels. More details are provided elsewhere (**chapter 3 and 4**) (184, 269).

6.2.5 Clinical reorientation time

Clinical recovery after seizures was assessed with the reorientation time questionnaire (ROT) comprising five items (193). Patients were asked to reproduce their name, age, birthday, current location (i.e., the hospital's name), and the day of the week. A score in minutes was assigned based on the number of correct responses out of five questions, with a minimum threshold of four correct answers compared to baseline responses. The resulting scores varied between 5 and 100 minutes.

6.2.6 Imaging data acquisition, preprocessing, and analyses

6.2.6.1 Data acquisition

High-resolution T_1-weighted (T_1W) and rs-fMRI data were acquired at baseline and in the postictal state, using a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) equipped with a SENSE eight-channel receiver head coil. The scanning protocol included a high-resolution T_1W turbo field echo MRI (sequence parameters = TR 7.5 ms, TE 4.6 ms, flip angle 8°, 145 sagittal slices, voxel size 1.1 mm isotropic, scan duration 5.5 min) and rs-fMRI (sequence parameters= TR 1981 ms, TE 27 ms, flip angle 90°, voxel size 3.0 x 3.0 x 3.0 mm, FOV 240 mm, 160 volumes). During the rs-fMRI scans, patients were instructed to relax and stay awake.

6.2.6.2 Preprocessing

Preprocessing was performed using a singularity image container running *fMRIPrep* (v21.0.2, https://fmriprep.org/en/21.0.2/) (270). *fMRIPrep* uses a standardized procedure involving generation of a reference volume, co-registration to the T_1W image, motion correction (ICA-AROMA), and normalization to MNI space

(MNI152NLin2009cAsym) using a combination of all spatial transformations. *fMRIPrep's* non-aggressive denoised motion corrected output was verified by visual inspection of the individual reports. Our subsequent preprocessing pipeline consisted of i) skull stripping, ii) spatial smoothing with an isotropic, Gaussian kernel of 6mm full-width-at-half-maximum, iii) nuisance regression (regressing out average white matter and cerebrospinal fluid signals to exclude physiological noise), iv) removal of first 5 non-steady state volumes, and v) high-pass filtering by 0.007 Hz. Volumes with excessive movement (i.e., framewise displacement of > 3 mm were removed from BOLD timeseries. Detailed information about the *fMRIPrep* pipeline is presented in the Supplementary material. After preprocessing, quality control was performed, selecting scans that retained at least 4 min of sufficiently motion-free data, with a mean framewise displacement of < 0.6 mm.

6.2.6.3 Spatially constrained independent component analysis

A multivariate-objective optimization ICA with reference (MOO-ICAR) algorithm was used (271, 272). This analysis has been conducted within the Group ICA for fMRI toolbox (icatb.sourceforge.net) (271). In MOO-ICAR, first, twelve large-scale brain networks from 160 healthy controls were used as templates to extract ICs on the subject and session level (272-274). This analysis preserved independence of ICs at the subject level while ensuring correspondence of ICs across subjects and enables more accurate longitudinal ICA analyses (272). Twelve large-scale resting state networks were selected for further analysis, with the DMN, ATN, SN, and CEN as primary networks of interest (273).

6.2.6.4 Mean network connectivity strength

Mean network connectivity strength within each IC was investigated with average Z-scores, reflecting the magnitude of functional connectivity within a RSN (i.e., IC) (275). We binarized all group-level ICs (Z-score > 1), which were combined with the subject specific ICs. The mean of all voxels within an IC was calculated, yielding one Z-score per participant and per time point (i.e., baseline, postictal, follow-up) for each IC. Difference IC maps between two time points were calculated and then overlayed with the binarized group-level ICs.

6.2.7 Statistical analyses

For all clinical, demographic, and mean network connectivity strength data, the statistical program R version 4.2.3 was used (174). Quantitative variables were reported as medians with interquartile ranges (IQR). Patients and healthy controls were compared with respect to age, sex, and level of education with *t*-tests and chi-square tests, where appropriate. *P*-values < 0.05 were considered statistically significant.

We investigated mean network strength with Bayesian regression models to explore group by time interaction effects (i.e., patients and healthy controls corrected for age and sex) and relations with clinical variables (i.e., seizure duration, electrode placement, and time interval between ECT-stimulus and rs-

fMRI acquisition) in the ICs of interest, and exploratively in the remaining ICs, using the package brms (202). Exploratory regression analyses were used to investigate the effect of the use of postictal midazolam on mean network strength per resting state network. In the Bayesian analyses, we used 4 chains with 2000 draws of the posterior distribution per chain. A gaussian likelihood and default priors were used for the b eta coefficients. The first 1000 draws of each chain were considered warmup and therefore discarded. Beta coefficients that were large or smaller than 0 with a probability of 95% were considered credible (which may compared with the label 'significant' in frequentist statistics). For equivalence testing, region of practical equivalence was defined at the interval (0.02, 0.02) based on the standard deviation of the outcome variables. If 95% of the posterior beta coefficient fell within the ROPE, equivalence was inferred (237).

To investigate voxel-wise changes between baseline and postictal ICs, controlled for test-retest effects in healthy controls, subject specific difference IC maps were used as input for nonparametric permutation tests in Parametric Analyses of Linear Models (PALM; www.fmrib.ox.ac.uk/fsl). First, we investigated changes in the DMN, ATN, SN, and CEN (i.e., divided in left and right CEN) between baseline and the postictal state, compared to changes in healthy controls (i.e., group by time interaction effect), with an omnibus *F*-test. In case of a significant *F*-test, one-tailed two-sample *post hoc t*-test were performed to assess simple effects. Age and sex were entered as covariates of no interest. Threshold-free cluster enhancement (TFCE) for family wise error (FWE) correction with an α-level of 0.05 and correction for multiple components (i.e., five RSNs of interest) and contrasts were applied (236). Second, to investigate changes in RSNs in relation with seizure duration, we used separate regression models for the networks of interest, and, again, controlled for multiple components. All analyses were also performed exploratively with the remaining RSNs (i.e., auditory, cerebellar, language, somatomotor, subcortical, primary and secondary visual networks) with statistical significance corrected for multiple comparisons across voxels and RSNs ($p < 0.05$, with TFCE and FWE-corrected). For all voxel-wise analyses MATLAB version 2022a was used (Natick, Ma, The Math Works, 2022 Inc.).

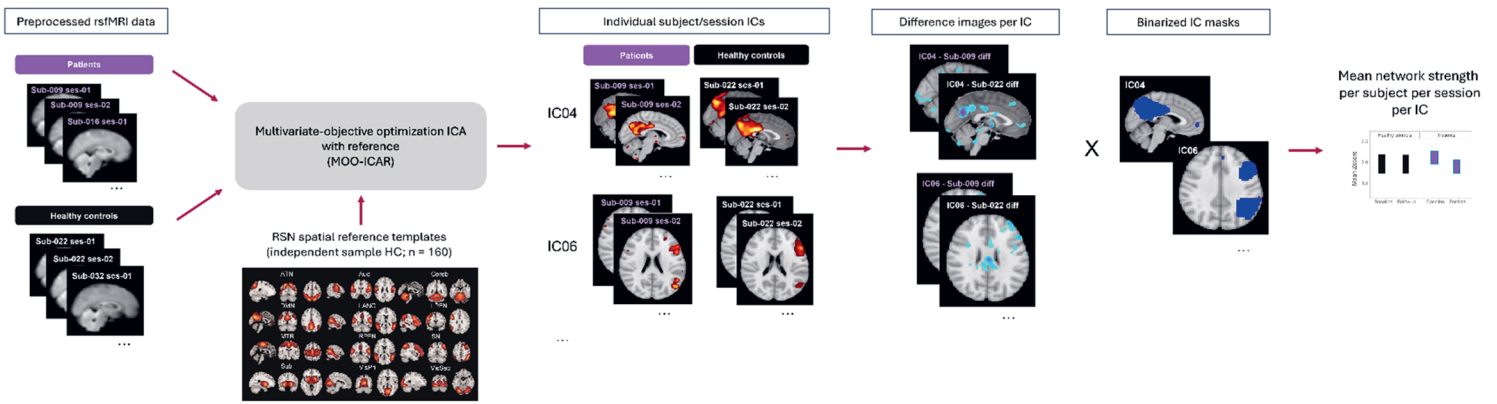


Figure 6.1 Flowchart depicting resting-state functional magnetic resonance imaging (rs-fMRI) data analyzed with the multivariate-objective optimization independent component analysis with reference (MOO-ICAR; A) algorithm, yielding 12 canonical large-scale resting state networks (RSNs; B). Mean network strength was computed per resting state network (i.e., IC), using individual subject ICs overlayed with binarized IC masks (Z-score >1) of each IC. A detailed overview of all RSNs can be found in the supplementary material (Figure S6.1). ATN = attention network, Aud = auditory network, Cereb = Cerebellar network, DMN = default mode network, LANG = language network, LCEN = left central executive network, MTR = somatosensory network, RCEN = right central executive network, SN = salience network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network.

6.3 Results

6.3.1 Participants

Twenty patients (median age 57 years [IQR = 21.3], 11 females [55%]) and 27 healthy controls (median age 55 years [IQR = 23], 15 females [56%]) were included, who did not differ in age ($p = 0.748$), sex ($p = 0.826$), or level of education ($p = 0.227$). Eleven patients were treated with BL electrode placement and nine with UL (i.e., one with left and eight with right UL placement). At the ECT-session before rs-fMRI acquisition, median seizure duration was 53 sec (IQR = 31), elicited by applying a median delivered electrical charge of 303.4 mC (IQR = 182.5). Patient and ECT characteristics are provided in Table 6.1.

Table 6.1 Patient and ECT characteristics

Characteristic	Patients (N = 20)
Age in years, median (IQR; range)	57.5 (21.3; 21 – 82)
Female, n (%)	11 (55)
Bifrontotemporal electrode placement*, n (%)	11 (55)
Median delivered charge at the ECT-session before rs-fMRI acquisition, in millicoulombs (IQR; range)	303.4 (182.5; 125.6 – 659.7)
Median seizure duration at the ECT-session before rs-fMRI acquisition, in seconds (IQR; range)	53 (31; 31 – 114)
Number of ECT-sessions in which postictal midazolam was administered before rs-fMRI acquisition, n (%)	7 (35)
Median interval between the ECT-stimulus and postictal rs-fMRI image acquisition, in minutes (IQR; range)	77.5 (12.3; 64 – 101)

*Four patients were initially treated with right unilateral electrode placement, which was changed to bifrontotemporal electrode placement until the end of their ECT-course. IQR = interquartile range, ECT = electroconvulsive therapy, rs-fMRI = resting-state functional magnetic resonance imaging

6.3.2 Mean network connectivity strength

6.3.2.1 Networks of interest

In the Bayesian regression models, we established a credible group by time interaction in the left CEN (-0.18 [CI95 -0.26, -0.10], see Table 6.2 and Figure 6.2A), meaning that patients had lower mean network connectivity strength in the postictal state compared to baseline, relative to changes over time in healthy

controls. These results were confirmed when examining mean network connectivity changes in patients, controlling for clinical variables (i.e., seizure duration, electrode placement, ROT, or time interval between ECT-stimulus and rs-fMRI acquisition; see Supplementary Table S6.1). We did not establish credible interactions in any of the other networks (see Table S6.2). Postictal midazolam did not affect change in mean network connectivity strength in any RSN (see Table S6.3). In patients, none of the clinical variables were credibly related to changes in mean network connectivity strength in the remaining RSNs (see Table S6.4). Between the two measurements, healthy controls showed no change of mean network connectivity strength in any of the RNSs (see Table S6.5).

6.3.2.2 Other networks

In exploratory analyses, we established a credible postictal decrease in mean connectivity strength in the auditory network (-0.22 [CI95 -0.36, -0.07]), compared to healthy controls (Figure 6.2B). None of the remaining RSNs showed any credible group by time interaction effects.

Table 6.2 Bayesian regression results highlighting credible group by time interactions in the left central executive and auditory networks

	Networks of interest										Other networks	
	ATN		DMN		LCEN		RCEN		SN		AUD	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	-0.1	-0.4 – 0.2	0.0	-0.3 – 0.3	-0.1	-0.3 – 0.1	0.1	-0.2 – 0.4	0.1	-0.1 – 0.3	-0.2	-0.5 – 0.1
Group (Patients)	-0.1	0.2 – 0.1	-0.1	-0.2 – 0.1	-0.2	-0.3 - - 0.1	-0.1	-0.3 – 0.0	-0.0	-0.1 – 0.1	-0.2	-0.4 – - 0.1
Age (years)	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
Sex (Female)	0.1	-0.0 – 0.3	-0.1	-0.2 – 0.1	-0.0	-0.1 – 0.1	0.1	-0.1 – 0.2	0.0	-0.1 – 0.1	0.0	-0.1 – 0.2
ROPE interpretation					Credible						Credible	

ATN = attention network, AUD = auditory network, DMN = default mode network, LCEN = left central executive network, RCEN = right central executive network, SN = salience network, ROPE = region of practical equivalence, CI = credibility interval

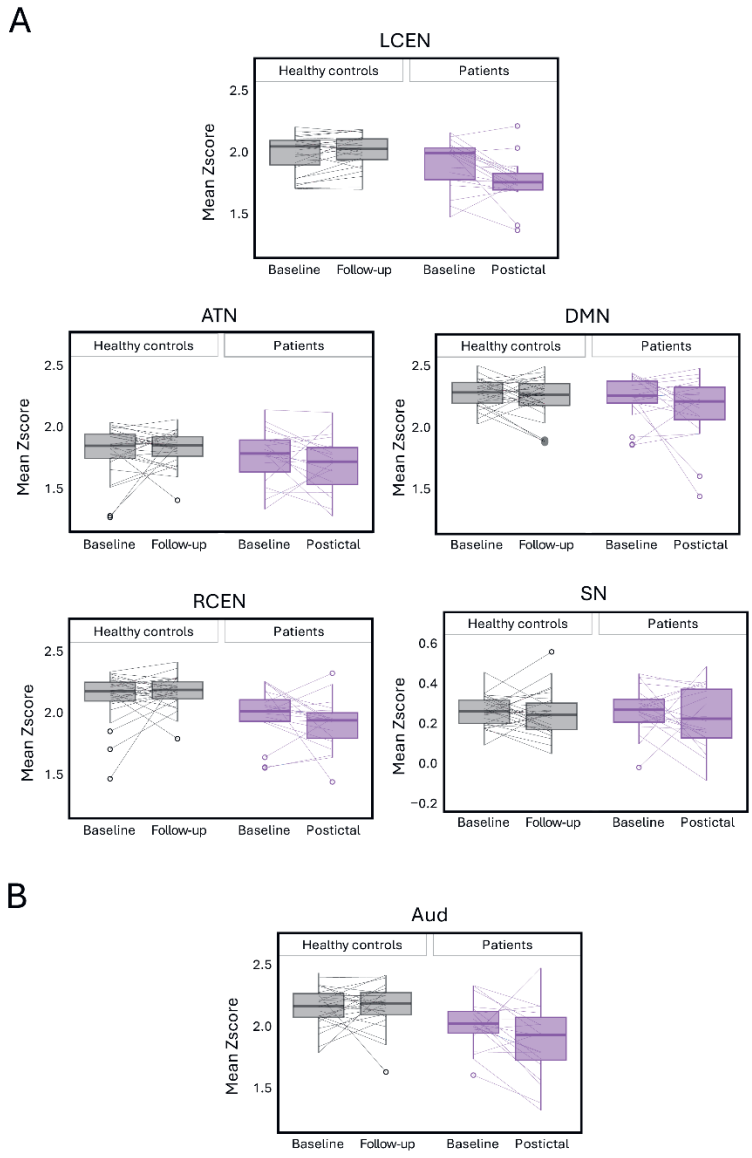


Figure 6.2 Changes in postictal mean network connectivity strength in the resting state networks (RSNs) of interest (A) and changes in the exploratory auditory network (B). Postictal mean network connectivity strength was decreased in the left central executive and auditory network in electroconvulsive therapy patients (n = 20) compared to healthy controls (n = 27). Note that y-axis ranges for the salience network were adjusted for improved readability. ATN = attention network, DMN = default mode network, LCEN = left central executive network, RCEN = right central executive network, SN = salience network.

6.3.3 Voxel-wise analyses

6.3.3.1 Networks of interest

We established a significant group by time interaction effect in the LCEN (i.e., inferior frontal gyrus) due to a relative decrease in connectivity over measurements in patients and an increase in healthy controls (number of voxels = 321, *p*-value = 0.007, MNI voxel location = -52, 24, -4, see Figure 6.3). Follow-up *t*-tests did not reveal any significant changes over measurements in patients or healthy controls. We did not establish baseline differences between patients and healthy controls nor a relation between connectivity changes and seizure duration. The other RNSs of interest did not show any changes in patients compared to those in healthy controls.

6.3.3.2 Other networks

No significant group by time interactions were observed in other RSNs.

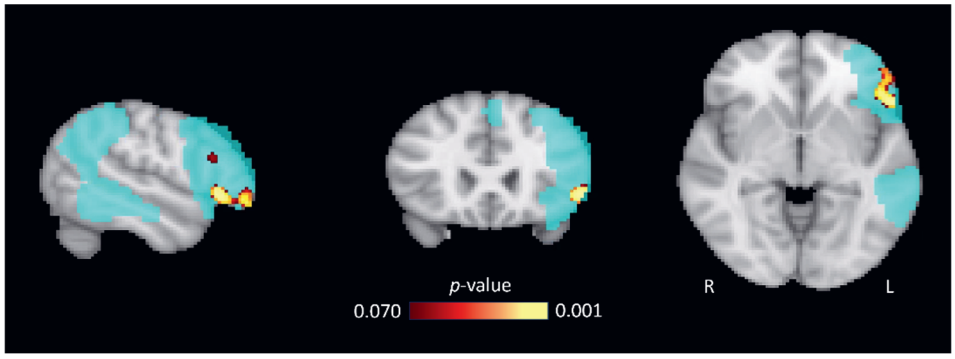


Figure 6.3 Voxel-wise analyses revealed local postictal changes in the left central executive network (LCEN) in electroconvulsive therapy patients (n = 20) controlled for test-retest variability in healthy controls (n = 27). Patients show a blunted decrease in within-network connectivity compared to healthy controls (i.e., showing increased connectivity at the second measurement). The blue areas represent the LCEN mask. *P*-value maps are shown, with presented *p*-values ranging from 0.070 to 0.001 for illustration purposes. MNI voxel location is -52, 24, -4. R = right, L = left.

6.4 Discussion

In this study, we investigated postictal changes in RSN functional connectivity in patients after ECT-induced seizures. The results showed reductions in mean network connectivity strength in the left CEN and auditory network. We also found a relative decrease in voxel-wise within-network connectivity in the left CEN in patients, when compared to healthy controls. Age, sex, ECT electrode placement,

time interval between ECT-stimulus and rs-fMRI acquisition, seizure duration, and postictal midazolam administration were not related to network changes.

Little is known about RSNs in the early postictal state, directly after a seizure. Our findings are largely in line with our hypotheses, which were based on studies of delirium, which closely resembles the postictal state clinically (266-268). We hypothesized to find decreased connectivity in the ATN, DMN, CEN, and SN, as such changes have been established in delirium (266-268). As expected, we found decreased functional connectivity changes in the (left) CEN, which underlie postictal impairments as disorientation, confusion, and memory disturbances.

Although unanticipated, we also found decreased mean connectivity strength in the auditory network. One explanation for this change in the auditory network may be the location of the electrodes to apply the electrical stimulus (i.e., the UL or BL electrode placement). The auditory network comprises, amongst other, the right and left primary auditory cortex, lateral superior temporal gyrus and posterior insular cortex (276) Possibly, these networks were disrupted due to the flow of electricity through these regions (see Figure 6.4) (33). This argument is supported by findings in epilepsy patients, where decreased functional connectivity has been found in seizure onset zones (277).

Decreased functional connectivity in the auditory network has also been reported in patients with idiopathic epilepsy and generalized tonic-clonic seizures in the interictal state (258). Patients with temporal lobe epilepsy similarly showed decreased functional connectivity in the auditory network (278). Furthermore, decreased functional connectivity in the CEN has been reported in epilepsy patients during cognitive tasks (279-281). In these studies, measurements were performed in the interictal state (i.e., also possibly in the late postictal state), implying that decreased connectivity would endure far beyond the postictal state.

Although we did not relate our rs-fMRI findings to the clinical measure of recovery at the time of scanning (i.e., ROT), our findings are probably related to the clinical manifestations of the postictal state. It has been suggested that the CEN interacts with the DMN and the ATN to mediate memory and attention, which are both cognitive functions that are impaired in the postictal state (282-284). In ECT, impaired attention, anterograde and retrograde amnesia are well-known cognitive side-effects, which may persist up to half a year after the treatment course (29, 285). Dysfunction in the CEN may also be related to disorganization of thought, which may be associated with postictal psychosis (264, 286, 287). We have previously shown that ECT is a good model for epilepsy, because the ictal and postictal states after ECT-induced seizures are sufficiently similar to that of spontaneous seizures in epilepsy patients (184). We – therefore – may conclude that our findings may be generalized to epilepsy patients.

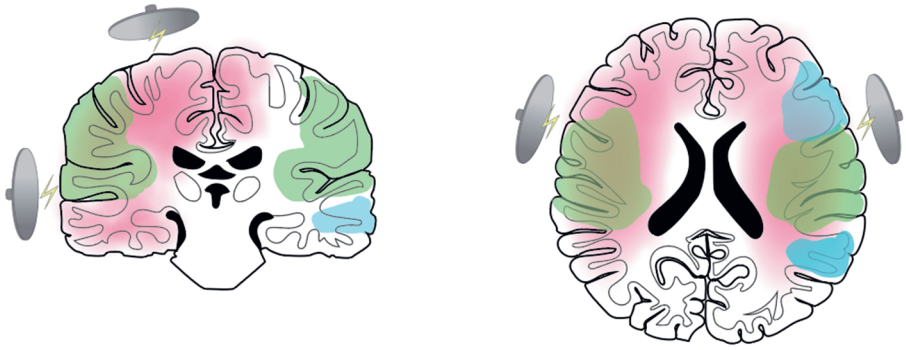


Figure 6.4 Schematic representation of disruption of the left central executive network (blue) and the auditory network (green) induced by the electrical stimulus (red) administered with right unilateral (left) or bifrontotemporal (right) electrode placement, in electroconvulsive therapy.

