CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsia®

The postictal state — What do we know?

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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, we discuss postictal sypmtoms, their clinical manifestations, and related findings. Moreover, pathophysiological advances are reviewed, followed by current treatment options.

KEYWORDS

epilepsy, postictal suppression, postictal symptoms, postictal treatment, SUDEP

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.[1–5] Furthermore, psychiatric symptoms may occur, including postictal depression and psychosis.[1,6,7] 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.[4] A recent systematic review of 45 studies identified postictal clinical symptoms and characteristics in various epilepsy types.[4] 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.[1,8]

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.[6] Although postictal symptoms were first described in 1849 by Todd,[9] a clear definition is still lacking. In Figure 1, a timescale of the postictal state is presented. The duration of the postictal state differs in terms of clinical manifestation; T1 (red) represents the short duration of seconds to minutes; T2 (orange) includes hours, reflecting physical and cognitive symptoms; and T3 (yellow) 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 on electroencephalography (EEG) as suppression of physiological rhythms (T1-T2; Figure 1).[6] 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).[10] 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.

2 | SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed, MEDLINE, and the Cochrane databases for English-language articles published 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.

3 | CLINICAL MANIFESTATIONS

The postictal state shows a rich phenomenology of neurological deficits and/or psychiatric symptoms, summarized in Table 1.

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).[11,12] Recovery of

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 are mostly limited to preclinical models.
- Current treatment options consist mainly of symptom suppression and are not strongly established in clinical trials.

consciousness may, in some cases, reveal neurological lateralized deficits, including paresis.[13] After an individual awakens from coma, memory is often temporarily impaired (T2).

3.2 | Cognitive dysfunction

Cognitive functions that decline most after seizures are alertness and short-term memory (T2).[3] Sixty-six of 100 patients with refractory focal epilepsy showed postictal memory impairments depending on the location of seizure foci.[14] 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.[1] In right temporal lobe epilepsy (TLE), a decline in visual attention and spatial orientation was reported, whereas verbal memory was impaired in left TLE.[3] The more seizures a patient experiences, the larger the likelihood of severe postictal cognitive impairment.
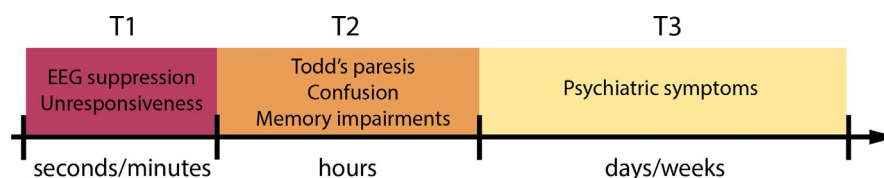

FIGURE 1 Timescales of the postictal state. The duration of the postictal state differs in terms of clinical manifestation; T1 (red) represents the short duration of seconds to minutes; T2 (orange) includes hours, reflecting physical and cognitive symptoms; T3 (yellow) represents days to weeks, in which 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

TABLE 1 Clinical manifestation of the postictal state

Category	Signs and symptoms
Altered consciousness	Unresponsiveness Confusion Coma Delirium[a]
Cognitive dysfunction	Declined alertness and short-term memory Visual and spatial memory impairments Delirium[a]
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[a] 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

[a]Delirium is a syndrome in which consciousness, cognitive functions, and psychiatric symptoms (eg, hallucinations, delusions, mood disturbances) may occur.

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).[15] In addition, postictal hypersalivation, nose rubbing, cardiovascular dysfunction (arrhythmia, bradycardia, and tachycardia), myocardial infarction, neurogenic pulmonary edema, and transient systemic hypotension and hypertension have been reported (T1-T3).[3,16] Postictal hyperthermia resulting from ictal muscle activity was found to be related to seizure duration in several patients.[16] Neurogenic edema is an uncommon complication in the postictal state also, resulting from changes in the

alveolar capillary endothelium, which typically resolves within 24 hours.[17]

3.4 | Headache

Postictal headache occurs in approximately 66% of patients.[4,18] It ranges from moderate to severe in intensity, frequently with migrainous features, and in durations from minutes to hours (T1-T2).[19] 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.[13,19]

3.5 | Changes in mood and affect

Postictal depressive and anxiety symptoms may occur for >24 hours and within 5 days postictally (T3).[5] In a sample of patients with focal epilepsy, 18 of 100 showed postictal depressive symptoms, characterized by anhedonia, helplessness, self-deprecation, or suicidal thoughts.[14] Postictal anxiety may include constant worrying, agoraphobia, and unpleasant feelings due to increased self-awareness (ie, self-consciousness), and is often accompanied by a depressive disorder.[20] 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.[21] Postictal hypomania is also common (T1-T2).[5]