Apart from the ECT stimulus or the seizure itself, decreased connectivity may be induced by the use of general anesthesia. Propofol-induced loss of consciousness has been related to decreased connectivity in the DMN and CEN (288). We used etomidate as anesthetic agent in this study. However, at the time of rs-fMRI acquisition, all patients were conscious and adequate, so anesthesia effects were probably small.

6.4.1 Strengths and limitations

In this study, we were able to systematically investigate RSNs during the immediate postictal state by using ECT-induced seizures. We controlled for test-retest effects by investigating healthy controls twice on the same MRI-scanner. Herewith, we show that systematic investigation of postictal RSNs in patients is feasible. Interpretation of our results is limited by the relatively small sample size, which may have reduced our ability to find credible postictal differences in other networks.

6.5 Conclusion

In this analysis or prospectively collected rs-fMRI data, ECT-induced seizures were associated with a postictal decrease of connectivity strength in the left CEN and the auditory network. These network changes may underlie clinical features of the postictal state.

6.6 Supplementary material

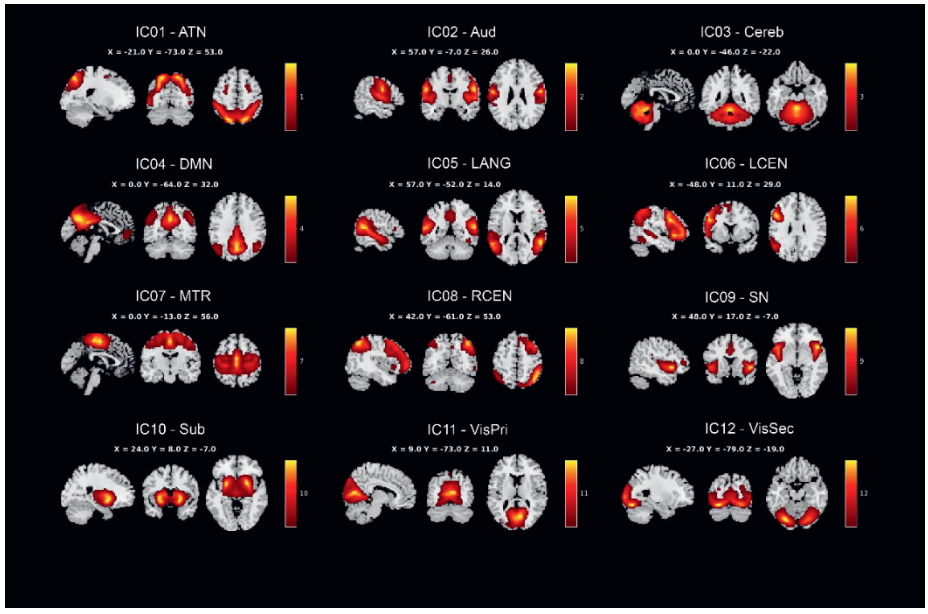


Figure S6.1 Overview of all RSN templates based on an independent sample of healthy controls (n = 160). ATN = attention network, AUD = auditory network, Cereb = Cerebellar network, DMN = default mode network, LANG = language network, LCEN = left central executive network, MTR = somatosensory network, RCEN = right central executive network, SN = salience network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network

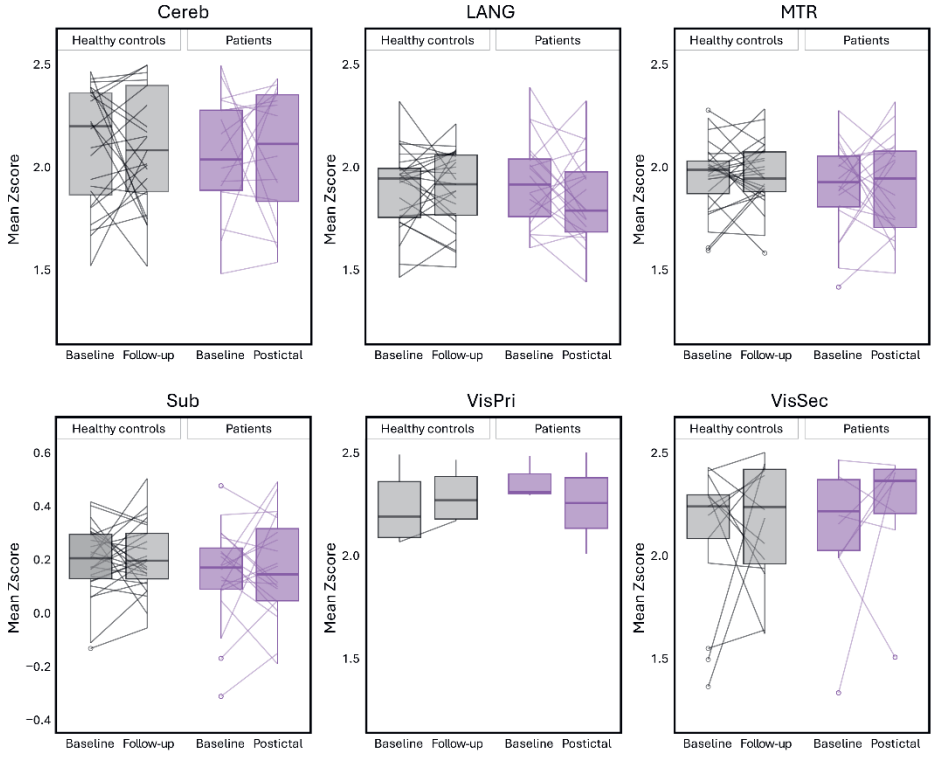


Figure S6.2 Postictal mean network connectivity in exploratory resting-state networks (RSNs) that did not show any changes compared to baseline in electroconvulsive therapy patients (n = 20) compared to healthy controls (n = 27). Cereb = cerebellar network, LANG = language network, MTR = sensorimotor network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network.

Table S6.1 Bayesian mixed model results in patient showing decreased postictal mean network connectivity strength in the left central executive and auditory networks

	ATN		DMN		LCEN		RCEN		SN		AUD	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	1.2	0.0 – 2.3	2.1	1.2 – 2.9	1.9	1.0 – 2.9	2.2	1.5 – 2.9	0.2	-0.3 – 0.8	2.2	1.2 – 3.2
Session (Postictal)	-0.0	-0.2 – 0.1	-0.1	-0.2 – 0.1	-0.2	-0.3 – -0.1	-0.1	-0.2 – 0.0	-0.0	-0.1 – 0.1	-0.2	-0.3 - -0.1
Age (years)	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	-0.1	-0.3 – 0.1	-0.1	-0.2 – 0.1	-0.1	-0.3 – 0.1	-0.2	-0.3 - -0.1	-0.1	-0.2 – 0.0	-0.2	-0.4 – 0.0
Seizure duration (s)	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
Electrode placement (UL)	0.1	-0.2 – 0.3	0.1	-0.1 – 0.3	0.0	-0.1 – 0.2	0.1	-0.1 – 0.2	-0.0	-0.1 – 0.1	0.2	-0.0 – 0.4
Δt ECT-stimulus – rs-fMRI (min)	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
ROT	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
ROPE interpretation					Credible		Credible				Credible	

ATN = attention network, Aud = auditory network, DMN = default mode network, LFPN = left central executive network, RCEN = right central executive network, SN = salience network, ROPE = region of practical equivalence, CI = credibility interval, UL = unilateral, Δt ECT-stimulus – rs-fMRI = time interval between the electroconvulsive therapy stimulus and acquisition of resting state functional magnetic resonance imaging, ROT = reorientation time.

Table S6.2 Bayesian regression results of patients and healthy controls showing no group by time interaction effects in any of the remaining RNSs

	Cereb		LANG		MTR		Sub		VisPri		VisSec	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	-0.6	-1.1 - -0.1	-0.1	-0.3 – 0.2	-0.1	-0.4 – 0.3	0.1	-0.2 – 0.3	0.0	-0.4 – 0.5	0.0	-0.5 – 0.5
Group (Patients)	-0.0	-0.2 – 0.2	-0.1	-0.2 – 0.1	-0.0	-0.2 – 0.1	0.0	-0.1 – 0.1	-0.0	-0.2 – 0.2	0.1	-0.1 – 0.4
Age (years)	0.0	0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	0.2	-0.1 – 0.4	0.0	-0.1 – 0.2	-0.0	-0.2 – 0.1	0.0	-0.1 – 0.1	0.1	-0.1 – 0.2	0.1	-0.2 – 0.3

Cereb = Cerebellar network, LANG = language network, MTR = somatosensory network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network, ROPE = region of practical equivalence, CI = credibility interval.

Table S6.3 Bayesian mixed model results of the influence of postictal midazolam administration on changes of mean network connectivity strength in any of the RNSs

	ATN		DMN		LCEN		RCEN		SN		AUD	
Predictors	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*Cr (95%)*
Intercept	0.0	-0.9 – 0.9	-0.1	-1.1 – 0.9	-0.3	-1.0 – 0.5	-0.2	-1.2 – 0.7	0.0	-0.6 – 0.6	-0.2	-1.2 – 0.8
Age (years)	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
Sex (Female)	-0.0	-0.4 – 0.4	-0.1	-0.5 – 0.4	-0.1	-0.4 – 0.2	0.0	-0.4 – 0.4	0.2	-0.1 – 0.5	-0.0	-0.5 – 0.4
Postictal midazolam (Yes)	-0.1	-0.5 – 0.3	0.0	-0.5 – 0.5	0.0	-0.3 – 0.4	-0.0	-0.5 – 0.4	0.1	-0.1 – 0.4	-0.1	-0.5 – 0.4
	Cereb		LANG		MTR		Sub		VisPri		VisSec	
Predictors	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*	*Estimates*	*CI (95%)*
Intercept	-0.7	-2.3 – 0.9	0.2	-0.7 – 1.2	0.2	-0.9 – 1.2	0.0	-0.7 – 0.8	0.2	-1.0 – 1.2	0.4	-0.8 – 1.6
Age (years)	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	0.3	-0.5 – 1.1	-0.1	-0.6 – 0.3	-0.2	-07 – 0.3	0.1	-0.2 – 0.5	-0.0	-0.5 – 0.5	0.0	-0.6 – 0.6
Postictal midazolam (Yes)	0.0	-0.8 – 0.8	-0.1	-0.5 – 0.3	-0.1	-0.6 – 0.4	0.0	-0.3 – 0.4	0.0	-0.5 – 0.5	-0.0	-0.6 – 0.6

ATN = attention network, AUD = auditory network, DMN = default mode network, LFPN = left central executive network, RCEN = right central executive network, SN = salience network, CI = credibility interval, Cereb = Cerebellar network, LANG = language network, MTR = somatosensory network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network.

Table S6.4 Bayesian mixed model results in patients showing decreased postictal mean network connectivity strength in females in language network

	Cereb		LANG		MTR		Sub		VisPri		VisSec	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	1.6	0.4 – 2.9	2.4	1.7 – 3.2	2.1	1.0 – 3.1	0.3	-0.1 – 1.1	3.4	2.3 – 4.5	2.7	1.5 – 4.0
Session (Postictal)	0.0	-0.2 – 0.2	-0.1	-0.2 – 0.0	0.0	-0.1 – 0.2	0.0	-0.1 – 0.1	-0.0	-0.2 – 0.1	0.1	-0.0 – 0.3
Age (years)	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	-0.2	-0.5 – -0.0	-0.24	-0.4 – -0.1	-0.1	-0.3 – 0.1	-0.0	-0.3 – 0.0	-0.2	-0.4 – 0.1	-0.2	-0.5 – 0.0
Seizure duration (s)	0.0	-0.0 -0.0	0.0	-0.0 -0.0	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 -0.0	-0.0	-0.0 -0.0
Electrode placement (UL)	0.0	-0.2 – 0.3	-0.0	-0.2 – 0.1	-0.0	-0.3 – 0.2	-0.1	-0.2 – 0.1	-0.1	-0.3 – 0.2	-0.1	-0.4 – 0.2
Δt ECT-stimulus – rs-fMRI (min)	0.0	-0.0 – 0.0	-0.0	-0.0 -0.0	0.0	-0.0 – 0.0	0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	0.0	-0.0 – 0.0
ROPE interpretation	Undecided		Credible									

Cereb = Cerebellar network, LANG = language network, MTR = somatosensory network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network, ROPE = region of practical equivalence, CI = credibility interval, UL = unilateral, Δt ECT-stimulus – rs-fMRI = time interval between the electroconvulsive therapy stimulus and acquisition of resting state functional magnetic resonance imaging

Table S6.5 Bayesian regression results of patients and healthy controls showing no group by time interaction effects in any of the remaining RNSs

	ATN		AUD		DMN		LCEN		RCEN		SN	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	1.8	1.6 – 2.0	1.8	1.7 – 2.0	1.8	1.6 – 2.0	1.8	1.6 – 2.0	1.8	1.7 – 2.0	1.8	1.6 – 2.0
Session (Follow-up)	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1
Age (years)	-0.0	-0.0 – 0.0	-0.0	-0.0 -0.0	-0.0	-0.0 -0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.0	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0

ATN = attention network, Aud = auditory network, DMN = default mode network, LFPN = left central executive network, RCEN = right central executive network, SN = salience network, ROPE = region of practical equivalence, CI = credibility interval,

Table S6.5 (continued) Bayesian regression results of patients and healthy controls showing no group by time interaction effects in any of the remaining RNSs

	Cereb		LANG		MTR		Sub		VisPri		VisSec	
Predictors	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)	Estimates	CI (95%)
Intercept	1.8	1.6 – 2.0	1.8	1.7 – 2.0	1.8	1.6 – 2.0	1.8	1.6 – 2.0	1.8	1.7 – 2.0	1.8	1.6 – 2.0
Session (Follow-up)	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1	0.0	-0.1 – 0.1
Age (years)	-0.0	-0.0 – 0.0	-0.0	-0.0 -0.0	-0.0	-0.0 -0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0	-0.0	-0.0 – 0.0
Sex (Female)	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.0	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0	-0.1	-0.2 – 0.0

Cereb = Cerebellar network, LANG = language network, MTR = somatosensory network, Sub = subcortical network, VisPri = primary visual network, VisSec = secondary visual network, ROPE = region of practical equivalence, CI = credibility interval

Chapter 7

Acetaminophen or nimodipine to improve postictal recovery after ECT-induced seizures: A randomized cross-over trial

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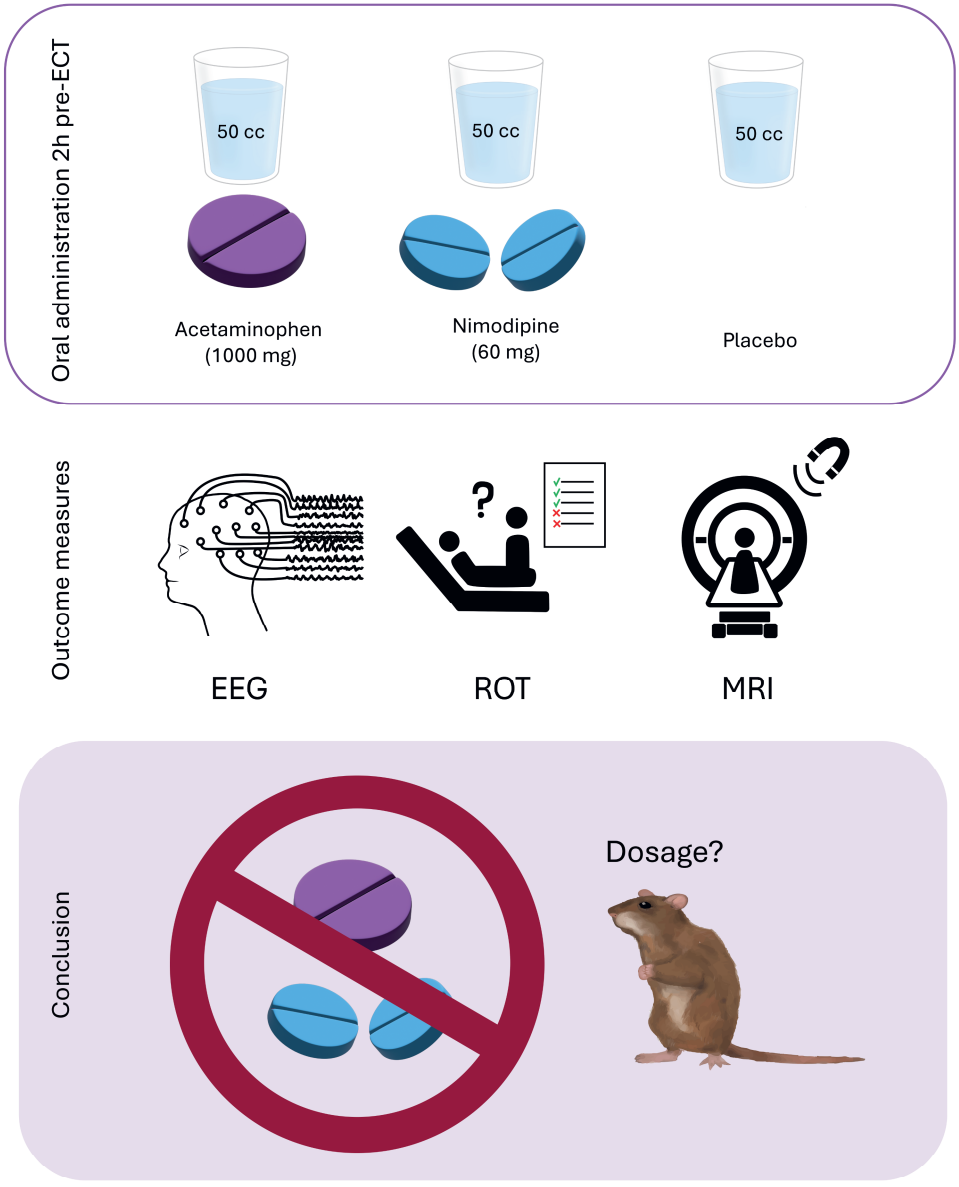
Submitted

Graphical abstract



Abstract

Background The postictal state is a largely underrecognized part of epilepsy management, with currently no effective preventive or treatment options. Electroconvulsive therapy (ECT) presents an opportunity to systematically study the postictal state and possible treatments, especially since ECT-induced postictal states have similar characteristics as those of epilepsy patients. Here, we aimed to investigate the effects of acetaminophen or nimodipine on postictal electroencephalographic (EEG) recovery, clinical reorientation, and postictal hypoperfusion after ECT.

Methods This was a prospective clinical trial with three-condition randomized cross-over design. Study enrollment was between December 3, 2019, and November 15, 2022, at Rijnstate Hospital Arnhem, The Netherlands. Two hours before ECT, 50cc of water with either acetaminophen (1000 mg), or nimodipine (60 mg), or no medication was orally administered. Before trial inclusion, four randomization blocks were computer-generated by an external hospital party and allocated sequentially. The main outcome measure was speed of postictal EEG recovery, where higher values represent slower EEG recovery, analyzed with Bayesian generalized mixed-effects models. Secondary outcomes were extent of postictal EEG recovery, clinical reorientation time, and postictal cerebral blood flow.

Findings Thirty-three patients were included with a median age of 53 years (IQR = 21.3), with 19 female patients (56%). Administration of acetaminophen or nimodipine was not associated with change in speed of EEG recovery compared to placebo (1.13 [95%CI 0.92, 1.40] and 1.07 [95%CI 0.87, 1.31], respectively). Also, the study medications did not affect our secondary outcomes, though nimodipine altered regional CBF in the posterior cortex.

Interpretation Despite promising findings from animal studies, treatment with acetaminophen or nimodipine did not improve postictal EEG recovery, clinical recovery, or global postictal cerebral blood flow (CBF) in patients with ECT-induced seizures. Study of the postictal state is feasible in ECT-induced seizures.

Key points

- Animal studies showed that acetaminophen or nimodipine can alleviate postictal symptoms
- To replicate these findings, thirty-three ECT-patients with a total of 328 EEGs and clinical measures and 72 postictal MRIs were thoroughly investigated in a clinical trial with three-condition randomized cross-over design
- Promising findings from animal studies were not replicated
- Acetaminophen or nimodipine did not improve postictal EEG recovery, clinical reorientation measures, or postictal perfusion
- Medication dosages were seventeen times lower compared to those in animal studies, limiting definite conclusions on the mechanism in humans
- Studying the postictal state is feasible, which should be considered in new studies investigating other candidate drugs (i.e., ibuprofen)

7.1 Introduction

Postictal manifestations may consist of neurological phenomena, cognitive deficits, and psychiatric symptoms. These symptoms also include sudden unexpected death in epilepsy and strongly add to the morbidity of epilepsy. The postictal state has been appointed as a neglected entity in the management of seizures (12, 14, 162, 289). The exact pathophysiology of the postictal state remains unclear. Postictal cerebral hypoperfusion through (local) vasoconstriction is a tentative mechanism (15, 16, 290). In an animal model, postictal behavioral symptoms were strongly related to local cerebral arteriolar vasoconstriction, resulting in a drop of local brain tissue oxygenation and cerebral perfusion (15, 16). This vasoconstriction could be prevented by targeting cyclooxygenase (COX)-2 or L-type Ca^{2+}-channels. When rats were pretreated with acetaminophen (i.e., selective COX-2 inhibitor) or nifedipine (i.e., Ca^{2+}-channel blocker), postictal behavioral symptoms diminished (15, 16). Nifedipine even reduced postictal symptoms when administered *after* the seizure (15). Acetaminophen and nifedipine are safe and widely available regular medications.