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).[22] Diagnostic tools with high specificity or sensitivity to differentiate between Todd's paresis, transient ischemic attacks, or stroke (mimics) are currently lacking.[23,24] Careful clinical assessment including physical and neurological evaluation and brain imaging is advised.[24] Todd's paresis can develop after focal and generalized seizures involving the (contralateral) sensorimotor cortex, and can even be present bilaterally.[25] In a sample of 229 patients with focal to bilateral tonic-clonic seizures, approximately 6% developed Todd's paresis.[26] 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.[13]

3.7 | Visual and auditory disturbances

Postictal blindness (amaurosis[27]) is reported in two-thirds of patients with childhood occipital epilepsy of Gastaut,[28] with seizure foci being occipital or occipitotemporal (T1-T2).[29,30] Older patients may have postictal visual loss as well, if seizures started in occipital areas.[29] 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.[31] In the few cases of palinacousis, none of the patients had electrographic seizures during the event.

3.8 | Language dysfunction

Postictal speech disturbances can be indicative of seizure location and seizure spread, and they often involve postictal dysphasia (T1).[3,32] Approximately 38% of patients experience language impairments.[4] Most postictal speech disturbances occur in patients with TLE of the dominant hemisphere or if seizures spread to the dominant temporal lobe.[32] 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.[32]

3.9 | Sleep

If seizures occur during sleep, postictal phenomena may range from confusion on awakening to disturbances in sleep patterns (T1-T3).[33] This also introduces challenges for the differential diagnoses of sleep disorders as parasomnia. For instance, sleep disturbances may affect memory consolidation and attention, but this may also be directly related to the postictal state.[33] Sleep apnea may also occur after nocturnal seizures, introducing a risk for sudden unexpected death in epilepsy (SUDEP).[34] Postictal sleep may also be a symptom related to activation of cerebral inhibitory systems to terminate seizures.[12] Postictal sleep has been reported in approximately 6% up to 45% of patients.[4,18]

3.10 | Psychiatric symptoms and syndromes

Postictal psychiatric symptoms include delirium, changes in perception (eg, hallucinations), thoughts (eg, incoherence, delusions), and motor disturbances (eg, catatonia) (T2-T3).[18,35–37] Postictal delirium may transition to a postictal psychosis, including violent behavior.[1,36,38] In some patients, violent, bizarre, or sexual inappropriate behavior occurs.[39,40] Two meta-analyses have shown that the estimated prevalence of postictal psychosis ranges between 2% and 4%, independent of type of epilepsy.[4,39] Diagnostic criteria include return of normal mental function within 1 week and duration of 1 day to 3 months.[1,41] However, no clear definition of postictal psychosis is provided in the literature. In addition, it remains unclear whether the psychosis is part of the ictal period alone or represents an underlying psychiatric illness, which makes its diagnosis and treatment challenging,[2] but diagnostic criteria designed by Logsdail and Toone may be used.[42] In a study with 100 epilepsy patients, approximately half presenting with isolated psychotic symptoms also had a history of psychiatric disorders such as depression, anxiety, and attention deficit disorders.[14] Psychic auras and grandiose and religious delusions occurred frequently in a sample of 30 patients with TLE, compared to interictal and chronic psychosis.[43]

Postictal Cotard and Capgras delusion have been reported in case studies.[44] Affective symptoms may occur during postictal psychosis,[45] including the Cotard and Capgras delusion, which may lead to a discussion of whether the patient has a postictal mood disorder or psychotic disturbance. A higher incidence of violent behavior was established in postictal compared to interictal psychosis with risk for suicidal attempts and acting violently.[38,40] 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,[46] but others suggested the opposite relationship.[41] In which way genetic predispositions play a role in postictal psychosis is uncertain.[40] Catatonia has been reported rarely in the postictal state, as it seems to be more commonly associated with the ictal state.[47,48]

3.11 | Sudden unexpected death in epilepsy (SUDEP)

SUDEP is defined as an unidentifiable cause of death that is nonaccidental and nonsuicidal, excluding status epilepticus as possible cause, occurring during or immediately after a seizure (T1).[49] Patients with epilepsy are 20 times more likely than the general population to die unexpectedly, but the risk of SUDEP varies widely within the epilepsy population.[50] The most important risk factor for SUDEP is a high frequency of generalized tonic-clonic seizures.[22] The MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) identified postictal respiratory depression and cardiac dysfunction occurring after generalized tonic-clonic seizures as critical factors in SUDEP.[51] Postictal generalized EEG suppression (PGES) has been observed in all monitored SUDEP cases. This could be referred to as an early postictal neurovegetative breakdown.[51] Respiratory and cardiac dysfunction has also been observed and related to SUDEP in a small sample of 42 patients.[52] 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.[53]