Assessing the postictal state is not straightforward in epilepsy patients, because of the unpredictable nature of seizures. Electroconvulsive therapy (ECT) provides an unique possibility to study the postictal state in a well-controlled, reproducible environment (184). ECT is widely used to treat severe psychiatric disorders, such as treatment-resistant depression (291-293). In ECT, generalized tonic-clonic seizures are induced by a short current pulse administrated by two electrodes on the patients' head. ECT-induced seizures are generally followed by acute postictal side-effects, similar to those in epilepsy patients (27, 184). As a clinical measure of the135ostictall state, the time it takes for patients to reorient in person, place, and time can be assessed (194). Furthermore, continuous electroencephalography (EEG) before, during, and after ECT-induced seizures can provide quantitative features for postictal recovery (184). Arterial spin labeling magnetic resonance imaging (ASL-MRI) enables the measurement of postictal cerebral blood flow (CBF) (231).

In this prospective clinical trial with three-condition randomized cross-over design, we aimed to investigate the effect of acetaminophen or nimodipine on the postictal state in patients with ECT-induced seizures. We hypothesized that treatment with acetaminophen or nimodipine would lead to faster postictal EEG recovery, a shorter time to complete clinical reorientation, and less postictal cerebral hypoperfusion, compared to the placebo condition.

7.2 Methods

7.2.1 Trial design

The StudY of effect of Nimodipine and Acetaminophen on Postictal Symptoms after Electroconvulsive therapy (SYNAPSE) trial (NCT04028596) was a prospective,

monocenter, single-blind, clinical trial with a three-condition randomized cross-over design, executed at Rijnstate Hospital, Arnhem, The Netherlands. The trial was approved by the local medical-ethical authority and conducted according to standards of good clinical practice. Exact trial details are described elsewhere (35).

7.2.2 Trial population

Fifty-nine patients were screened for participation (Figure 1). The trial population consisted of 33 adult patients, who were indicated for ECT because of severe depressive episodes, and who were willing and able to provide written informed consent. The method to collect sex data was self-report. Exclusion criteria were known adverse or allergic reactions to acetaminophen or nimodipine, chronic use of acetaminophen, Ca^{2+}-antagonists or non-steroidal anti-inflammatory drugs, and contraindications for undergoing MRI. Unilateral (UL) and bifrontotemporal (BL) ECT were performed in accordance with the Dutch clinical guidelines which are comparable to international standards (21, 159).

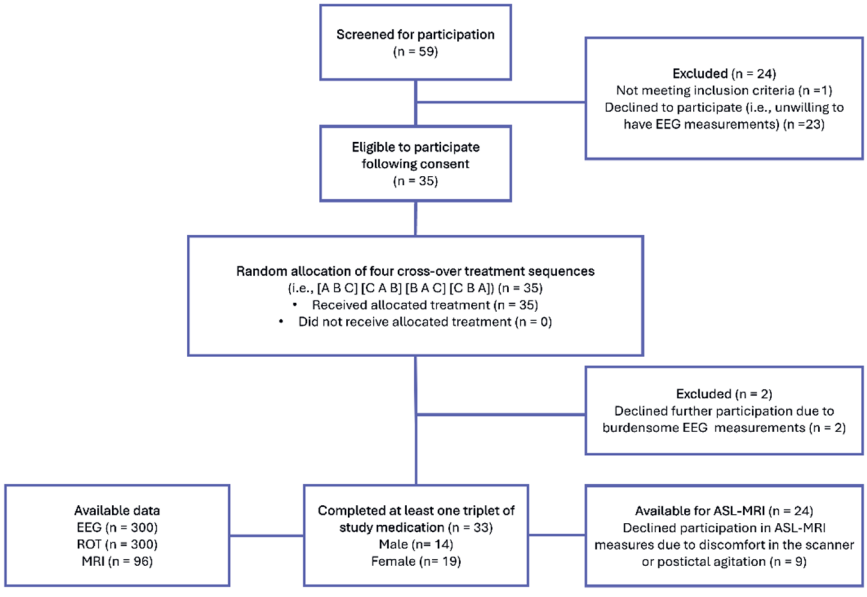


Figure 7.1. Trial profile. EEG = electroencephalography; ROT = reorientation time; MRI = magnetic resonance imaging; ASL-MRI = arterial spin labeling MRI

7.2.3 Randomization and masking

Before trial inclusion, four randomization blocks of each three interventions were randomly computer-generated by an external hospital party and allocated sequentially (Figure S7.6.1). The allocation sequence was concealed in a closed closet, not accessible by the investigator performing inclusion. Patients were enrolled by the ECT-nurse or the treating psychiatrist, who had no further involvement in the rest of the trial. Interventions were assigned by a coordinating doctor in training who was not involved in data acquisition. Outcome assessors were blinded to the treatment allocation. Patients were partly blinded, as they could recognize the differences between the treatment conditions.

7.2.4 Procedures

At a maximum of 2 h prior to each ECT-session, patients received one of three treatment conditions in random and counterbalanced order (i.e., 50cc of only water, 50cc of water with 60 mg nimodipine, or 50cc of water with 1000 mg acetaminophen). The first ECT-session served as baseline and was used to collect clinical and EEG data without exposure to any of the treatment conditions (290).

7.2.5 Primary outcome measure

Continuous EEG was monitored before, during, and 1 h following each ECT-session. The primary outcome measures was '*speed* of postictal EEG recovery' (quantified with a time constant τ; FigureS7.2 and our earlier work in **chapter 4 and 5**) (224). This measure was obtained by fitting an exponential function to the postictal EEG data of a modified version of the temporal brain symmetry index (tBSI) (195, 196). Larger values of τ indicate slower postictal recovery.

7.2.6 Secondary outcome measures

Secondary outcomes were the '*extent* of postictal EEG recovery' at 1 h, clinical reorientation time (ROT), and postictal CBF. The extent of postictal EEG recovery at 1 h compared to baseline was estimated based on the tBSI, as described previously (see **chapter 4**) (224). ΔBSI values range from 0 to 1, where smaller values indicate a greater difference between baseline and the postictal state, reflecting more enduring postictal EEG disturbances.

To assess the postictal state clinically, we used the ROT questionnaire (193, 194). In five-minute intervals, patients were asked questions about their orientation in person, time, and place. The ROT was defined as the time (in minutes) between seizure onset and the first instance in which the patient correctly answered at least four out of five questions (relative to their baseline). If a patient was not reoriented within 100 minutes, the maximum ROT score (i.e., 100 min) was assigned.

Postictal CBF was obtained by ASL-MRI ~1 h after administration of the ECT-stimulus and after anesthesiologic clearance. ASL-MRI data were collected before the ECT-course (i.e., baseline), and after three different ECT-sessions, one in each

experimental condition. Postictal *global* and *regional* CBF were calculated to investigate the magnitude of CBF differences (ΔCBF) between the treatment conditions, respective to baseline. In advance, we selected 10 regions-of-interest (ROI), that showed postictal CBF changes in earlier studies (217, 218, 220, 294). Information about ASL-MRI preprocessing is presented in **chapter 5** (Figure S5.1) (269).

7.2.7 Power calculation

Sample size calculation was performed based on a mixed model with repeated measurements with an estimated effect size of 0.25, a type 1 error rate of 5%, and a correlation of 0.4 between measurements, resulting in a total of 33 patients with repeated seizures to achieve a power of 0.80 (290).

7.2.8 Statistical analyses

All statistical analyses have been conducted conforming the predefined statistical analysis plan for SYNAPSE (290). Numbers and percentages are presented for categorical variables and medians and interquartile ranges (IQR) for continuous variables. We checked for completeness of all relevant data ahead of unblinding. No imputation of missing data was performed. Weakly informative priors with a mean of 0 and standard deviation of 50 were included in all Bayesian models for all predictors, using R (version 4.2.3) with brms (201, 202).

7.2.8.1 Speed of postictal EEG recovery

We fitted a Bayesian generalized mixed-effects model with random intercept and random slope, which is appropriate for analysis of longitudinal cross-over data having within-subject correlations. The outcome variable, the time constant τ, was modeled with a lognormal distribution. Logarithm and logit links were used for linearization (198, 200). Fixed effects were the interventions (i.e., acetaminophen, nimodipine, placebo), age, sex, time (i.e., number of the ECT-session), and electrode placement (i.e., UL or BL). Acetaminophen or nimodipine were compared to the placebo condition, which served as reference. Random effects were patient ID, intervention, and time, to account for within-patient variability that might be partly determined by time and intervention effects.

A post-hoc model was developed to compare treatment (i.e., both active interventions pooled) versus no treatment (i.e., placebo) for speed of postictal EEG recovery. A region of practical equivalence (ROPE) analysis was conducted to test the hypothesis of no practically relevant effect of the study medications. This hypothesis was accepted if 95% of the posterior distribution of the main contrasts (study medication versus placebo) fell in the range of -0.1 to 0.1 standard deviation (232).

7.2.8.2 Extent of postictal EEG recovery and clinical reorientation time

Bayesian generalized mixed-effects models with random intercept and random slope were fitted for the secondary outcome variables ΔBSI and ROT, modeled with beta distributions. The same fixed effects were included, followed by the same post-hoc models to compare treatment versus no treatment. Parameter estimates and credibility intervals are presented as multiplication factors, where numbers larger (or smaller) than 1 indicate a positive (or negative) effect. Multiplication factors are inherent to generalized models because of the utilized link function, which transforms the parameter estimates to the log scale. The estimates need to be exponentially transformed for interpretability (200). This allows us to interpret the influence of the interventions with a clear reference (i.e., credible multiplication factor 1.13 for acetaminophen versus placebo means that acetaminophen leads to a 13% longer postictal EEG recovery compared to placebo).

7.2.8.3 Postictal cerebral blood flow

Postictal change from baseline in mean *global* and *regional* CBF (ΔgCBF and ΔrCBF, respectively) were compared between all interventions in Bayesian random intercept mixed-effects models, with Gaussian response distributions. Fixed effects were intervention, age, sex, electrode placement, and interval between ECT-stimulus and start of the ASL-MRI sequence. Because of a previously established relationship between seizure duration and postictal CBF changes, seizure duration was added as fixed effect (269). Random effect was patient ID.

In addition, a full-factorial voxel-wise repeated measures analysis of variance was performed to explore the effects of the interventions on ΔCBF. Post-hoc comparisons were performed after a significant omnibus F-test (i.e., acetaminophen versus placebo, nimodipine versus placebo, acetaminophen versus nimodipine). Age, sex, electrode placement, time interval between ECT-stimulus and start of the ASL-MRI sequence, and seizure duration were entered as covariates of no interest. Voxel-wise tests were considered significant, if these were family wise error cluster-level corrected ($p < 0.05$, or for post-hoc comparisons $p < 0.017$) at a height threshold of $p < 0.001$. Finally, post-hoc mixed-effect models were used to investigate the relationship between ROT and ΔgCBF and ΔrCBF, because we expected that more clinical disorientation would be associated with more severe global or regional postictal hypoperfusion (15).

7.3 Results

7.3.1 Patients

Fifty-nine ECT-patients were screened for participation. Thirty-five appeared eligible and provided informed consent to participate (Figure 7.1). Two of these patients dropped out of our analyses because they did not tolerate some of the EEG recordings. In total, we collected 328 EEGs with 328 ROT measures in 33 patients.

Because 28 EEGs appeared of insufficient quality, 300 EEGs and 300 ROT measures were included in our final analyses. The median number of EEGs and ROT measures per patient was 9 (IQR = 3), ranging from 3 to 14.

As nine patients were unable to undergo MRI-sessions, 24 patients were included in ASL-MRI analyses, leading to 24 baseline and 72 postictal CBF measures. In Table S7.1, patient-, ECT-, and trial-characteristics of the included sample are summarized. Median age was 53 (IQR = 21.3) years and 19 patients were female (56%). Most patients (n = 24, 73%) were treated with BL ECT, and concomitant medication use was as expected.

7.3.2 Primary outcome measure

Medians of *speed* of postictal EEG recovery (i.e., time constant τ) after treatment with acetaminophen, nimodipine, and placebo were 6.2 min (IQR = 8.1), 6.3 min (IQR = 9.3), and 5.8 min (IQR = 7.0), respectively. Bayesian analyses revealed no effects on *speed* postictal EEG recovery of acetaminophen or nimodipine (1.13 [95% CI 0.92, 1.40] or 1.07 [95% CI 0.87, 1.31], respectively; Table 7.1; Figure 7.2, upper left panel), nor of any active treatment (1.10 [95% CI 0.91, 1.31], Figure 7.2, upper right panel).

7.3.3 Secondary outcome measures

7.3.3.1 Extent of postictal EEG recovery

Medians of ΔBSI after treatment with acetaminophen, nimodipine, and placebo were 0.27 (IQR = 0.1), 0.26 (IQR = 0.1), and 0.27 (IQR = 0.1), respectively. Bayesian analyses revealed no effects on ΔBSI of acetaminophen or nimodipine, nor of any active treatment (Table 7.1, Table S7.2, and Figure 7.2, middle panel).

7.3.3.2 Clinical reorientation time

Medians of ROT after treatment with acetaminophen, nimodipine, and placebo were 40 min (IQR = 25), 35 min (IQR = 15), and 35 min (IQR = 20), respectively. Bayesian analyses revealed no effects of acetaminophen or nimodipine, and neither of any treatment versus placebo (Table 7.1, Table S7.2, and Figure 7.2, lower panel).

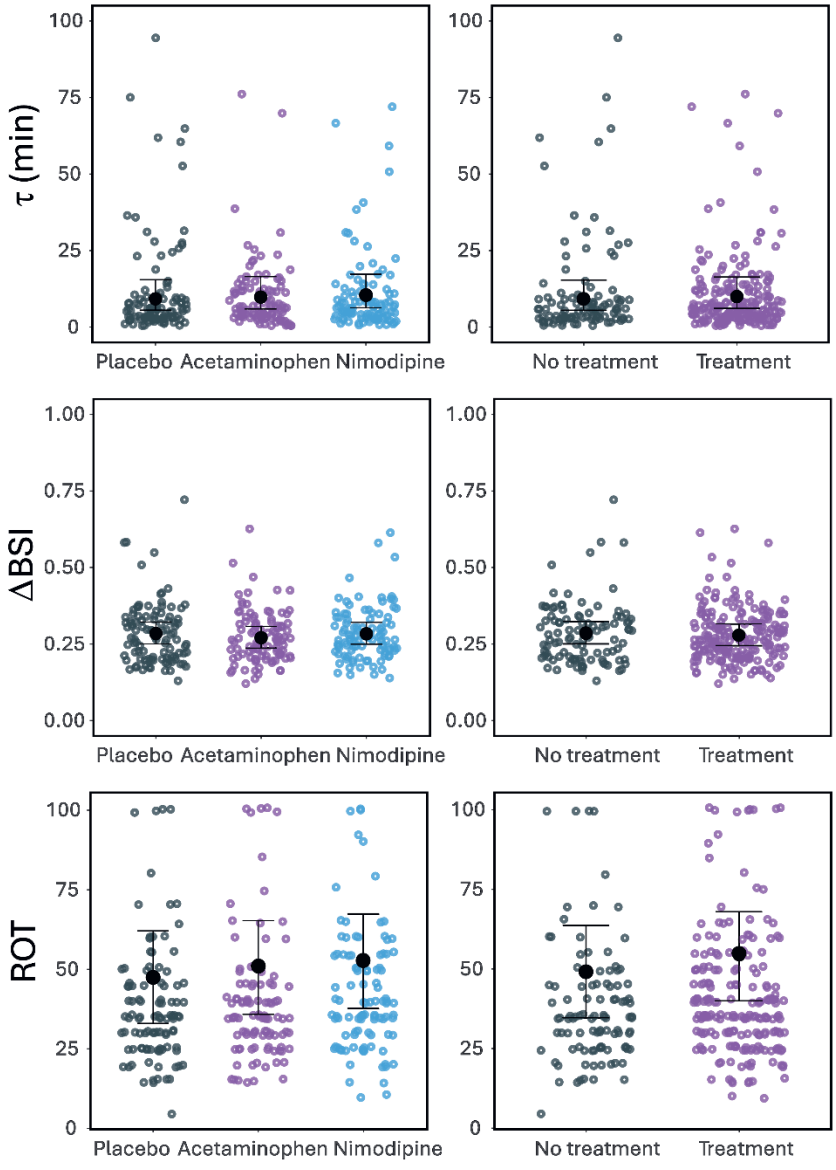


Figure 7.2 Overview of main findings. The left panels show the three conditions (i.e., placebo, acetaminophen, nimodipine) and the right panels show no treatment (i.e., placebo) and treatment (i.e., acetaminophen or nimodipine). Upper panels: time constants τ, in minutes, *speed* of postictal EEG recovery. Middle panels: *extent* of postictal EEG recovery (ΔBSI). Lower panels: clinical reorientation time (ROT), in minutes. None of the Bayesian models revealed credible differences between any of the conditions (i.e., indicated by black credibility intervals). Details are presented in Table S7.2.

Table 7.1 Results of Bayesian mixed-effects models

							Equivalence test *Acetaminophen versus Placebo and Nimodipine versus Placebo*	**Equivalence test** *Treatment versus placebo*
	Speed of postictal EEG recovery (τ, min)						ROPE [-1.4, 1.4]	
Predictors	*Estimate*	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Intercept	10.42	2.65	40.14	10.56	2.80	39.69		
Acetaminophen versus Placebo	1.13	0.92	1.40				Accepted	
Nimodipine versus Placebo	1.07	0.87	1.31				Accepted	
Treatment versus Placebo				1.10	0.91	1.31		Accepted
Extent of postictal EEG recovery (ΔBSI)							ROPE [-0.01, 0.01]	
	Estimate	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Intercept	0.42	0.26	0.65	0.42	0.27	0.66		
Acetaminophen versus Placebo	0.99	0.89	1.09				Undecided	
Nimodipine versus Placebo	0.93	0.84	1.03				Undecided	
Treatment versus Placebo				0.96	0.88	1.05		Undecided
Clinical reorientation time (ROT, min)							ROPE [-1.9, 1.9]	
	Estimate	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Intercept	0.72	0.14	3.75	0.83	0.16	4.39		
Acetaminophen versus Placebo	1.24	0.86	1.77				Accepted	
Nimodipine versus Placebo	1.15	0.90	1.47				Accepted	
Treatment versus Placebo				1.24	0.99	1.55		Accepted
Change in postictal *global* CBF (gCBF, ml/100g/min)							ROPE [-1.7, 1.7]	
	Estimate	*CI95 lower*	*CI95 upper*					
Intercept	-8.38	-31.27	14.46					
Acetaminophen versus Placebo	2.47	-1.36	6.24				Accepted	
Nimodipine versus Placebo	-2.12	-5.69	1.46				Accepted	

Note: Bayesian analyses were performed twice, with the same outcome variables, however, with an additional fixed effect active treatment (i.e., acetaminophen or nimodipine) versus placebo. However, it was not possible to run the analysis on treatment vs placebo for postictal global CBF as both acetaminophen or nimodipine had opposite effects. EEG = electroencephalography, CBF = cerebral blood flow, CI = credibility interval, ROPE = regional of practical equivalence. Empty cells indicate that fixed effects were not included in the respective model; Accepted = The posterior distribution falls completely within the ROPE, leading to acceptance of the null hypothesis (i.e., there is no effect on the outcome measure); Undecided = The posterior distribution falls partly within the ROPE, which prevents definitive conclusion.

7.3.3.3 Postictal CBF

Median baseline gCBF was 55.2 ml/100g/min (IQR = 22.5). Median postictal gCBF was 49 ml/100g/min (IQR = 27) with acetaminophen, 46.6 ml/100g/min (IQR = 26.1) with nimodipine, and 52 ml/100g/min (IQR 24.8) in the placebo condition (Figure 7.3A). Median postictal ΔgCBF after acetaminophen treatment was -2.6 ml/100g/min (IQR = 11.9), after nimodipine treatment -5.7 ml/100g/min (IQR = 10.1), and after placebo -1.6 ml/100g/min (IQR = 13.6) (Figure 7.3B). The Bayesian mixed-effects models showed no effects of the interventions on mean ΔgCBF or ΔrCBF (Table 7.1, Table S7.2 and S7.3, Figure S7.1).

The omnibus voxel-wise F-test was significant in the left precuneus (p = 0.030) and the right superior parietal lobule (p = 0.014). Post-hoc comparisons revealed more postictal CBF decreases after nimodipine treatment compared to placebo in one cluster in the precuneus. Increased postictal CBF was found after treatment with acetaminophen compared to nimodipine in one cluster in the precuneus, and two clusters in the superior parietal lobule (Figure S7.2 and Table S7.4). In our exploratory analyses, we did not find any relationship between ROT and ΔgCBF (-0.18 [%95 CI -0.38, 0.03]) or ΔrCBF (Table S7.5). Time interval between ECT-stimulus and start of the ASL-MRI sequence had no influence in any analyses.

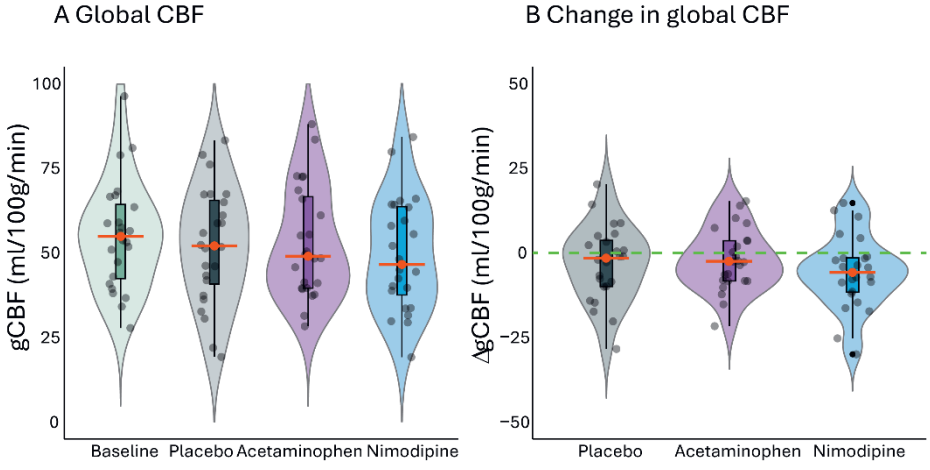


Figure 7.3 Postictal *global* cerebral blood flow (gCBF) median values (in ml/100g/min) were comparable for acetaminophen, nimodipine, and placebo treatment. (A) gCBF values at baseline and in the postictal state with placebo, acetaminophen, or nimodipine treatment. (B) Change in gCBF (ΔgCBF) after placebo, acetaminophen, or nimodipine treatment. The dashed green line indicates no change of postictal CBF with respect to baseline. Red lines indicate median (change in) CBF.

7.4 Discussion

In this clinical trial with three-condition randomized cross-over design, we could not replicate findings from animal models showing attenuation of postictal manifestations after treatment with acetaminophen or nimodipine. Treatment with acetaminophen or nimodipine, compared to placebo, did not improve the *speed* or *extent* of postictal EEG recovery, the clinical reorientation time, or postictal global CBF in humans with ECT-induced seizures. Although previous findings in animal studies with electrically-induced seizures showed that acetaminophen or nifedipine pre-treatment diminished postictal hypoxia, there are several possible explanations for our null findings (15, 162).

Looking back, at first, we suppose that our chosen medication dosages may have been too modest. The study medication doses were seventeen times lower in our patients compared to those administered to rats (in averaged weighted patients of 70kg, acetaminophen dose was ~14 mg/kg and nimodipine ~0.4 mg/kg, versus 250 mg/kg and 15 mg/kg in rats) (15). We chose such medication doses in SYNAPSE, because these are very standard and safe for regular indications (e.g., cerebrovascular incidents), and a dosage of 250 mg/kg acetaminophen is regarded as toxic. Therefore, we were limited in our translation of the animal model to our patients. However, in the animal study, 20 mg/kg dosed ibuprofen showed similar effects as acetaminophen on inhibiting severe hypoxia. Therefore, and hopefully, ibuprofen may serve as new candidate drug in future studies, because such dosage is much more common in patients (15).

Another factor responsible for our null finding may be the timing and method of medication administration, which differed substantially from the animal model. We gave oral medications approximately two hours before ECT, while rats were injected intraperitoneally 30 min pre-seizure (15). Therefore, oral medication administration in our study may not have led to sufficient concentrations in the brain. Future studies may address these shortcomings in type of intervention, dosage, timing, and administration.

Furthermore, on the mechanistic level, the postictal pathophysiology in humans may differ from those in animals, as explanation for no demonstrable effects of our study interventions. Additionally, we studied exclusively patients suffering severe and often treatment resistant depression, because this was the indication for ECT. In previous studies in such depressed patients, baseline EEG and cerebral perfusion were shown to differ from healthy individuals, which may have interfered with our outcome measures (295, 296).

Interestingly, by using ASL-MRI scans, clear patterns of postictal cerebral hypoperfusion, were estimated in some patients and divergent patterns in others. For example, one patient showed clear postictal hypoperfusion (i.e., decrease of >10 ml/100g/min) after nimodipine treatment, with *global* and *regional* decreases up to 30 ml/100g/min, which corresponds to a decrease of 47% respective to baseline (15). Another patient had postictal *global* CBF increases up to 48%

compared to baseline after both interventions and placebo. Moreover, looking for more spatial effects, our voxel-wise analyses showed CBF decrease in the superior parietal lobule after nimodipine treatment. Otherwise, postictal CBF increased in the superior parietal lobule after acetaminophen treatment. These divergent findings may be partly explained by the effects of anesthesia (217, 297). Also, the ECT patients differed regarding the used electrode placement, administered electrical charges and elicited seizure durations. These treatment varieties may have resulted in different seizure onset zones, seizure propagations and postictal cerebral perfusion patterns (269). However, the subsets of patients with different treatment characteristics were too small to analyze discrete regional effects. The explanation for the differences between patients and the apparent regionally restricted findings is still unclear, especially because no associations were shown with our clinical and EEG measures. Nevertheless, because individual patient and treatment factors, of which some can be manipulated in ECT, may have influenced how acetaminophen and nimodipine altered cerebral perfusion, further study is worthwhile.

Until date, there is no gold standard to study the postictal state or possible treatments. In our study, we applied a combination of clinical, EEG, and MRI measures. With EEG, the tBSI can reliably capture ischemic changes. However, in our study, it is unclear whether tBSI was sensitive enough to investigate postictal spatiotemporal changes, as these appear relatively short-lasting (196). We noticed that, after more previous ECT-induced seizures, the 'pre ECT-session' EEGs showed more delta and theta activity compared to earlier sessions, which may have influenced the fitting of the curves. Moreover, in 9% of all postictal EEGs, fitting an exponential function did not result in a good model fit. Furthermore, instead of including frequencies between 1 and 25 Hz, focusing on individual frequency bands may yield more information about postictal EEG recovery. With ASL-MRI, we tried to 'catch' cerebral perfusion in patients' postictal states. However, because CBF has shown to vary in the first hour after seizures, the exact timing of our MRI scan may have influenced the postictal perfusion findings (217, 297). Future studied should address these methodological issues in advance.

Strengths of this study are the prospective randomized cross-over design, with systematic collection of 300 analyzable EEG's, 200 ROTs, and 72 postictal ASL-MRI scans. This study does show that it is feasible to study the postictal state in patients with ECT-induced seizures. Limitations regard, first, the small sample size which has impacted our ability to detect meaningful differences in our secondary analyses. Second, the ASL-MRI scans may have been performed too late postictally to capture the expected acute perfusion effects. Third, the anesthesia needed for ECT and the concomitant used medications may have interfered with working mechanisms of the study medications.

7.5 Conclusion

Despite promising findings from animal studies, treatment with acetaminophen or nimodipine did not improve postictal EEG recovery, clinical recovery, or global postictal CBF in patients with ECT-induced seizures. Study of (interventions in) the postictal state in ECT-induced seizure is feasible, which should be considered in new studies investigating higher dosages or other candidate drugs.

7.6 Supplementary materials

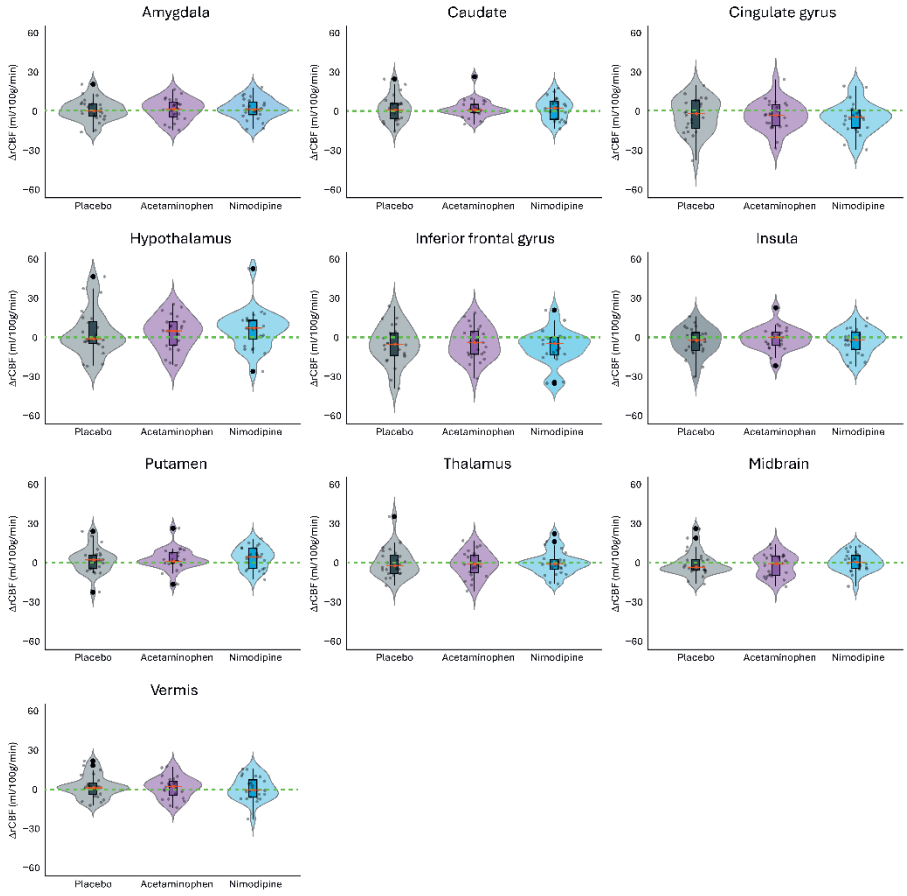


Figure S7.1 In all pre-selected regions-of-interest in the postictal state, no effects of treatment with acetaminophen or nimodipine compared to placebo was found on change in regional cerebral blood flow (ΔrCBF). The dashed green lines indicate no change of postictal CBF with respect to baseline. Red lines indicate median (change in) CBF.

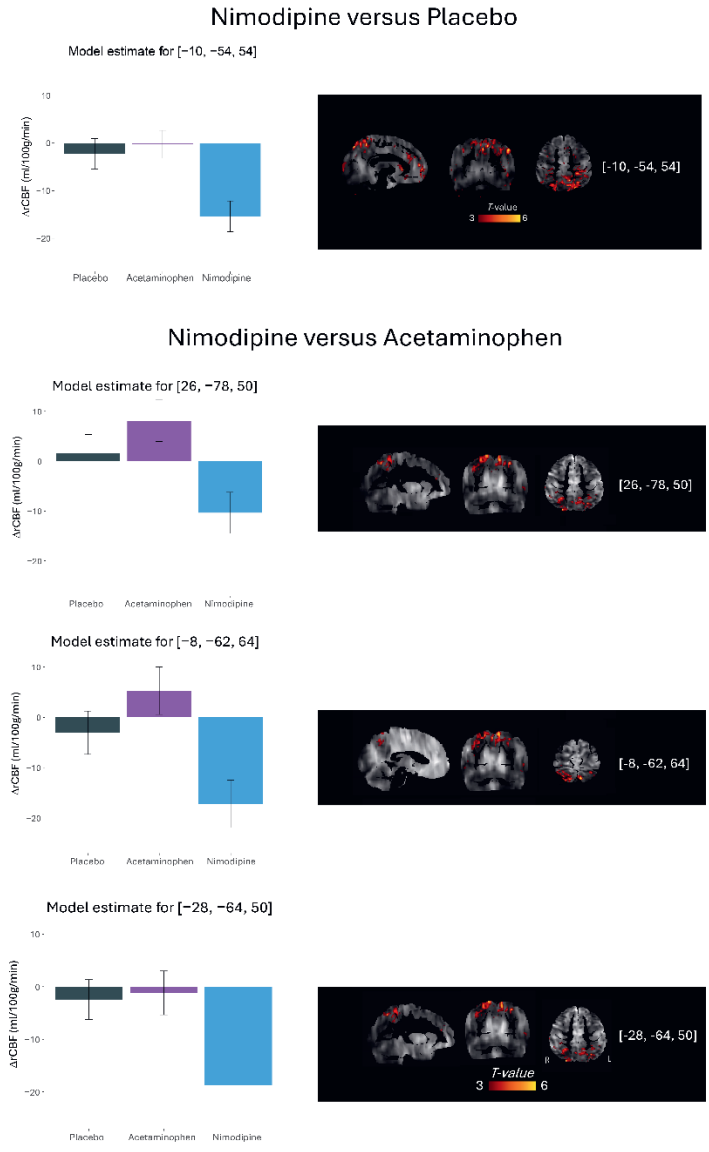


Figure S7.2 Results of voxel-wise CBF analyses. (A) Voxel-wise comparison between nimodipine and placebo treatment, indicating a significant cluster in the precuneus shown in CBF maps on the right with corresponding model Estimate on the left. (B) Voxel-wise comparison between nimodipine and acetaminophen treatment, highlighting three significant clusters, one in the precuneus, and two in the superior parietal lobule. Anatomical locations are defined based on the Tailairach Daemon atlas. The *T*-value map is superimposed to a patient's ΔCBF map, with *T*-values ranging between 3 and 6. Clusters are shown with $p < 0.05$ (Family-wise error corrected). Bar plots with model Estimate are shown with standard errors for visual representation. CBF = cerebral blood flow.

Table S7.1 Patient-, electroconvulsive therapy (ECT)-, and trial-characteristics of the SYNAPSE trial

Characteristics		**Patient population for EEG analyses (n=33)**	**Patient population for ASL-MRI analyses (n=24)**
Patient characteristics			
Age in years, median (IQR; range)		53 (21.3; 24 – 82)	56 (22.5; 24 – 82)
Female sex, n (%)		19/33 (56)	15/24 (63)
ECT characteristics			
Bilateral electrode placement at the end of the ECT-course, n (%)		24/33 (73)	15/24 (63)
Electrical charges to elicit seizures in milliCoulombs, median (IQR; range)		304.7 (228.8; 125.6 – 813.0)	304.4 (250.2; 125.6 – 813.0)
Seizure duration of all included ECT-sessions during the ECT-course in seconds, median (IQR; range)		51 (25.5; 16.3 – 178.2)	55 (24.5; 19.6 – 140.1)
Total number of ECT-sessions during the ECT-course, median (IQR; range)		12 (9; 7 – 100)	12 (8; 8 – 100)
Concomitant psychopharmacological drug use during the ECT-course, n (%)			
	Antidepressants	24/33 (73)	18/24 (75)
	Antipsychotics	23/33 (70)	17/24 (71)
	Antiepileptics	7/33 (21)	4/24 (17)
	Benzodiazepines	20/33 (61)	17/24 (71)
	Lithiumcarbonate	2/33 (1)	2/24 (8)
Number of patients needing medication for severe postictal symptoms after ECT*, n (%)		12/33 (36)	8/24 (33)
Trial characteristics			
Number of EEGs/ASL-MRI scans per intervention, n (%)			
	Acetaminophen	100/300 (33)	24/72 (33)
	Nimodipine	99/300 (33)	24/72 (33)
	Placebo	101/300 (34)	24/72 (33)
Interval between administration of study medication and application of ECT-stimulus in minutes, median (IQR; range)**			
	Acetaminophen	145.5 (31.8; 221 - 50)	144.5 (27; 212 - 93)
	Nimodipine	137 (36; 265 - 88)	136 (24; 265 - 100)
	Placebo	147 (44; 245 - 77)	146 (34.5; 245 - 77)
Interval between application of the ECT-stimulus and postictal ASL-MRI acquisition in minutes, median (IQR; range)		NA	64 (15; 35 – 94)

ASL = arterial spin labeling; BL = bifrontotemporal; EEG = electroencephalography; ECT = electroconvulsive therapy; IQR = inter quartile range; EEG = electroencephalogram; MRI = magnetic resonance imaging; NA = not applicable
*Postictal medication consisted of a single dose of midazolam, ranging between 2-5 mg.
**Differences in medication administration were tested statistically between the interventions and revealed no significant differences (p=0.482).

Table S7.2 Results of Bayesian mixed-effects models (remaining factors)

							Equivalence test *Acetaminophen versus Placebo and Nimodipine versus Placebo*	**Equivalence test** *Treatment versus placebo*
	Speed of postictal EEG recovery (τ, min)						ROPE [-1.4, 1.4]	
Predictors	*Estimate*	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Time	1.03	1.00	1.07	1.03	1.00	1.07	Accepted	Accepted
Electrode placement (UL)	0.81	0.49	1.34	0.82	0.50	1.33	Accepted	Accepted
Age (years)	0.99	0.97	1.01	0.99	0.97	1.01	Accepted	Accepted
Sex (female)	0.79	0.43	1.45	0.80	0.44	1.45	Accepted	Accepted
Extent of postictal EEG recovery (ΔBSI)							ROPE [-0.01, 0.01]	
	Estimate	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Time	0.99	0.97	1.01	0.99	0.97	1.00	Undecided	Undecided
Electrode placement (UL)	1.02	0.85	1.25	1.02	0.85	1.24	Undecided	Undecided
Age (years)	1.00	0.99	1.01	1.00	0.99	1.01	Accepted	Accepted
Sex (female)	0.98	0.81	1.19	0.97	0.81	1.19	Undecided	Undecided
Clinical reorientation time (ROT, min)							ROPE [-1.9, 1.9]	
	Estimate	*CI95 lower*	*CI95 upper*	*Estimate*	*CI95 lower*	*CI95 upper*		
Time	0.96	0.91	1.01	0.95	0.90	1.00	Accepted	Accepted
Electrode placement (UL)	0.78	0.42	1.45	0.77	0.41	1.47	Accepted	Accepted
Age (years)	1.01	0.98	1.03	1.01	0.98	1.03	Accepted	Accepted
Sex (female)	0.69	0.34	1.38	0.65	0.32	1.29	Accepted	Accepted
Change in postictal *global* CBF (gCBF, ml/100g/min)							ROPE [-1.7, 1.7]	
	Estimate	*CI95 lower*	*CI95 upper*					
Electrode placement (UL)	-0.64	-8.92	7.60				Undecided	
Age (years)	-0.01	-0.30	0.29				Accepted	
Sex (female)	-0.27	-8.73	8.44				Undecided	
Seizure duration (s)	-0.08	-0.20	0.03				Accepted	
Δt ASL acquisition (min)	0.16	-0.01	0.33				Accepted	

Note: Bayesian analyses were performed twice, with the same outcome variables, however, with an additional fixed effect active treatment (i.e., acetaminophen or nimodipine) versus placebo. However, it was not possible to run the analysis on treatment vs placebo for postictal global CBF as both acetaminophen or nimodipine had opposite effects. Fixed effect time refers to the number of the ECT-session. EEG = electroencephalography, CBF = cerebral blood flow, CI = credibility interval, ROPE = regional of practical equivalence, Δt ASL acquisition = time interval between the electroconvulsive therapy stimulus and arterial spin labeling acquisition. Empty cells indicate that fixed effects were not included in the respective model; Accepted = The posterior distribution falls completely within the ROPE, leading to acceptance of the null hypothesis (i.e., there is no effect on the outcome measure); Undecided = The posterior distribution falls partly within the ROPE, which prevents definitive conclusion.

Table S7.3 Results of Bayesian generalized mixed model analyses regarding perfusion changes in regions-of-interest

	Change in amygdala CBF (ml/100g/min)		Change in caudate CBF (ml/100g/min)		Change in cingulate gyrus CBF (ml/100g/min)		Change in hypothalamus CBF (ml/100g/min)		Change in inferior frontal gyrus CBF (ml/100g/min)	
Predictors	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*
Intercept	-15.48	-31.67 – 0.72	12.92	-4.89 – 30.44	0.72	-48.82 – 49.27	-6.27	-41.52 – 29.14	-23.54	-75.26 - 28.55
Acetaminophen versus placebo	-0.93	-3.68 – 1.97	2.88	-0.61 – 6.35	-0.33	-4.18 – 3.49	-3.50	-12.09 – 4.95	1.21	-2.94 – 5.41
Nimodipine versus placebo	0.79	-1.35 – 2.94	0.16	-2.51 – 2.80	-1.69	-5.49 – 2.06	2.62	-4.09 – 9.26	-2.47	-6.66 – 1.76
Seizure duration (s)	0.11	0.04 – 0.18	-0.03	-0.12 – 0.06	-0.01	-0.25 – 0.23	-0.08	-0.27 – 0.11	0.13	-0.14 – 0.39
Age (years)	0.13	-0.09 – 0.36	0.08	-0.15 – 0.31	0.10	-0.43 – 0.64	-0.06	-0.44 – 0.33	0.04	-0.52 – 0.60
Sex (female)	-1.53	-8.42 – 5.35	1.03	-5.69 – 7.87	-6.29	-20.40 – 7.87	-2.87	-13.48 – 7.70	7.33	-7.54 – 21.79
Electrode placement (Unilateral)	4.53	-2.92 – 12.22	-1.92	-9.40 – 5.49	3.14	-7.06 – 13.65	-3.47	-15.15 – 8.12	-5.38	-16.64 – 5.67
Δt ASL acquisition (min)	0.02	-0.14 – 0.18	-0.21	-0.40– -0.02	-0.08	-0.27 – 0.11	0.36	-0.09 – 0.82	0.10	-0.11 – 0.32
ROPE interpretation acetaminophen versus placebo	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation nimodipine versus placebo	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation seizure duration	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation Δt ASL acquisition	Undecided		Undecided		Undecided		Undecided		Undecided	

Note: Δt ASL acquisition = time interval between the electroconvulsive therapy stimulus and arterial spin labelling acquisition; CI = credibility interval; ROPE = region of practical equivalence; CBF = cerebral blood flow

Table S7.3 (continued) Results of Bayesian generalized mixed model analyses regarding perfusion changes in regions-of-interest

	Change in insula CBF (ml/100g/min)		Change in putamen CBF (ml/100g/min)		Change in thalamus CBF (ml/100g/min)		Change in midbrain CBF (ml/100g/min)		Change in vermis CBF (ml/100g/min)	
Predictors	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*	*Estimate*	*CI (95%)*
Intercept	2.56	-17.44 – 22.37	13.09	-3.88 – 30.07	-5.91	-48.01 – 36.46	23.11	-11.33 – 57.86	-7.85	-42.91 – 27.88
Acetaminophen versus placebo	3.21	-0.66 – 7.06	0.24	-3.32 – 3.77	-1.01	-4.63 – 2.62	-1.27	-4.84 – 2.30	-0.44	-4.27 – 3.41
Nimodipine versus placebo	0.06	-2.91 – 3.08	1.67	-1.10 – 4.34	-0.18	-3.75 – 3.41	1.40	-2.11 – 5.00	.1.52	-5.27 – 2.26
Seizure duration (s)	-0.01	-0.11 – 0.09	0.04	-0.04 – 0.13	-0.08	-0.30 – 0.13	-0.21	-0.39 - -0.02	0.15	-0.04 – 0.35
Age (years)	-0.11	-0.37 – 0.15	-0.20	-0.41 – 0.01	0.04	-0.41 – 0.49	-0.10	-0.44 – 0.24	-0.00	-0.36 – 0.35
Sex (female)	6.22	-1.34 – 13.86	-4.93	-11.06 – 1.13	4.98	-6.87 – 16.55	-3.24	-11.69	-1.97	-10.89 – 6.89
Electrode placement (Unilateral)	3.41	-4.97 – 11.64	0.36	-6.10 – 6.91	-4.95	-13.88 – 3.60	-0.92	-7.26 – 5.38	-1.55	-8.06 – 5.07
Δt ASL acquisition (min)	-0.07	-0.29 – 0.14	-0.01	-0.21 – 0.18	0.11	-0.08 – 0.30	-0.05	-0.22 – 0.11	0.06	-0.12 – 0.24
ROPE interpretation acetaminophen versus placebo	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation nimodipine versus placebo	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation seizure duration	Undecided		Undecided		Undecided		Undecided		Undecided	
ROPE interpretation Δt ASL acquisition	Undecided		Undecided		Undecided		Undecided		Undecided	

Table S7.4 Voxel-wise results comparing nimodipine with placebo and acetaminophen treatment showing decreased postictal cerebral blood flow with nimodipine treatment compared to placebo or acetaminophen treatment.