Postictal hypoxemia and PGES seem to be risk factors for SUDEP (T1).[54] Recent work on periictal central apnea and SUDEP in 218 patients established that postconvulsive central apnea was associated with longer oxygen saturation recovery times to mild hypoxemia but not with total hypoxemia duration.[55] Whether prolonged ictal central apnea and postconvulsive 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 1 second increase in duration of PGES after generalized convulsive seizures (N = 67).[49] Contrary to this finding, SUDEP patients may have shorter durations of PGES after generalized convulsive seizures.[56] PGES and postictal hypoxemia showed a strong correlation (N = 73), which may indicate its involvement in SUDEP.[54] In a study with N = 59 patients, longer PGES (ie, >20 seconds) was no reliable predictor of SUDEP.[57] However, antiepileptic drug reduction and PGES during sleep may be associated with a higher risk of SUDEP.[57] Limited sample sizes in the aforementioned studies have to be considered.

There have been a few breakthroughs pointing to a key mechanism relating to SUDEP.[22,58,59] It is proposed that spreading depolarization propagating to brainstem cardiorespiratory centers has an active role in the postictal cardiorespiratory collapse, based on animal models of human SUDEP.[58]

3.12 | Social and economic impact

Patients' health and well-being are severely affected by postictal symptoms (T3).[60] Higher mortality and morbidity in patients with epilepsy in childhood as well as higher age are well-known clinical characteristics.[61–64] 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).[13] 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 such as burns, fractures, and tongue biting. Patients, caregivers, and their loved ones may be confronted with an increased burden of homicidal and suicidal behavior.[38,41] Postictal cognitive and behavioral impairment may also lead to lowered self-esteem, increased stigma, and employment difficulties.[65]