	Anatomical location based on Talairach atlas	**Voxel cluster size**	***p*-value**	***T*-value**	**MNI coordinates (x, y, z)**		
Omnibus F-test	Left precuneus	86	0.030	12.91	-8	-64	58
	Right superior parietal lobule	100	0.014	11.27	18	-62	60
Post-hoc comparisons							
Nimodipine versus placebo	Left precuneus	212	0.001	4.55	-10	-54	54
Nimodipine versus Acetaminophen	Right superior parietal lobule	781	0.000	4.93	26	-78	50
	Left precuneus	243	0.000	4.81	-8	-62	64
	Left superior parietal lobule	169	0.004	4.27	-28	-64	50

7.7 SYNAPSE study protocol adapted from Verdijk et al. (2022)

Study of effect of nimodipine and acetaminophen on postictal symptoms in depressed patients after electroconvulsive therapy (SYNAPSE)

Verdijk, J. P. A. J., Pottkämper, J. C. M., Verwijk, E., van Wingen, G. A., van Putten, M. J. A. M., Hofmeijer, J., van Waarde, J. A., *Trials* (2022). 23(1): 324

Abstract

Background Postictal phenomena as delirium, headache, nausea, myalgia, and anterograde and retrograde amnesia are common manifestations after seizures induced by electroconvulsive therapy (ECT). Comparable postictal phenomena also contribute to the burden of patients with epilepsy. The pathophysiology of postictal phenomena is poorly understood and effective treatments are not available. Recently, seizure-induced cyclooxygenase (COX)-mediated postictal vasoconstriction, accompanied by cerebral hypoperfusion and hypoxia, has been identified as a candidate mechanism in experimentally induced seizures in rats. Vasodilatory treatment with acetaminophen or calcium antagonists reduced postictal hypoxia and postictal symptoms. The aim of this clinical trial is to study the effects of acetaminophen and nimodipine on postictal phenomena after ECT-induced seizures in patients suffering major depressive disorder. We hypothesize that (1) acetaminophen and nimodipine will reduce postictal electroencephalographic (EEG) phenomena, (2) acetaminophen and nimodipine will reduce magnetic resonance imaging (MRI) measures of postictal cerebral hypoperfusion, (3) acetaminophen and nimodipine will reduce clinical postictal phenomena, and (4) postictal phenomena will correlate with measures of postictal hypoperfusion.

Methods SYNAPSE is a prospective, monocenter, single-blind, clinical trial with a three-condition randomized cross-over design. Thirty-three patients (age > 17 years) suffering from a depressive episode treated with ECT will be included. Randomly and alternately, single doses of nimodipine (60 mg), acetaminophen (1000 mg), or water will be given two hours prior to each ECT-session with a maximum of twelve sessions per patient. The primary outcome measure is 'postictal EEG recovery', expressed and quantified as a time constant derived from an adapted version of the temporal brain symmetry index, yielding a time constant for the duration of the postictal state on EEG. Secondary outcome measures include postictal cerebral perfusion, measured by arterial spin labeling MRI, and the postictal clinical 'time to orientation'.

Discussion With this randomized clinical trial, we will systematically study postictal EEG, MRI and clinical phenomena after ECT-induced seizures and will test the effects of vasodilatory treatment intending to reduce postictal symptoms. If an effect is established, this will provide a novel treatment of postictal symptoms in ECT patients. Ultimately, these findings may be generalized to patients with epilepsy.

7.7.1 Introduction

7.7.1.1 Postictal phenomena: burden in electroconvulsive therapy and epilepsy

In electroconvulsive therapy (ECT), seizures are induced to treat various psychiatric disorders, mostly pharmacotherapy-resistant mood disorders (292, 293). Side effects of ECT include postictal phenomena such as confusion, delirium, headache, nausea, myalgia, and anterograde and retrograde amnesia (291). These postictal phenomena cause a significant burden for patients receiving ECT and their relatives. Also, these symptoms may cause premature cessation or failure of this otherwise highly effective treatment. Moreover, postictal phenomena may impact the patient due to perceived stigma and rejection.
Patients with epilepsy suffer from reoccurring unpredictable seizures. The postictal state in patients suffering epilepsy is strikingly similar to those of ECT patients (184). In patients with epilepsy, postictal phenomena may present as unresponsiveness, sensory, motor, or memory deficits, impaired cognition, headache, delirium, or psychosis, which may last several minutes to hours (12, 14, 162, 289). All postictal manifestations add to the morbidity of epilepsy and have been appointed as a neglected entity in the management of seizure (14). For patients and their relatives, postictal phenomena enhance the burden of epilepsy. Given the erratic nature of epileptic seizures, investigating the postictal state is not straightforward (162). The predictability of ECT-induced seizures, on the other hand, offers a unique opportunity to examine postictal phenomena systematically. In humans, though, epileptologic studies in ECT patients are very limited.

7.7.1.2 ECT as a human seizure model

We propose to study postictal phenomena after ECT-induced seizures. In ECT patients, postictal electroencephalographic (EEG) evolution (Figure S7.7.1) and clinical postictal phenomena are similar to those in patients with epilepsy (162, 298). The planned and standardized nature of ECT-induced seizures allow us to systematically examine various characteristics of the postictal state (i.e., clinical manifestations, EEG features, cerebral perfusion), including potential effects of interventions. This is a unique model, in a controlled clinical setting, to phenomenologically validate the hypothesis of vasoconstriction-mediated postictal phenomena derived from animal research. The aim of the model is to reap benefits for both psychiatric and epilepsy patients and bridge the gap between both specialisms in neuroscience.

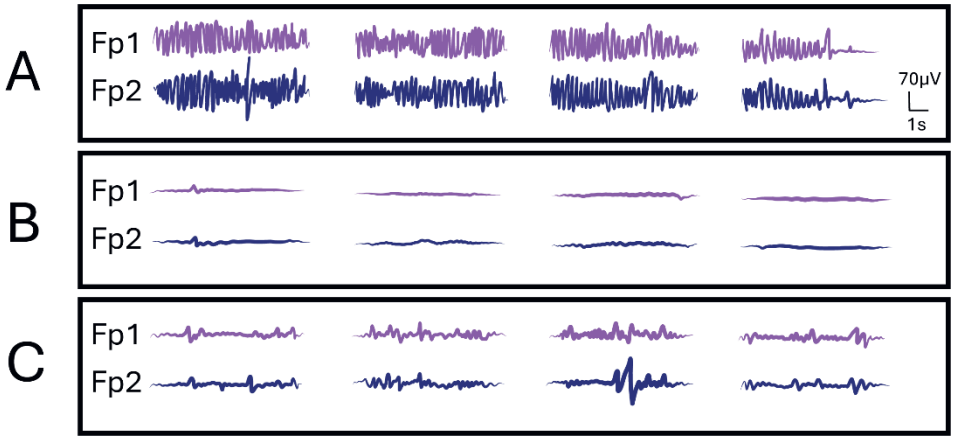


Figure S7.7.1 Induced seizure (A) and immediate postictal state (B) EEG epochs of 10 seconds in an ECT patient. Note the flattening of the EEG immediately after the seizure. EEG activity gradually returns after approximately 15 min (C). This EEG evolution is very similar to post-ictal patterns after spontaneous epileptic seizures. Data from an ECT patient treated in Rijnstate Hospital.

7.7.1.3 Pathophysiology of postictal phenomena is poorly understood

The mechanisms of postictal phenomena, in ECT as well as in epilepsy, are poorly understood and effective treatment is not available. Described major pathophysiological mechanisms involved in the postictal state include changes in extra- and intracellular ion concentrations (e.g. neurotransmitter depletion, decreased extracellular calcium), active inhibition, neurovascular decoupling, blood brain barrier dysfunction, and cerebral perfusion changes (14, 162). While it has been suggested that neuronal exhaustion is a prominent mechanism in the seizure termination process, neurons are able to generate action potentials even after long periods of activation (14, 299). The best management of postictal phenomena is still uncertain. In the absence of prophylactic treatment aside from anti-epileptic agents, current treatments of severe postictal symptoms vary from symptomatic symptom suppression with sedatives and triptans to antipsychotic medication (12). More research is needed to gain insight in the pathophysiology of the postictal state and to identify effective treatment targets.

7.7.1.4 Vasoconstriction-induced hypoperfusion as candidate mechanism

In 2016, substantial evidence was presented for an alternative mechanism of the postictal state: seizure-induced postictal vasoconstriction with hypoperfusion and hypoxia (15, 16). Postictal local hypoperfusion had already been observed in patients with temporal lobe epilepsy since the early 1990s (117, 300, 301). Recently, systematic measurements in various commonly used animal models revealed a consistent drop of local blood flow of approximately 50% after brief

hippocampal seizures, with a consequent decrease of local partial oxygen pressure. The hypoperfusion and hypoxia lasted more than 1 h postictally. In epileptic patients, equivalent local perfusion deficits were demonstrated with perfusion-weighted MRI, 1 h after seizures. The severity of hypoperfusion correlated with seizure duration, both in rats and patients. Sustained hypoperfusion was associated with local vasoconstriction after electrically induced seizures in rats and after seizure-like activity in acute brain slices (15, 16). Additionally, in ECT patients, the postictal EEG evolution shows the same characteristics as EEG evolution in patients recovering from cerebral ischemia (Figure S7.7.2) (302). Both in ECT and epilepsy patients, cerebral hypoperfusion may explain postictal clinical phenomena, because of the similar symptoms of postictal paresis, confusion, psychosis, and cognitive deficits. Moreover, EEG in the postictal period presented as similar to what was observed in patients with transient focal or global ischemia (302).

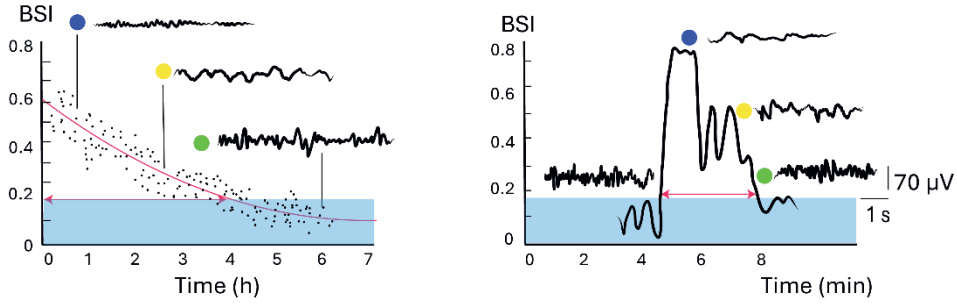


Figure S7.7.2 Left: EEG-recovery from global ischemia in a patient after cardiac arrest ($t = 0$). The nearly iso-electric EEG (blue dot) evolves to a diffusely slowed pattern (yellow dot) to a normal pattern (green dot). Right: EEG traces in a patient with a generalized seizure (red arrow, start around $t = 4.5$ min). After the seizure, the EEG is nearly iso-electric (blue dot) and evolves to a diffusely slowed pattern (yellow dot) to a normal pattern (green dot). While the time courses are different in these examples (hours versus minutes), EEG patterns are similar. Only channel P4-O2 is plotted. Data from MST hospital.

7.7.1.5 Acetaminophen and calcium-antagonists reduce postictal hypoperfusion in rats

Multiple mechanisms are established in neurovascular coupling, with activation of L-type calcium channels as a final common pathway. Cyclooxygenase (COX)-2 inhibitors, acetaminophen, and calcium-antagonists were tested to prevent vasoconstriction and hypoperfusion. Indeed, acetaminophen (a partial COX-inhibitor) and nifedipine (a calcium-antagonist) prevented postictal vasoconstriction, hypoperfusion, and subsequent tissue hypoxia (15, 16). The effect was dose dependent. Prostaglandins were also known to cause vasodilation but—paradoxically—inhibiting the COX-enzyme reduced postictal

vasoconstriction and hypoxia. Acetaminophen was more effective in reducing postictal phenomena than other COX-inhibitors, indicating the involvement of currently unknown mechanisms. Exposure to COX-2 inhibitors, acetaminophen and calcium-antagonists did not alter seizure duration, indicating that effects were attributable to a neurovascular mechanism and not via seizure-altering mechanisms (25, 303). Acetaminophen was only effective if administered before seizure onset, whereas nifedipine also prevented vasoconstriction administered during the postictal state. To further substantiate the possible mediating role of COX-2 in postictal hypoperfusion and hypoxia, experiments were repeated in COX-2 knock-out mice. While local severe hypoxia was observed in control mice, mutants remained normoxic (15).

7.7.1.6 Preventing hypoperfusion reduces postictal clinical phenomena

In animal models, hypoperfusion and hypoxia were associated with clinical postictal phenomena (15, 16). A postictal recognition memory task was used to compare the influence of acetaminophen and nifedipine treatment in rats. The inability to form new memories, 45 min after the seizure, was recorded in the absence of treatment. Rats receiving acetaminophen or nifedipine before seizures reduced postictal behavioral symptoms to the level of controls. Also, postictal motor deficits in rats as measured by the hanging bar test were significantly reduced after treatment with nifedipine (15).

7.7.1.7 Studying effects of acetaminophen and calcium-antagonists in human seizures

Motivated by the findings in animal models, we aim to systematically study the putative role of acetaminophen and nimodipine in vasoconstriction-mediated hypoperfusion and hypoxia on postictal phenomena in humans. In the SYNAPSE study, patients receiving ECT-induced seizures as standard care for severe often treatment-resistant depression will be studied. We will systematically investigate postictal EEG and clinical parameters before, during and after seizures. Various structural and functional MRI parameters will be measured during the postictal period, with additional baseline (before start of ECT) and follow-up (after finishing the ECT course) measurements. If results support that postictal hypoperfusion is an important contributor to postictal phenomena that can be alleviated with vasodilatory treatment, we will identify the first treatment targeting postictal manifestations in humans. This may decrease the burden of ECT for patients with severe depression, and possibly also the burden of the postictal state in patients with epilepsy.

7.7.1.8 Objectives

Primary research question:

- Does prior treatment with acetaminophen or nimodipine influence 'postictal EEG recovery time' after ECT-induced seizures?

Secondary research questions:

- How does prior treatment with acetaminophen or nimodipine influence postictal hypoperfusion on ASL-MRI after ECT-induced seizures?
- How does prior treatment with acetaminophen or nimodipine influence the clinical 'time to orientation' after ECT-induced seizures?
- Are clinical and EEG postictal phenomena associated with ASL-MRI measures of brain perfusion?
- Is influence of acetaminophen or nimodipine on postictal phenomena—assessed with clinical, EEG, and ASL-MRI measures—associated with neurocognitive functioning after the ECT course?

Our hypothesis is that acetaminophen or nimodipine will reduce the 'postictal EEG recovery time' compared to control. Second, we suppose that acetaminophen or nimodipine will decrease ASL-MRI measures of postictal hypoperfusion compared to control. Third, we expect acetaminophen or nimodipine to reduce clinical time to orientation compared to control. Fourth, we hypothesize to find significant correlations between the established postictal phenomena on clinical, EEG, and ASL-MRI measures. Lastly, we expect to find significant correlations between higher scores of postictal phenomena—assessed with clinical, EEG, and ASL-MRI measures—and more impaired neurocognitive functioning of patients after the ECT course.

7.7.3 Methods

7.7.3.1 Trial design

To realize our primary objective, we will conduct a prospective, monocenter, single-blind, clinical trial with a three-condition randomized cross-over design. This indicates that patients will receive one of three treatment conditions prior to each ECT-session. Sequences of three conditions will be determined a priori (Figure S7.7.3). Patients will be randomized to a sequence prior to every consecutive period of three ECT-sessions. The number of blocks (i.e., a random sequence of three conditions) per patient will depend on the total number of ECT-sessions for that patient, with a maximum of 4 blocks (= 12 ECT-sessions). Baseline measurements include the first ECT titration session. The primary outcome measure is collected before, during, and directly after each ECT-induced seizure.

Figure S7.7.3 Schematic representation of random and counterbalanced treatment allocation at each session of electroconvulsive therapy (ECT). A, B, and C represent administration of 1000 mg acetaminophen, 60 mg nimodipine, and placebo condition (i.e., only 50cc of water). At all included ECT-sessions, continuous electroencephalogram (EEG) and the clinical reorientation time (ROT) was recorded. Blue circles indicate postictal magnetic resonance imaging measurements.

7.7.3.2 Study setting

This study will take place at the ECT Expertise Centre of the Department of Psychiatry, Rijnstate Hospital, Arnhem, The Netherlands (i.e., a large general teaching hospital with a catchment area of 650,000 inhabitants). In Rijnstate, 1400 ECT-sessions take place annually, of which approximately 700 are in ECT-naive patients. The Department of Clinical Neurophysiology of Rijnstate Hospital supports the EEG measurements during this study.

7.7.3.3 ECT procedures

ECT-sessions will be administered two times per week, according to the standard protocol of the Netherlands Psychiatric Association (21). Patients will be anesthetized with etomidate (0.1–0.2 mg/kg body mass), muscle relaxation will be secured with succinylcholine (0.5–1 mg/kg body mass), and appropriate oxygenation (100% oxygen, positive pressure) will be applied until the resumption of the patient's spontaneous respiration. Preferably, standardized procedures will be used. Start of the index ECT course will be with right unilateral electrode placement (RUL) and a switch to bifrontotemporal (BL) will be done if six RUL ECT-sessions appear ineffective or to left unilateral (LUL) in case of severe postictal confusion. Dosage determination will be done by using a dose-titration method—followed by 6 times seizure threshold (ST) in RUL/LUL ECT and 2.5 times ST in BL ECT—or by an age-based dosing method. The used pulse width will be 1 ms. If needed, post-ECT sedation will be administered by using midazolam, haloperidol or propofol, to provide comfort and safety to the patient. The ECT course will be terminated if complete remission will be reached, if no further improvement will be seen in two ECT-sessions, or if no improvement will be present after a minimum of ten BL ECT-sessions. The treating psychiatrist and anesthesiologist may decide on these treatment variables otherwise based on the clinical conditions. All ECT variables will be recorded for use in analysis.

7.7.3.4 Eligibility criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Adulthood (age > 17 years);
- Current clinical diagnosis of a major depressive episode (unipolar, bipolar, schizoaffective) as determined by the Mini International Neuropsychiatric Interview (MINI);
- Willingness and ability to give written informed consent and willingness and ability to understand, to participate and to comply with the study requirements;
- Indicated for ECT, according to the Dutch guideline for electroconvulsive therapy (e.g. medication resistant depressive episode, history of successful treatment with ECT, or preference of the patient) (21).

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Known adverse or allergic reactions to acetaminophen or nimodipine;
- Chronic use of acetaminophen, calcium antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs) that cannot be interrupted for less than two days before the ECT-session;
- Contraindications for MRI (e.g., ferromagnetic implants, pacemakers, claustrophobia). In that case, a participant can be included in the trial without undergoing MRI;
- Contraindications for EEG (e.g., eczema, dreadlocks, intolerability of the EEG procedure).

Oral and written informed consent will be obtained by one of the coordinating researchers or the dedicated research nurse. First, the treating psychiatrist will bring the study to the patient's (and their relatives) attention. Next, patients will be informed about the procedure by the coordinating researchers or the research nurse. Patients will have at least 3 days to freely decide whether to take part in the study. All remaining questions will be addressed before taking written consent.

7.7.3.5 Interventions

The intervention contrast is acetaminophen vs. nimodipine vs. no additional pharmacological intervention (i.e., a single dose of water). We chose these interventions because of the demonstrated efficacy of acetaminophen and calcium antagonists in rats (15). Nimodipine instead of nifedipine will be applied, because of its known vasodilatory effects specific to the human brain and profoundly less systemic effects (304).

Each patient will receive a single dose of water (50 cc) minimum 2 h, maximum 3 h before the ECT-session with either 1 tablet of 1000 mg of acetaminophen, or 2 tablets of 30 mg nimodipine. A minimum of 2 h is required because of the risk of regurgitation during the anesthetic procedure and the pharmacokinetic properties of both interventions. In the control condition, participants will receive the single dose of water and no tablet. Patients will receive the interventions on the ward. The consecutive locations to where patients will be transferred before and after the study-procedure are depicted in Figure S7.7.4.

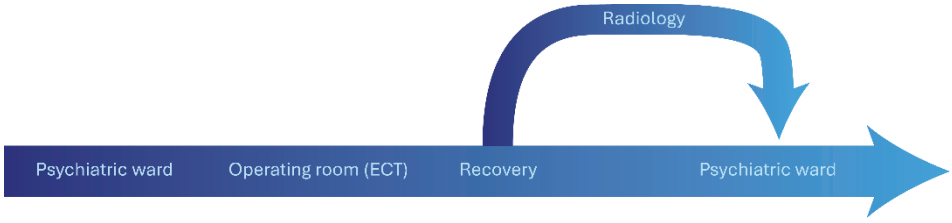


Figure S7.7.4 Schematic depiction of the route of stay of patients on the day of an ECT-session. Two hours before ECT, patients receive one of the interventions or control on the psychiatric ward. Next, ECT is performed in the operation room. Afterwards, patients are transferred to the recovery and adjacently back to the psychiatric ward. This route does not differ from standard treatment. Specifically for SYNAPSE, after 3 of the ECT-sessions, patients will be transferred directly to the radiology department for the MRI outcome measures before returning to the psychiatric ward.

Apart from the standard escape medication in ECT, no additional escape drugs are included in this trial. In clinical ECT practice, acetaminophen serves as first line medication in case of (severe) headache or myalgia within the first hours after ECT. Patients may take acetaminophen on the day after the ECT-session, but no later than 48 h before the next ECT-session. Therewith, due to the T_{max} of 2 h and half-life of 4 h, the influence of acetaminophen on the next ECT-session is minimized. If participants need pain relief within 48 h before the next ECT-session, this ECT-session will not be included in the study. Other options for pain relief are considered not to be suitable because of possible effects on cerebral perfusion (NSAID's, triptans) or increased risk of confusion (opioids) (305).

In case of profound side effects with the use of nimodipine (< 1%), in particular severe symptomatic hypotension, patients can be withdrawn from this drug condition; participation can continue for acetaminophen and the no-treatment condition.

In case of a serious adverse event causing a life-threatening situation or death attributable to our study interventions, the study will be terminated prematurely. After the ECT courses of ten included patients, an evaluation regarding unexpected deviations of effectiveness, observed (severe) side effects or other (severe) adverse events in the SYNAPSE group will be performed and compared to a matched control ECT patient group, without unblinding the interventions. If clinical effectiveness will be significantly lower or adverse events will occur significantly more prevalent in

SYNAPSE-patients compared to regular ECT patients, the study will be terminated as well.
All treatment conditions are supplied in the hospital under supervision of the researchers. Study medication is treated according to the hospital's pharmacist quality standards, including storage, temperature monitoring, and a drug accountability log.

7.7.3.6 Relevant concomitant care permitted or prohibited during the trial

The chronic use of acetaminophen, calcium antagonists and non-steroidal anti-inflammatory drugs (NSAID's) is prohibited during participation in this study, except acetaminophen as escape medication directly after the ECT-session and not within 48 h prior to a following ECT-session. Concomitant psychopharmacological medication and medication for other existing indications (e.g. physical conditions) are permitted and will be analyzed for confounding effects.

7.7.3.6 Outcomes

The primary outcome is 'postictal EEG recovery time', defined as the time interval between the induction of the seizure and return to the pre-ECT (baseline) EEG, quantified with a modified version of the temporal brain symmetry index (195, 306). An exponential function will be fitted to the data, which will yield a time constant. This provides a quantitative and robust metric of EEG background evolution over time, quantified in minutes. Continuous EEG will be assessed at baseline, during, and until 1 h after each ECT-session, as well as after completion of the total ECT course and at 3 months follow-up (Figure S7.6.5).

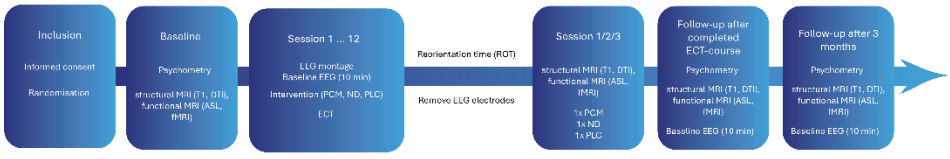


Figure S7.7.5 Schematic representation of time schedule and applied measures during SYNAPSE. At baseline, the psychometry battery, EEG and MRI measurements are taken. During and after a maximum of 13 ECT-sessions (the first session will be without intervention; in the other 12 ECT-sessions, the interventions are applied), intermittent ROT (interval: 5 min) and continuous EEG measures are recorded. Within 1 h after 3 ECT-sessions, MRI will take place (one for each intervention). The psychometric measures, EEG, and MRI measurements will be repeated at follow-up within 2 weeks after completion of the ECT course and after 3 months. ROT, reorientation time. ASL, arterial spin labeling. PCM, paracetamol (acetaminophen). ND = nimodipine, NI = no intervention, EEG = electroencephalography, ECT = electroconvulsive therapy

EEG will be measured with a full lead of 20 electrodes (including ground electrode) in three of the ECT-sessions, to gather more extensive data for further research. To reduce the time load and costs, in the other ECT-sessions, a lesser amount of 11

electrodes will be used, which still will be sufficient to analyze the primary outcome measure.
Apart from answering our research questions on effects of treatment with acetaminophen and nimodipine on postictal hypoperfusion measures, we will investigate and characterize ictal and postictal EEG dynamics during and after ECT-sessions as well as the total ECT course. Targeted future research questions address associations between ictal or postictal EEG phenomena and clinical effects of ECT, EEG network dynamics during and after seizures, and evolution of excitation-inhibition ratio (95, 307).

Secondary outcome measures include MRI and clinical measures. Pseudo-continuous arterial spin labeling (pCASL) MRI and structural MRI will be used as MRI-measures to capture a change in cerebral perfusion just after ECT seizures and after the completed ECT course compared to baseline. MRI measurements will be performed on a 3T MRI scanner (Philips Medical Systems, Eindhoven, Netherlands). Postictal hypoperfusion can reliably be detected within 1 h after seizures (15). Though not one of our research questions directly related to the hypothesis, we will additionally gather T1-weighted MRI data to examine volumetric changes, resting-state functional MRI (rs-fMRI) to measure functional organization and connectivity between brain areas, and diffusion tensor imaging (DTI) to measure diffusion in the brain to estimate the axonal organization. The goal of these additional imaging is to gather data for further research of mechanisms of mood disorders, ECT efficacy and side effects. All MRI measurements will be acquired at baseline, within the first hour after three ECT-sessions (one after each of the 3 interventions), after completion of the total ECT course, and at follow-up after 3 months (Figure S7.7.5).

The postictal reorientation time (ROT) will be used to indicate when patients are clinically reoriented after the ECT-session. Five questions regarding orientation to person, place, and time will be asked repeatedly within an interval of five minutes after administration of the ECT stimulus (193). Patients are scored as reoriented if 4 out of 5 questions are answered correctly or if a maximum of 90 min is achieved. If the patient is not reoriented at 90 min, a score of 100 min will be noted. The time between the ECT stimulus and reorientation will be expressed in minutes (i.e., the ROT). This measure has been proven to give a robust indication of clinical reorientation (308).

The incidence and severity of postictal headache, nausea and myalgia will be measured by using a visual analogue scale (VAS) (225, 308). This inquiry will be performed at baseline and at the first moment of full reorientation or at the cut-off of 90 min, as measured by the ROT.

Before start of ECT, after the completed total ECT course and at three months' follow-up, neurocognitive functioning will be assessed using the Montreal Cognitive Assessment (MoCA), Rey Auditory Verbal Learning Test (RAVLT), category fluency (CF), letter fluency (LF), digit span testing, STROOP task, Trail Making Test A and B (TMT A/B), and Subjective Assessment of Memory Impairment (SAMI).

These tests assess multiple cognitive domains (i.e., general cognitive functioning, executive functions, anterograde verbal learning, attention and subjective memory) and have frequently been used in ECT research (309-311).

7.7.3.7 Participant timeline

Participants will be informed, asked informed consent and included during a regular consultation in the outpatient Department of Psychiatry in Rijnstate Hospital. If a patient is included, an additional appointment will be made for baseline measurements (Figure S7.6.5). Outcome measurements during and after the ECT-sessions do not require additional visits, because these are integrated in the patient care as usual. After completion of the ECT course, the patients will be asked to participate in two follow-up appointments of this study, one within 2 weeks after the end of the total index ECT course, and another one after 3 months. Preferably, these appointments will be coupled to regular outpatient follow-up visits to the treatment team.

7.7.3.8 Sample size

Power calculations in humans are hampered by the lack of clinical data on effects of acetaminophen and nimodipine on recovery after seizures. For the sample size calculation, we used G*Power (312). Assuming an effect size of 0.25, a type 1 error rate of 5%, a correlation of 0.4 between measurements, and 12 included ECT-sessions per patient, a total of approximately 33 patients will be needed to achieve a power of .80. This calculation is based on a MANOVA within factors model with repeated measurements, considering a conservative correlation between measurements. In Rijnstate, recruiting patients completing this sample size is feasible in approximately two years (although the COVID-19 crisis will lead to some delay).

7.7.3.9 Recruitment

Each patient suffering a depressive episode and who is indicated for ECT will be screened by their treating psychiatrists for the inclusion criteria. If possible, patients and their relatives will be asked to consider participation after a thorough informed consent process. Afterwards, a researcher will explain the procedure and conditions for participating in the study again and more intensively. Every healthcare worker in the Department of Psychiatry of Rijnstate Hospital is educated in the inclusion and exclusion criteria for this trial to inform potential patients and their relatives to maximize inclusion.

7.7.3.10 Assignment of interventions: allocation and blinding

Randomized counterbalanced allocation to treatment sequences will be done by an independent team at the hospital's clinical trial office, using the computer program Research Manager. There are six possible combinations of the three interventions. In total, four sequences will be generated. The allocation sequence will be concealed in a closed closet until assignment of the participant, not

accessible by the investigator performing inclusion. An independent team at the hospital's clinical trial office will generate the allocation sequence. Patients are enrolled by the treating psychiatrists. The researchers or the research nurse acquire informed consent. Interventions will be implemented by one unblinded physician-researcher following the assigned order.

In this trial, one unblinded physician-researcher will be responsible for supplying the allocated interventions, which will be given to the patient by one unblinded nurse. This physician-researcher will not be involved in outcome assessment. The other researchers (i.e., the researchers that collect the outcome measures) and the treating psychiatrists will be blind to the treatment allocation. Participants will not be blinded.

Chapter 8

Summary

Epilepsy is one of the most common neurological disorders worldwide. Postictal symptoms, occurring after seizures, often form a great burden for patients and their caregivers. Approximately one-third of patients do not achieve seizure freedom with proper treatment (i.e., antiepileptic medication or surgical removal of epileptic tissue). These patients suffer from the seizure aftermath each time they have a seizure. Until today, it is unclear how we can treat the postictal state effectively. Promising findings from animal studies showed that acetaminophen (in The Netherlandsbetter known as 'paracetamol') or nimodipine (vasodilator) could improve postictal symptoms in rats.

The importance of postictal research is illustrated in **chapter 1** of this dissertation, because postictal symptoms last much longer than the seizure itself and add to the burden of patients with epilepsy and those who receive electroconvulsive therapy (ECT) for treating their psychiatric illness.

In **chapter 2**, we highlight that a clear definition for the postictal state was still lacking, which is why we provided a new definition that includes its manifestation (i.e., clinical and electroencephalography [EEG]) as well as temporal variability, based on our narrative literature review.

New definition of the postictal state

"The postictal state is a temporary brain condition following seizures a) manifesting neurological deficits and/or psychiatric symptoms,
b) often accompanied by EEG slowing or suppression,
c) lasting minutes to days."

ECT appears to be a useful human model to investigate seizures and postictal states because clinical and EEG characteristics (i.e., spatiotemporal dynamics) show sufficient similarities between both epilepsy and ECT patients, as is reported in our comparative case study in **chapter 3**. With ECT, ictal and postictal phenomena can be studied in a well-controlled environment, increasing practical feasibility of clinical studies.

In **chapter 4**, we describe that the postictal EEG shows a clear pattern of frequencies that return to baseline levels at approximately 1h after the seizure, which depends on seizure duration. Longer clinical reorientation time and repeated exposure to seizures are associated with longer postictal EEG recovery.

In **chapter 5**, we examined postictal cerebral blood flow, measured with arterial spin labeling magnetic resonance imaging (ASL-MRI), and show clear patterns of

hypoperfusion in some patients, while in others, discrete local hyperperfusion is seen. These opposite patterns depend on seizure duration.

Using functional MRI in **chapter 6**, we show that postictal mean network connectivity strength decreases in the left central executive network and in the auditory network compared to baseline and controlled for network connectivity changes in healthy controls.

Finally, with our prospective clinical trial with randomized three-condition cross-over design (**chapter 7**), we fail to replicate findings from animal models, possibly because our chosen doses of pre-ECT administered acetaminophen or nimodipine (much lower than in the animal studies) do not improve postictal EEG recovery, clinical reorientation time and postictal ASL-MRI perfusion.

Chapter 9

General discussion

In this dissertation, we have provided new insights in the postictal state of patients treated with electroconvulsive therapy (ECT) with multiple modalities (i.e., electroencephalography [EEG], clinical measures, and magnetic resonance imaging [MRI]). We attempted to find novel postictal treatments to relieve the burden for patients and their caregivers. In this last chapter, these findings will be placed in the broader context of the field. We will discuss which advances have been made in postictal research since 2020, what we have learned from our own data, which future research directions we suggest, and which possible impact our research may have.

9.1 Advances in postictal research since 2020

Since our narrative review in 2020, considerable additional insights have been gained regarding the extent of (rare) postictal manifestations, underlying pathophysiology, and treatment options.

Our list of postictal manifestations, as described in **chapter 2** (Table 2.1), may be updated with postictal stertor, petechial, ocular dipping, trismus, severe aggression, elevated body temperature, hyperglycemia, increased optic nerve sheath diameter, urinary retention, prosopagnosia, alveolar hemorrhage, and lumbar disc prolapse (313-324).

Recently, a new pathophysiological mechanism has been proposed underlying late postictal hypoperfusion. Early postictal hypoperfusion (< 30 min) seemed to be mainly caused by arteriolar constriction, whereas late hypoperfusion (> 30 min) seemed to be related to progressive neutrophil cerebral capillary adhesion (111). Furthermore, a metabolic basis for postictal hypoxia has been suggested, which may be ameliorated by mitochondrial uncoupling. More insights in the underlying pathophysiology of SUDEP (i.e., brainstem hypoperfusion, glymphatic clearance process, adenosine-induced respiratory depression) and its primary risk factor (i.e., PGES, GTCS) have been acquired (206, 325-328). Interestingly, in an ECT study, frontal oxygen saturation declined up until 1 h postictally in half of the measurements; however, if values dropped below baseline, they quickly recovered within seconds (329). These results shed light on postictal oxygen dynamics as pathophysiological mechanism of the postictal state.

Recently, more treatment options for relieving postictal headache have been reviewed, with suggestions of investigating flunarizine and sumatriptan as candidates for future clinical studies. However, no treatment options for other (mild or severe) postictal symptoms in humans have been found yet (330).

These above-mentioned new advances in research demonstrate that postictal manifestations and pathophysiology may be even more complex than initially assumed, which complicates the quest for treatments that are applicable to the whole spectrum of postictal manifestations.

9.2 What have we learned from our own data?

In the following we focus on whether we consider ECT a valid model for epilepsy. We reflect on how feasible assessment of the postictal state is and review our quantitative postictal EEG measures. Next, we discuss the importance of seizure duration. Our results will then be placed in the clinical context of ECT. Lastly, we highlight which postictal clinical manifestations we noticed in our patients.

9.2.1 Is ECT a valid model for epilepsy?

A question that may still linger is whether we can generalize findings from ECT research to epilepsy. We know from unmodified ECT (i.e., electrically inducing seizures without the use of anesthesia or muscle relaxants; **chapter 1** and unpublished data) that patients exhibit the same ictal and postictal clinical manifestations compared to generalized tonic-clonic seizures (GTCS) in epilepsy patients. These manifestations include, amongst others, tonic stiffening, clonic jerking, tongue biting, urinary incontinence, postictal unresponsiveness, headache, and myalgia.

However, we still need to consider that not all types of epilepsy have similar seizures as those induced by ECT. Moreover, mechanisms of seizure provocation (i.e., spontaneous versus electrically), seizure onset zones (i.e., dependent on underlying brain pathology versus electrode placement [see Figure 1.3]), patterns of seizure propagation (i.e., focal or generalized), and the influence of anesthesia differ between seizure in epilepsy and ECT patients. ECT-induced seizures and postictal characteristics can probably only be translated to GTCS in epilepsy, but not to other seizure types, such as absence seizures (which are short-lasting and generally do not show relevant postictal manifestations or severe postictal hypoxia) (38, 331). Additionally, and important for research of the postictal state, we show that duration and severity of the postictal state both depend on seizure duration (**chapter 4 and 5**). This indicates that ECT-induced seizure and postictal characteristics can probably be translated to GTCS, but not to other seizure types.

All in all, ECT can be considered a valid model for clinical research into ictal and postictal manifestations of GTCS and possibly also of focal-to-bilateral seizures, even though seizure onset zones may differ.

9.2.2 Assessing the postictal state with clinical, EEG, and MRI measures is feasible

SYNAPSE is the first study investigating the postictal state with extensive EEG, MRI, and clinical measures, simultaneously. In this dissertation, we show that it was possible to gather 300 useable EEGs (each containing pre-ictal, ictal, and postictal data), 96 MRIs (baseline and postictal), and 365 postictal reorientation measures. In addition, we collected patient demographics, neuropsychological measures, and follow-up MRIs after completion of the ECT-course. Also, we enriched our MRI analyses by including twenty-seven healthy controls (i.e., matched in age, sex, level of education, and used MRI scanner and software) providing us with a total of 81

scans, including thorough neuropsychological tests and structural, (resting-state) functional, and ASL-MRIs.

9.2.3 Quantitative EEG measures of the postictal state

We used the tBSI as a measure of postictal EEG recovery. We expected that the time constant τ derived by fitting an exponential function on the recovery curve of the tBSI would provide a good estimate for *speed* of postictal EEG recovery. The tBSI has been proven useful in EEG monitoring of cerebral ischemia (195, 196, 332, 333). The baseline we used in the calculation of the tBSI was a 5-minute resting-state EEG before each ECT-session.

However, we noticed that, over the ECT-course, interictal EEGs tend to get slower, showing increased amounts of delta and theta activity the further patients went into the treatment (see Figure 9.1). This may indicate that patients were still in the postictal state before each subsequent ECT-session, when the new 'baseline' measurement was recorded. We do not know whether postictal recovery is a linear process, whether the postictal state fully has resolved before the next ECT-session, and on which time scale EEGs will fully return to baseline. This probably depends on the frequency of ECT (i.e., once versus twice a week) and the time between consecutive seizures (i.e., one or four days in between ECT-sessions). Also, we do not know whether these uncertainties form any serious limitations for interpretation of the tBSI.

Furthermore, for the EEG measurements on postictal MRI acquisition days, we had to use a reduced montage for practical feasibility. In our studies, it was a potential concern that the reduced amount of spatial information influenced the accuracy of the estimated recovery. Also, data quality sometimes suffered from movement artifacts due to severe postictal confusion. Improved artifact removal, based on spatial and temporal features, may be used in future studies (334).

Taken together, the tBSI can be used to evaluate postictal EEG recovery. However, interpretation is hampered by baseline changes, a reduced montage, or artefacts, which needs to be evaluated in future work.

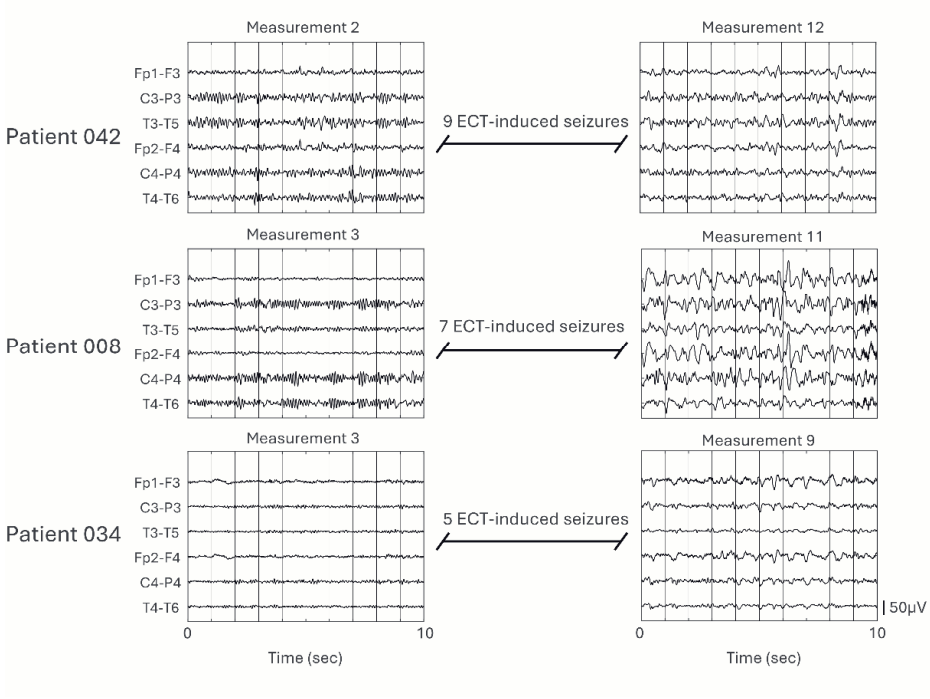


Figure 9.1 EEG Epochs representing the gradual slowing of baseline EEGs along the electroconvulsive therapy (ECT)-course. Patient 042 and patient 008 had bilateral ECT electrode placement, while patient 034 had right unilateral ECT electrode placement. Filter settings 1-25 Hz. Timescale: 1s per vertical line.

9.2.4 What did we learn from the relation between seizure duration, postictal EEG, and MRI measures?

Seizure duration may influence postictal measures. However, in previous research, seizure duration is often ill-defined or lacking (335, 336). Seizure duration is usually based on the observed motor activity on a non-paralyzed limb or on the EEG readout of the ECT device, relying on only two frontal electrodes (21, 150). In this method, seizure onset is defined as the onset of the ECT-stimulus, which may not be correct. In epileptic seizures, seizure onset is often defined as the onset of rhythmicity or initiation of spike-wave complexes (**chapter 2 and 3**). In ECT-induced seizures, we often see a delay of 1 to 15 seconds between application of the ECT-stimulus and such ictal EEG activity (Figure 9.2). Seizure offset marks the start of

postictal generalized suppression, which is defined as amplitudes <10μV (164). We recommend to incorporate a clear and standardized definition of seizure duration, as provided in **chapter 3**.

Definition for seizure duration

Seizure duration is the time interval between the onset of rhythmicity (i.e., 14-22 Hz), arhythmic polyspike activity, or rhythmic spike/polyspike activity (i.e., 2.5 – 3.5 Hz) up until postictal generalized EEG suppression (i.e., amplitudes <10μV).

9.2.4.1 How can we explain the contradictory observations on postictal cerebral perfusion in relation to seizure duration?

Both hyper- and hypoperfusion have been reported after seizures (**chapter 1 and 5**). We expected to find diffuse patterns of hypoperfusion after a seizure, by generalized vasoconstriction, because of the generalized nature of seizure activity (**chapter 2, 3, 4, and 5**). On group level, we did not establish postictal perfusion differences compared to baseline. However, as shown in **chapter 5**, seizure duration had an important relationship with postictal cerebral perfusion. Depending on the length of the seizure, the resulting postictal perfusion may be substantially different: increased postictal perfusion after shorter seizures and decreased postictal perfusion after longer seizures).

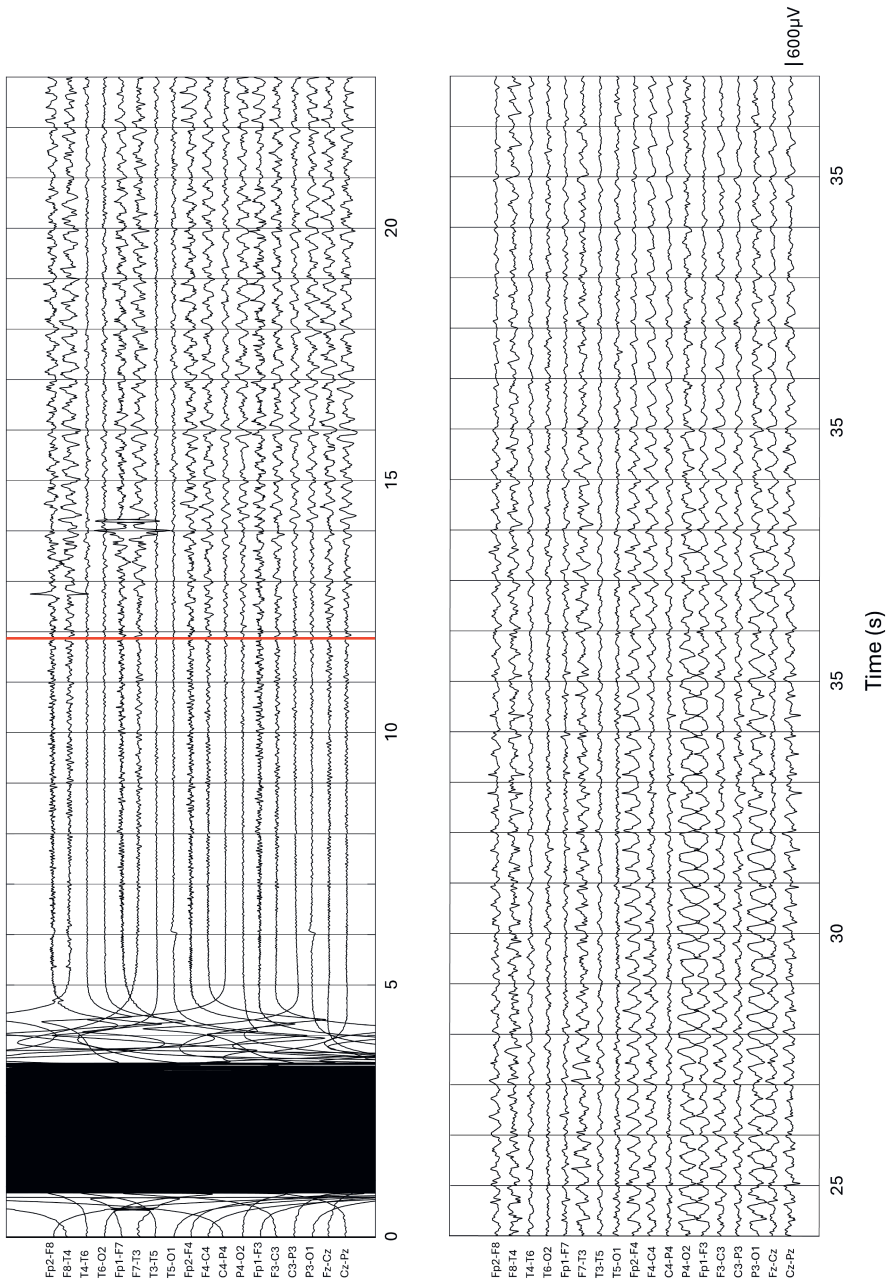


Figure 9.2 Ictal EEG during an ECT-induced seizure from patient #23 (ECT-session #14) showing that seizure onset (red line) starts approximately 11 seconds after the ECT-stimulus in frontal and central electrodes. Temporal-occipital electrodes (i.e., T3-O1, T3-T5, T4-O2, T4-T6) participate less in the seizure activity, indicated by less synchronicity and peak wave complexes. Filter settings 1-25 Hz. Timescale: 1s per vertical line.

The exact mechanism underlying these opposite effects remains puzzling. Glia cells may be responsible for these opposite effects, involving dysfunctional neurovascular coupling and the glymphatic system (206, 337, 338). Neurovascular coupling involves multiple mechanisms that regulate CBF in response to increased neuronal activity (250). In this process, astrocytes have a central role in regulating CBF, among other cell types (i.e., pericytes, vascular smooth muscle cells, and endothelial cells), and are essentially disrupted in epilepsy patients (i.e., reactive gliosis) (250, 253). Glia cells mediate the movement of water and other substances between the extracellular space and cytoplasm (339). During seizures, local astrocyte swelling may occur by enhanced water entry near synapses (339). We may speculate that short seizures lead to an excess of extracellular potassium, activating astrocytes and initiating potassium clearance, resulting in an overcompensation of the metabolic demands of the seizure and therefore increased CBF that persists at 1h post-seizure (251). Contrasting to this, longer seizures may induce astrocyte dysfunction due to astrocyte swelling, leading to more persistent excessive extracellular potassium and glutamate levels (252). Higher extracellular potassium has been related to decreased CBF in the penumbra in an ischemic animal model (340). These cascades may explain the long-lasting drop in CBF, which is in line with the hypothesis by Farrell et al. (2016, 2017), see **chapter 5**. A schematic overview of the speculative mechanism is given in Figure 9.3.

These arguments are in line with results of our own work on postictal diffusion tensor imaging (DTI). Eighty-three minutes after the seizure, postictal mean diffusivity was higher and fractional anisotropy was lower compared to baseline (341). This may imply that cell swelling, which can be measured by DTI, may result from reactive gliosis (342). This interesting mechanism may unify our findings.

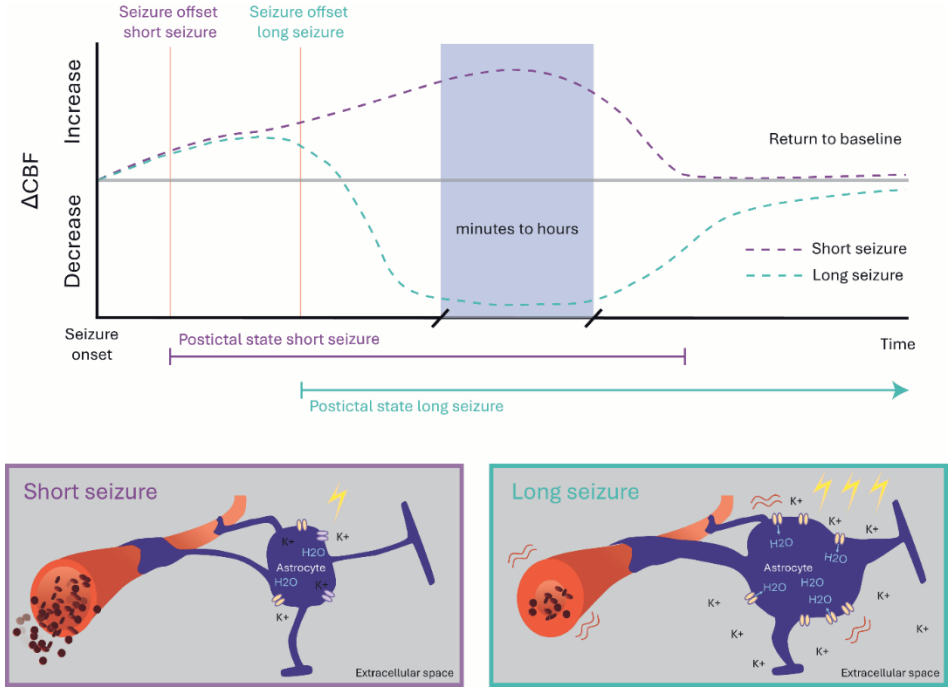


Figure 9.3 Schematic representation of the speculative mechanism how changes in postictal cerebral blood flow (ΔCBF) are related to electroconvulsive therapy-induced seizures duration and reactive gliosis. During short seizures, astrocytes functionality may recover faster (i.e., resulting in hyperperfusion) compared to longer seizures, where astrocyte swelling may occur, impacting regulation of CBF (i.e., hypoperfusion).

9.2.5 What did we learn for the clinical practice of ECT?

We established that seizure duration has an important relation with postictal manifestations. How may ECT clinicians interpret these insights in clinical practice? A possible consideration, deriving from our results in **chapter 4 and 5**, is that seizures should be terminated when an 'optimal' duration has been reached, in order to diminish postictal symptoms (i.e., faster EEG recovery, less hypoperfusion). Although, from sham-ECT studies, it is known for decades that some amount of actual seizure activity is essential for clinical effectiveness of ECT, with ongoing debate about the most optimal seizure duration. ECT-induced seizures should not be too short or only local (i.e., leading to less antidepressive effect), but also not too long (i.e., more risk of cognitive side-effects, and less antidepressive effective as well, due to stimulation near the seizure threshold instead of suprathreshold stimulation) (343-346). Especially in the beginning of the ECT course, a minimum of 15 sec motor seizure activity seems necessary for antidepressive effectiveness, and clinical guidelines also advise to terminate ECT-induced seizures when the duration exceeds 180 seconds (155, 347). According to

our results, seizure termination after 70 sec of seizure duration may potentially improve the patients' postictal recovery. This may be achieved by, for example, administration of short acting benzodiazepines or propofol intravenously. Less generalization to other brain regions may improve recovery and seizure-related side-effects as well, which may possibly also be achieved with specific electrode placements and lower electrical charges. However, these suggested strategies may also affect the antidepressive effectiveness of ECT. Therefore, more research is necessary to elucidate the relation between seizure duration, clinical therapeutic effect of ECT, and side-effects.

9.2.6 Which postictal clinical manifestations did we observe in our patients?

Within the framework of our SYNAPSE study, we had the opportunity to systematically observe patients, meticulously documenting their clinical and behavioral ictal and postictal manifestations. This level of detailed monitoring, uncommon in routine daily ECT practice because of the demanding ECT-schedule, allowed us to discern nuances that are typically overlooked. While routine ECT practices may not entail such comprehensive observation, instances necessitating close monitoring do arise, particularly in the management of postictal restlessness and confusion.

Interestingly, the postictal clinical manifestations that we observed (i.e., headache, myalgia, or nausea) were not as frequently present as we had expected initially (Figure 9.4). Hence, our efforts to establish a correlation between postictal clinical manifestations and MRI parameters were deemed unsuccessful.

Patients who reported one or more of these postictal symptoms experienced these irregularly, sometimes even only once in their entire ECT-course. In 23% of all ECT-sessions (n = 365), postictal headache occurred, and in 10% myalgia and nausea. Of all patients, 76% headache at least once during their ECT-course, in most cases after three or less ECT-sessions. Postictal manifestations were experienced as generally mild, never reaching the maximum visual analogue scale (VAS) score of 10 (i.e., extreme headache, myalgia, or nausea). In the ECT literature, incidences of postictal headache vary greatly, with a weighted incidence of 33 % for patients (i.e., corrected for the differences in sample size), while for ECT-sessions incidences ranged between 9 and 12% (28). These reported weighted incidences are lower compared to those found in our close observations, probably because we measured within the first hour post-ECT. These differences with the literature highlight the need for implementation of measures that reliably capture the full extent of postictal manifestations.

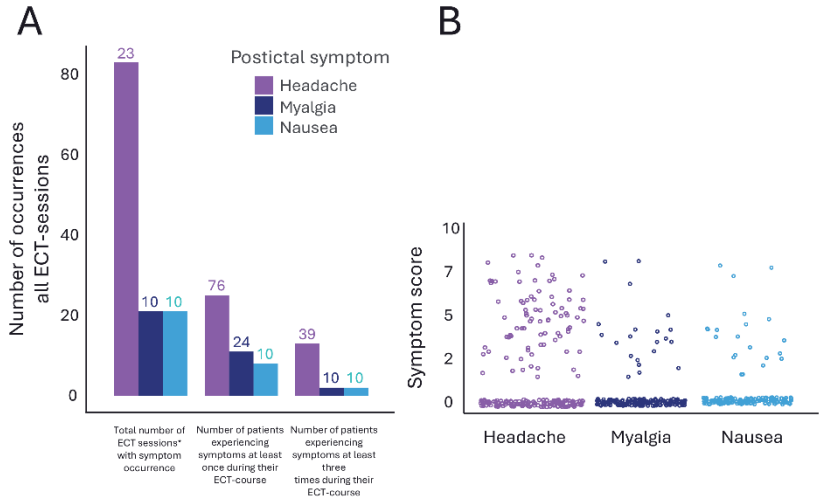


Figure 9.4 Postictal clinical manifestation based on the visual analogue scale in 33 patients and 365 ECT-sessions, assessed 1 h after the seizure. (A) Number of occurrences of postictal headache, myalgia, and nausea in all recorded ECT-sessions and patients and (B) the distribution of symptom scores for all ECT-sessions. Self-reported scores ranged from 0 (i.e., no headache/myalgia/nausea) to 10 (i.e., severe headache/myalgia/nausea). Numbers on bar plots indicate percentages. Data stems from unpublished results of the SYNAPSE trial. *Note that the total number of ECT-sessions measured in all patients is slightly higher (N = 365) than the number of EEGs that was suitable for analyses (N = 300).

9.3 Which future directions do we suggest?

Many research questions regarding the postictal state still have to be answered. Future perspectives regarding the possible treatments and the possibility to use clinical EEG and MRI measures of the postictal state will now be discussed.

9.3.1 Future treatment options of the postictal state

With the SYNAPSE trial, acetaminophen (1000 mg) and nimodipine (60 mg) showed no effects on postictal EEG recovery, clinical, and MRI measures., contrary to our expectations. Although our choices for the (lower compared to the animal model) dosages were based on patients' safety considerations. Other drugs may also be worthwhile to study. Ibuprofen is a candidate drug having similar effects on hypoperfusion in rats in a dosage that compares to use in humans (15). Currently, a clinical trial investigates the protective effects of ibuprofen and nifedipine on cerebral postictal perfusion in epilepsy patients (NCT03949478). In another animal study, pre-administration of a neutrophil antibody reduced capillary stalling, making this a candidate drug for postictal research in humans (111). In ECT research, dexmedetomidine, a sedative activating α2A-receptors, has been used

to successfully prevent postictal agitation (348-350). Interestingly, dexmedetomidine has shown vasodilatory effects, which may explain its preventive effects of postictal agitation (351, 352).

It is imperative to increase our understanding of underlying mechanisms of the postictal state in animals and humans, and how therapies would affect these mechanisms it to minimize the risk of neutral or negative results of clinical trials (353).

9.3.2 Future use of postictal clinical measures

Based on our observations in the SYNAPSE study, some remarks regarding the use of clinical measures for the postictal state can be made.

We noticed that reorientation is a dynamic process, where patients sometimes regressed to previous reorientation phases, forgetting (correct) answers they had already given. In order to capture this in future studies, the ROT may be asked for a longer duration than only until 4 out of 5 questions are answered correctly. Within a certain time frame (e.g., a few hours), the percentage of correctly answered questions may be an indicator of the fluctuation of reorientation over time, serving as a potential outcome measure in future studies.

Beside the above, a clear cut-off ROT value which indicates the duration of postictal confusion is not available. An alternative measure may be the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) (25, 354-358) to assess the occurrence and severity of postictal confusion. These questionnaires can be used at multiple times during the day to indicate duration of postictal confusion. Postictal delirium has been reliably detected in ECT and epilepsy research using these questionnaires (25, 354-358). Another more simple method could be time of initial recovery of awareness defined as the first of any responses by the patient: an appropriate verbal or motor response, or a spontaneous motor action implying recovery of awareness (i.e., covering themselves with bed sheets) (192). In future studies, it is advised to assess postictal manifestations for a longer period after the seizure and use more sensitive assessments for postictal confusion.

Clinically, relevant postictal confusion may be defined by the use of acute interventions to control for the situation, as happens frequently in patients treated with ECT. In our studies, we implied that patients who received postictal benzodiazepines were severely confused, based on Schuur et al. (31). Although this may be true in most cases, patients who did not receive benzodiazepines also showed milder signs of postictal confusion. Consequently, this clinical parameter appears insufficiently sensitive to fully capture postictal confusion.

To summarize, in future studies, it is advised to assess postictal manifestations for a longer period after seizures and to use more sensitive assessments for postictal confusion.

9.3.3 EEG

In SYNAPSE, the EEG emerged as a useful tool to assess the electrophysiological fingerprint of postictal recovery. Future utilization of the temporal brain symmetry index necessitates an investigation into the impact of a reduced montage. Connectivity measures could offer additional insights into functional postictal brain recovery, contingent on robust data quality and expanded electrode coverage. Temporal autocorrelations may illuminate ictal dynamics (i.e., sparing of brain areas) that may be relevant in predicting postictal dynamics or recovery (122). Extending EEG recordings beyond 1 h may be fruitful to characterize the temporal evolution in the late postictal state (> 1 h). Postictal suppression, a noteworthy EEG characteristic, warrants attention in future research due to its predictive value for SUDEP and other postictal manifestations (i.e., immobility or headache) (96, 97, 359, 360). Interestingly, in ECT research, higher levels of postictal EEG suppression were associated with better antidepressive effectiveness, suggesting that postictal EEG features may predict ECT effectiveness (361).

9.3.4 MRI

In **chapter 5 and 6,** we demonstrated the feasibility and valuable insights provided by postictal MRI measurements in understanding postictal dynamics. While a quantitative measure of cerebral perfusion is desirable to correlate with postictal clinical manifestations, these measures are influences by various individual and technical factors (i.e., age, sex, coffee consumption, stress, post label delay depending on age, CBF calculation, timing of the postictal imaging acquisition) (133, 231, 235, 362, 363). Future studies should define seizure onset zones for ECT-induced seizures, considering electrode placement and individual factors like skull thickness and cerebrospinal fluid, to enhance the sensitivity of perfusion results. Exploring seed-based connectivity analyses with the seizure onset zones may offer a nuanced understanding of postictal dynamics compared to other global resting-state network analyses (i.e., independent component analysis [ICA], **chapter 7**). Investigating postictal (structural and functional) MRIs at multiple postictal time points (i.e., several minutes, 1 h, 2 h, and 3 h after the seizure) would be intriguing for comprehending evolution of postictal recovery.

9.4 Which possible impact does our research have?

This dissertation holds potential to exert a profound influence across diverse scientific and medical domains. Since 2020, our narrative literature review (outlined in **chapter 2**) has already been cited 68 times and attracted over 1000 views on ResearchGate. These metrics signify the provision of valuable insights within an underexplored research field requiring further advancements.

Methodologically, our SYNAPSE trial demonstrates the feasibility of utilizing ECT-induced seizures as a means to investigate a research question within the epilepsy field, employing a clinical trial with randomized cross-over design. The introduction

of postictal clinical, EEG, and MRI measures in our study offers innovative potential outcome metrics for future trials in this particular research domain.

From a neuroscientific viewpoint, our investigation unveiled the correlation between seizure duration and postictal EEG recovery, as well as between seizure duration and postictal perfusion changes. Alongside these findings, we also revealed discernible alterations in network connectivity during the postictal state. These findings may impact the broader field of epilepsy and ECT research.

Clinically, we have deepened our understanding of postictal dynamics in relation to seizure duration. If it can be verified that shorter seizures do not impact ECT effectiveness, our insights into the relationship between seizure duration and postictal perfusion may lead to earlier seizure termination in ECT (than advised in the current clinical guidelines, i.e., after 180 seconds).

Finally, it is remarkable how a patient population with a serious mental illness can significantly contribute to research into a neurological condition. Implicitly, this dissertation reconnects neurology and psychiatry, a connection that has been minimized since the 19th century (364).

9.9 Conclusion

The postictal state is an overlooked topic, even though it greatly impacts the life of many patients with epilepsy and ECT. In this dissertation, we provided a comprehensive definition of the postictal state. We showed that postictal clinical and EEG features in epilepsy and ECT patients are similar. We learned that postictal recovery after ECT-induced seizures is characterized by typical EEG (frequency) recovery. We substantiated that seizures probably induce duration-dependent changes in postictal EEG recovery and cerebral perfusion changes. Also, we provide preliminary evidence that connectivity changes in the left central executive and auditory resting-state networks occur in the postictal state. We showed that studying effects of interventions in the postictal state is possible after ECT-induced seizures. Unfortunately, our administered dosages of acetaminophen and nimodipine were not associated with improved postictal recovery after ECT.

I hope that this dissertation encourages scientists to continue postictal research to broaden our understanding of underlying mechanisms and new treatments. Our findings of EEG recovery, cerebral perfusion, and brain network changes provide a starting point for future studies in relation to treatment effect.

To conclude this dissertation, we present paraphrased citations of SYNAPSE patients after their last measurement:

"I am happy that I could participate in the SYNAPSE study and help other ECT patients who suffer from treatment-related side-effects. Hopefully, the side-effects can be diminished so that ECT will also gain wider acceptance. It has helped me to get rid of my depression."

"It is amazing that my contribution to this study may also help epilepsy patients."

"Even though I still suffer from memory impairments, I am glad I completed the treatment and contributed to this important research."

Chapter 10

Nederlandse samenvatting

Epilepsie is een van de meest voorkomende neurologische ziektes wereldwijd. Postictale klachten ontstaan na het insult en zijn een grote last voor patiënten, hun naasten en soms zorgverleners. Bij ongeveer een-derde van alle patiënten helpt geen medicatie of operatie om aanvalsvrij te worden. Dit betekent dat deze patiënten iedere keer na het insult lijden onder de postictale klachten. Tot op heden is niet duidelijk hoe we de postictale fase efficiënt kunnen behandelen. Uit dieronderzoek bleek een veelbelovende hypothese voor de behandeling van de postictale fase, namelijk dat acetaminophen (beter bekend als paracetamol) of nimodipine (een bloedvat verwijder) postictale klachten kunnen verminderen.

In dit proefschrift in **hoofdstuk 1** bespreken we waarom het belangrijk is om onderzoek te doen naar de postictale fase. Postictale klachten duren vaak veel langer dan het insult zelf en belemmeren het leven van epilepsiepatiënten. Maar ook patiënten die elektroconvulsietherapie (ECT) ondergaan ervaren grotendeels dezelfde postictale klachten. Bij ECT wordt een stroomimpuls op de schedel toegediend, die een epileptische aanval uitlokt, die verschillende ernstige psychiatrische aandoeningen kan behandelen.

In **hoofdstuk 2** geven we een nieuwe definitie voor de postictale fase omdat een gestandaardiseerde definitie in de literatuur ontbrak. Deze definitie beschrijft de aard van (klinische) symptomen en elektro-encefalografie (EEG) patronen en de variabele duur.

Nieuwe definitie voor de postictale fase

”De postictale fase is een tijdelijke verstoring van hersenfunctie na een epileptisch insult waarbij

a) neurologische en/of psychiatrische symptomen voorkomen, als ook
b) vertraging van het EEG of EEG suppressie en
c) deze symptomen minuten tot dagen kunnen aanhouden.”

ECT kan als humaan model voor epilepsie gebruikt worden om insulten en postictale fasen te bestuderen. Dit konden we concluderen, omdat de klinische en EEG karakteristieken (met name de spatiotemporele dynamieken) tussen epilepsie en ECT-patiënten vergelijkbaar zijn, zoals aangegeven in **hoofdstuk 3**. Met behulp van ECT kunnen we ictale en postictale fenomenen systematisch en in een gecontroleerde omgeving onderzoeken. Daardoor worden klinische studies bij epilepsie haalbaar.

In **hoofdstuk 4** beschrijven we dat het postictale EEG een specifiek frequentie patroon toont, welk na ongeveer een uur na het insult terug naar baseline herstelt. Dit postictale EEG herstel hangt af van de lengte van het insult. Het klinisch herstel in de postictale fase (gemeten met de klinische reoriëntatie vragenlijst) hangt evenzeer af van insultduur. Dit betekent dat langere insulten samenhangen met een langer klinisch herstel en met een langer EEG herstel.

We hebben onderzoek gedaan naar postictale hersendoorbloeding (ook wel perfusie genoemd) in **hoofdstuk 5**. Met arterial spin labeling magnetic resonance imaging (ASL-MRI) zijn duidelijke patronen van hypoperfusie in de hersenen van enkele patiënten gevonden. Sommige andere patiënten, daartegenover, toonden verhoogde postictale perfusie. Deze tegenovergestelde effecten bleken samen te hangen met de lengte van het insult.

Met functionele MRI in **hoofdstuk 6** laten we zien dat twee hersennetwerken veranderen in de postictale fase, vergeleken met de uitgangs-fMRI-scan. De connectiviteit in de linker central executive en auditory network namen af, gecontroleerd was voor test-hertest effecten in gezonde mensen die geen psychiatrische aandoening hadden.

Tot slot presenteren we de resultaten van onze gerandomiseerde klinische studie met drie condities (toediening van acetaminophen, nimodipine of placebo), uitgevoerd in een cross-over onderzoeksopzet (**hoofdstuk 7**). Wij konden niet aantonen dat behandeling met acetaminophen of nimodipine voor ECT een effect hadden op het EEG herstel, het klinische herstel, of op de postictale perfusie.

Chapter 11

Deutsche Zusammenfassung

Epilepsie ist eine der meist vorkommenden neurologischen Krankheiten weltweit. Mit der postiktalen Phase bezeichnet man den Zeitraum nach einem epileptischen Anfall. In dieser Phase können verschiedene neurologische oder psychiatrische Symptome entstehen. Diese sind eine große Last für Patienten, Angehörige und die Pflegekräfte der Betroffenen. Bei ungefähr einem Drittel der Patienten helfen weder Medikamente noch eine Operation, um anfallsfrei zu werden. Das bedeutet, dass diese Patienten jedes Mal nach einem Anfall postiktale Symptome aufweisen. Bis heute ist es unklar, wie wir die Symptome in der postiktalen Phase effizient behandeln können. Allerdings gibt es aus der Tierforschung eine vielversprechende Hypothese, nämlich, dass die Behandlung mit Acetaminophen (in Deutschland auch besser bekannt als „Paracetamol“) oder Nimodipine (ein Gefäßerweiterungsmittel) die Auswirkung von postiktalen Symptomen mildern kann.

In dieser Dissertation in **Kapitel 1** besprechen wir wieso es von großer Relevanz ist, die postiktale Phase zu erforschen. Postiktale Symptome können oft viel länger andauern als der Anfall selbst. Durch diese Symptome wird das Leben von sowohl Epilepsie, als auch von Elektrokonvulsionstherapie (EKT)-Patienten beeinträchtigt. In der EKT wird mit geringen Stromimpulsen am Schädel ein epileptischer Anfall ausgelöst, um verschiedenste psychiatrische Störungsbilder zu behandeln. Jedoch erfahren auch diese Patienten zum Großteil die selben postiktalen Symptome wie Epilepsiepatienten.

In **Kapitel 2** stellen wir eine neue standardisierte Definition für die postiktale Phase dar, weil diese in der Literatur nicht aufzufinden war. Unsere neue Definition umfasst die möglichen (klinischen) Symptome, sowie Elektroenzephalographie (EEG)-Muster und die variable Dauer der postiktalen Phase.

Neue Definition der postiktalen Phase

”Die postiktale Phase ist eine zeitlich begrenzte Gehirnerkrankung nach einem epileptischen Anfall, wobei

a) neurologische und/oder psychiatrische Symptome,
b) eine EEG-Verlangsamung oder EEG-Unterdrückung/Inaktivität vorkommen können.
c) Diese Symptome können Minuten bis Tage anhalten.”

In **Kapitel 3** erarbeiten wir warum man EKT als menschliches Modell für Epilepsie nutzen kann um die iktale und postiktale Phase systematisch zu erforschen. Zu dieser Schlussfolgerung kamen wir durch die erstaunliche Ähnlichkeit von klinischen und EEG-Merkmalen (raumzeitliche Dynamik) zwischen Epilepsie und

EKT-Patienten. Durch die Nutzung von EKT in der Epilepsieforschung können klinische Studien durchgeführt werden.

Wir beschreiben den Verlauf und die Entwicklung des postiktalen EEG in **Kapitel 4**. Es zeigte sich ein spezifischer Verlauf der Frequenzmuster innerhalb der ersten Stunde der postiktalen Phase, welche sich am Ende zurück zu den Ausgangswerten entwickelte. Diese Entwicklung des EEG, sowie auch das Wiedererlangen der basalen kognitiven Fähigkeiten hingen mit der Länge des Anfalls zusammen. Das bedeutet, dass längere Anfälle sowohl mit einer längeren klinischen, als auch einer EEG-Regeneration zusammenhängen.

Der postiktale zerebrale Blutfluss (auch genannt Gehirndurchblutung) eine Stunde nach der EKT wird in **Kapitel 5** beschrieben. Mit einer speziellen Magnetresonanztomographie (MRT)-Technik, bezeichnet als Arterial Spin Labeling, ist bei vielen Patienten eine deutlich verminderte Perfusion im Gehirn feststellbar. In anderen Patienten, wurde jedoch erstaunlicherweise ein erhöhter postiktaler zerebraler Blutfluss festgestellt. Diese gegenteiligen Effekte hingen mit der Länge des Anfalls zusammen.

Mit dem funktionellem MRT in **Kapitel 6** zeigen wir, dass einige postiktale Gehirnnetzwerke eine verminderte Konnektivität (auch genannt Vernetzungsgrad) aufweisen. Diese Effekte sind im linken zentralen exekutiven und dem auditiven Netzwerk gefunden worden. Wir haben diese Zusammenhänge mit denen (neurologisch und psychisch) gesunder Partizipanten verifiziert.

Schlussendlich präsentieren wir die Ergebnisse unserer randomisierten kontrollierten Studie mit cross-over Forschungsdesign (**Kapitel 7**). Acetaminophen oder Nimodipine hatten keinen Effekt auf unsere Resultate (klinische oder EEG-Regeneration oder auf den postiktalen zerebralen Blutfluss).

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Acknowledgements

As many of you know, completing this dissertation was no walk in the park. Many people stood by me during this journey and I would like to take a moment to thank everyone who played a part in making this time special for me.

First, I extend my sincere gratitude to my promotors, **Michel** and **Jeannette**. **Michel**, your profound expertise ahs been instrumental in guiding me through my doctoral journey. I am deeply appreciative of your invaluable assistance, particularly in matters pertaining to programming and critical thinking. Your support has been a cornerstone in my academic endeavors. **Jeannette**, I hold in high regard your exceptional work ethic and critical attitude. Your constructive criticism has played a pivotal role in refining my work, and I am grateful for the depth of insight you have shared. Under the collective guidance and counsel of both of you, I am confident that I have undergone significant personal and academic growth.

Jeroen, I am grateful for your prompt and inventive feedback. Your insights consistently encouraged me to explore new perspectives. I am deeply impressed by your exceptional writing skills, and I trust that our collaboration has equipped me with valuable tips and tricks to enhance my own writing.

Guido, thank you for your support, especially regarding the MRI analyses. Your broad knowledge always impressed me and I always had the feeling I could ask anything that was unclear. I look forward to working together with you on the BOOST project to successfully complete another clinical trial.

Dr. Jordan Farrell, prof. dr. ir. Srirang Manohar, dr. Ciska Heida, prof. dr. Cornelis J. Stam, prof. dr. Wiepke Cahn, and **dr. Edwin van Dellen**, thank you for your time and critical questions.

Joey, I am very thankful for our time together during this project. I know the beginning has been bumpy, with uncertainty about our responsibilities and papers we want to write. But I wouldn't have liked to do this with anyone else. I admire your determination and flexibility and how you manage to do a PhD next to your medical training. I will never forget the long programming sessions when we ran into an error with fMRI prep again and couldn't make it work .. until we did! We are both very persistent, and I like that about us working together. :)

I want to specifically thank my paranymphs, **Marlous** (read: Marlaus) and **Sven**. You both played a crucial role in assisting me to complete this journey. **Marlous**, without our many evenings where I could complain over frustrating work experiences, I would have probably gone mad. You are such an easy-going, strong, intelligent, and unwavering person, which is exactly what I needed at most times. Thank you so much for being there for me and supporting me. I enjoyed our car drives together to

the university, where we always make it a fun experience and talk about literally anything. I will always remember our time in Marseille, where we ended up kitesurfing on the open sea. I am glad we both survived the high waves (and that we did not vomit on the small boat). **Sven**, I enjoyed being your mentor and afterwards your colleague so much. You always stayed positive about the – sometimes – stressful measurements for the SYNAPSE study, where I was mostly a nervous wrack because I wanted everything to go perfect and smooth. Your view on this enlightened me to relax a bit more ;). I enjoyed our stay in Portugal for the Brainstimulation conference, where we ended up laughing a lot about how much time Joey spends in the bathroom to dry and style his hair (sorry Joey :D). You are such a positive, funny, intelligent, and warm person. I am very happy that you got a job at the psychiatry department and started your PhD on the SYNAPSE data. I am very excited to see what you will find out!

I want to thank all of the (former) members of the Rijnstate research group (**Astrid, Hanneke, Tijn, Tonia, Eva, Nienke, Nicole, Stanley, Thijs, Simon, Anna, Quinty**) and members of the Clinical Neurophysiology group. **Vale**, the countless hours we spent preparing and mentoring students at the EMG and EEG practicals were so much more fun together, thank you for everything! **Catarina**, I enjoyed our evenings together when I was staying over and cooking together. **Suzanne**, I enjoyed our trip to America very much, I am sure you will ace your PhD. A special thanks also to **Sophie** who supported me interpreting the ASL analyses. **Carin**, thank you for your assistance with the Neurocenter, it was very much appreciated! **Eva, Nina, Maria Carla, Marloes, Gerco, Sjoukje** (my fellow vegan colleague!), **Martina**, **Tanja, Cyrilla**, **Joost**, thank you for making the times at the UT so fun and light, I enjoyed having you as colleagues and will miss you all!

I want to thank all patients that have participated in this clinical trial, as well as the hospital staff that made it possible. Special thanks to all employees at the clinical neurophysiology department (**Els**, thank you for the many hours looking at EEGs together; **Masha, Floor**, and **Rajco**, thank you for assisting and teaching me how to apply the 10-20 system), employees of the psychiatry department (**Oscar, Nancy, Joep, Maarten, Roy, Boudewijn, Jolanda, Michael, Stef, Anna, Benny, Annero, Willemijn, Talip, Eva, Annemiek, Els, Marente, Anita, Carin, Nelis, Bianca, Yvonne**, and all nurses), employees at the radiology department (**Marit, Marieke, Hugo** among others), employees at the recovery and operating room including all anesthesiologists who contributed. A special thanks to all of our volunteers who helped make this clinical trial a success: **Marleen, Arnoud, Simon**, **Gijsbert, Max, Amber**, and **Tessa**. **Paul**, thank you for providing support for the Neurocenter system. **Esmée**, I enjoyed working together with you a lot, thank you for your training of the neuropsychologic tests and support. **Laurens** and **Freek**, thank you so much for the countless hours of statistical and (f)MRI support.

1.1I want to thank all of my friends that I haven't yet named. **Katrin**, we have been through so much together. You are one of my closest friends that I have and probably ever will have. Thank you so much for your support throughout those years. You understand me and always find the right positive words to change my perspective on challenging situations, this is a great strength of yours! I hope we will experience many (surf-)vacations together :) **Channah**, you are the most reflected person that I know. Your ability to see the world and your own actions from many perspectives always inspires me. I am so happy to have you as one of my closest friends that I can always count on. I remember how we met – at the student pole dance association in Nijmegen. I sincerely hope to continue our close friendship until our old days. **Sarah**, our extensive cooking (frying) and baking sessions always brought me joy. It is essential for me to have such a great vegan friend that understands my ethical believes. **Michela**, we have known each other for a couple of years and you are very dear to me. I love to dance with you and I appreciate how well you understand me and give useful advise in challenging situations. **Stephan**, you always help me seeing a different perspective. I love that we share a common hobby (Anime) and will continue to nerd about it together. **Maria**, you have been a life-long friend, I am so very grateful to still have you in my life. I appreciate everything you have done for me, and I sincerely miss our squash-sessions! **Cynthia**, I am happy to have you as a friend and I am glad that we still are in contact after such a long time, even though the distance separates us physically. **Kieran**, you have been such a good friend over the years, thank you for your support. **Marie Jose**, I could not with for a better neighbor who always finds time to listen to my struggles and difficult poop-stories of my dogs, thank you for being there! **Nina**, I love having you as my neighbor and our culinary evenings. To my former neighbors **Liza** and **Geert**, thank you for making the first year at High Park an amazing experience. **Ilonka**, thank you for showing me bikejöring, I love that we can share this very special hobby with our dogs. Special thanks as well to **Janice**, you helped me a lot to find myself.

Thank you **Felicia** for introducing me to your pole dance trainer team. I enjoy teaching and taking your classing very much and it helped me through these years to keep a sane mind. **Manouk**, you are such a bright and positive person, I will forever enjoy training together with you! **Maya**, thanks for insulting me in every class that I teach, and thanks for your help with Illustrator and Photoshop, especially for making this cover glow even more ;)! **Lory**, you are always a core member of my classes and so enthusiastic, thank you for being there. **Ivanna**, I love to train together and hope we will continue this for a long time! Thanks to all other members of the studio!

Zum Schluss möchte ich meiner Familie danken, dass sie mich über die Jahre hin immer unterstützt haben. Ohne euch wäre ich nie so weit gekommen. **Mama**, du bist so eine starke Frau. Wenn du mich damals nicht ermutigt hättest, wäre ich

wahrscheinlich nicht ins Ausland gegangen, sondern hätte in Deutschland studiert. Danke, dass du mich an meine Grenzen bringst, sodass ich weiter wachsen kann. **Papa**, ich bewundere deine Ruhe. Davon hätte ich auch gerne mehr. **Eva**, du bist die beste Schwester, die ich mir vorstellen kann. Du bist so unglaublich witzig, intelligent, und warmherzig. Ich bin sehr dankbar dafür, dass unser Verhältnis so eng ist. Ein großes Dankeschön auch an meine Familie – **Conny, Wolfgang, Luisa, Niki, Joshua**, **Birgit** und **Heike** – Ich hab euch lieb.

List of publications

Pottkämper, J. C. M., Hofmeijer, J., van Waarde, J. A., & van Putten, M. J. A. M. (2020). The postictal state — What do we know?. *Epilepsia*, *61*(6), 1045-1061.

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Submitted

Pottkämper, J. C. M., Verdijk, J. P. A. J., Stuiver, S., Aalbregt, E., ten Doesschate, F., Verwijk, E., Schmettow, M., van Wingen, G. A., van Putten, M. J. A. M., Hofmeijer, J., van Waarde, J. A. Acetaminophen or nimodipine to improve postictal recovery after electroconvulsive therapy-induced seizures: a randomized crossover trial. *Under review*

In preparation

Pottkämper, J. C. M., Verdijk, J. P. A. J., Stuiver, S., ten Doesschate, F., van Putten, M. J. A. M., Hofmeijer, J., van Waarde, J. A., van Wingen, G. A. Decreased connectivity in the central executive and auditory network after electroconvulsive therapy-induced seizures: A postictal resting-state fMRI study

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Bovy, L., Berkers, R. M., Pottkämper, J. C. M., Varatheeswaran, R., Fernández, G., Tendolkar, I., & Dresler, M. (2020). Transcranial magnetic stimulation of the medial prefrontal cortex decreases emotional memory schemas. *Cerebral Cortex*, *30*(6), 3608-3616.

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Poster presentations

StudYing the effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT (SYNAPSE). SYNAPSIUM 2020

StudYing the effect of Nimodipine and Acetaminophen on Postictal Symptoms after ECT (SYNAPSE). SWO midwinter meeting 2020

Electroconvulsive therapy-induced seizures as a human epilepsy model. International society for electroconvulsive therapy and neurostimulation 2021

Electroconvulsive therapy-induced seizures as a human epilepsy model. Voorjaarscongres Nederlandse Vereniging Voor Psychiatrie 2022

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Postictal perfusion changes after electroconvulsive therapy-induced seizures. American epilepsy society 2023

Disrupted default mode network connectivity after electroconvulsive therapy-induced seizures. European conference clinical neurophysiology 2023

Decreased regional postictal perfusion after electroconvulsive therapy-induced seizures measured with arterial spin labeling. European conference clinical neurophysiology 2023

More preceding electroconvulsive therapy-induced seizures predict slower postictal EEG recovery. International Brain Stimulation Conference 2023

Postictal perfusion after electroconvulsive therapy-induced seizures measured with arterial spin labeling. International Brain Stimulation Conference 2023

About the author

Photo by The Nordic River Photography ©

Julia Christine Marianne Pottkämper, born on July 3rd 1992, in Remscheid, Germany, embarked on a journey that led her to The Netherlands In 2012, where she pursued and successfully completed her Bachelor's degree in Psychology, followed by a Master's degree in Healthy Psychology at Radboud University Nijmegen. Her commitment to research became evident as she earned a Master's degree in Cognitive Neuroscience, with cum laude, marking the initial stride toward her career aspirations. In a harmonious integration of psychology and neuroscience, she commenced her Ph.D. in Clinical Neuroscience at the University of Twente in collaboration with Rijnstate Hospital in Arnhem. Following the completion of her Ph.D., she is set to continue on a postdoctoral journey in clinical neuroscience with the hopeful aim of contributing to the discovery of biomarkers for depression and its successful treatment.

Beyond her academic pursuits, she is a dedicated advocate for a vegan lifestyle, a conscious choice stemming from her conviction that animals are not meant for human consumption. This ethical stance, maintained for more than 12 years, reflects her belief in the unnecessary infliction of suffering upon animals for human sustenance.

Julia has cultivated a passion for sports, particularly pole dancing, a pursuit that spans eight years and continues to thrive. Whether executing acrobatic tricks on or off the pole, she findings genuine joy in the art. Beyond her personal practice, Julia plays an integral part of the pole dance community, contributing as a teacher at Pocahontas Studio in Arnhem for the past two years.

The most enriching aspect of Julia's life involves her decision to adopt two dogs, a choice she deems as her best decision yet. They joy they bring, coupled with her dedication to their training and well-being, adds a fulfilling dimension to the everyday life.

The end