4 | ELECTROENCEPHALOGRAPHY (EEG) CHARACTERISTICS OF THE POSTICTAL STATE

The most common EEG characteristics during the postictal state are suppression and slowing of brain rhythms.[66] Postictal EEG suppression is defined as abnormal slow-wave activity or suppression with amplitudes <10 μV within 30 seconds of seizure cessation, lasting more than 2 seconds (T1).[6,7,49,67] It has been found in 84% of seizures in 94% of epilepsy patients.[68] Different definitions of postictal EEG suppression have been proposed; for example, EEG attenuation of more than 2 seconds.[49] The underlying mechanism of postictal EEG suppression remains unknown.[69] It may be related to anoxia, acute hypercapnia, or cortical spreading depression.[69]
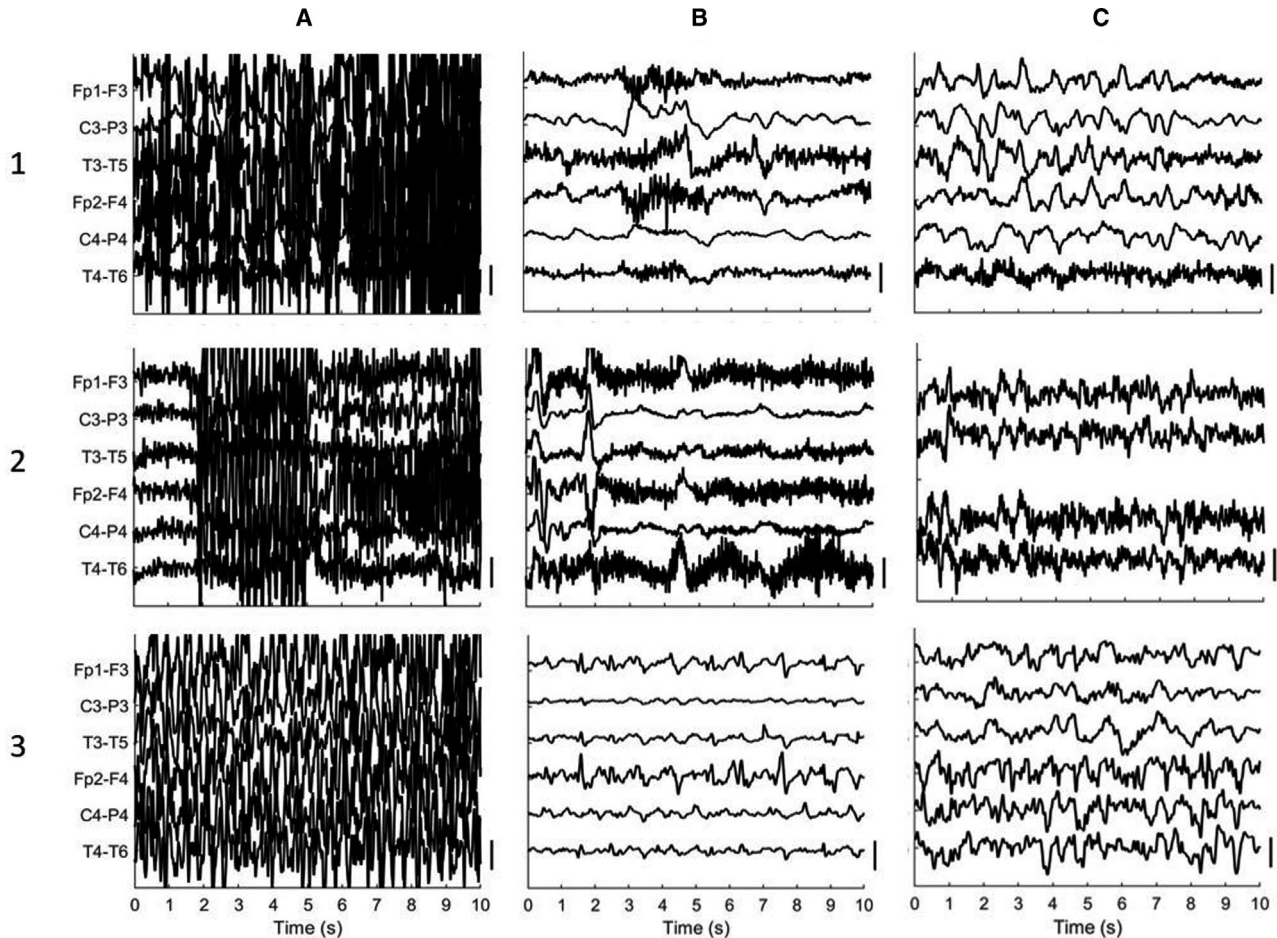
FIGURE 2 Examples of EEG recordings, showing A, seizure activity; B, postictal suppression or slowing; and C, return of background activity. Patient 1 was 88-years-old and had a generalized seizure that was followed by EEG suppression after approximately 3 min postictally, and postictal slowing occurring approximately 25 min postictally. Row 2 represents data from a 77-year-old patient with a generalized seizure. Postictal suppression occurred after approximately 1 min after seizure activity, with postictal slowing after 9 min 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 bands, with postictal suppression 25 min postictally and slowing approximately 1-h postictally (3C). Filter settings 0.5-35 Hz. Vertical scale bar: 50 µV
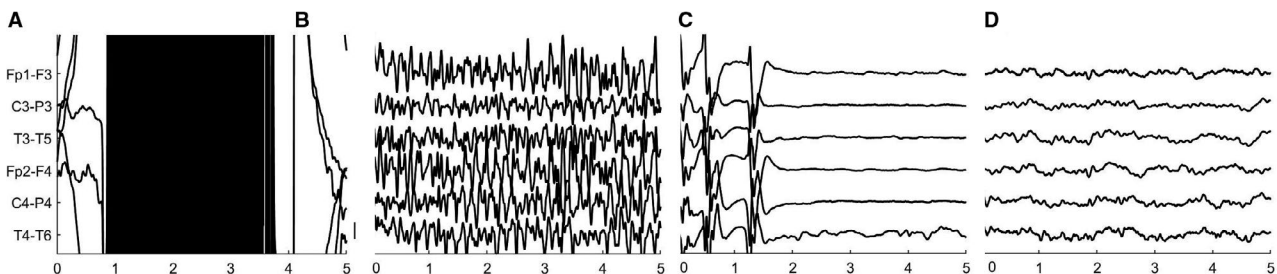

FIGURE 3 Electroencephalographic activity during and after electroconvulsive therapy (ECT). A, Artifact resulting from the ECT stimulus with (B) subsequent seizure activity; C, EEG suppression 80 s postictally; D, EEG slowing 22 min after seizure activity. Note the similarities between ECT-evoked seizures and spontaneous epileptic seizures, shown in Figure 1. Filter settings 1-35 Hz. Vertical scale bar: 50 µV

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).[6,66] 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 (ie, postictal spikes).[66]

Postictal EEG changes can last up to 24 hours (T1-T2).[3] 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.[3,70]

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.[3]

In TLE patients, increased seizure severity was associated with global postictal elevation of relative spectral delta power in several brain areas.[7] 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 behavioral manifestations (eg, impairments in responsiveness and consciousness).[7] 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.[66]

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).[68] 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.[46]

5 | DURATION OF THE POSTICTAL STATE

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.[6] 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 (<15 seconds) generally do not have a postictal state (T1).[6] 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.[71,72]

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.[73] 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.[18] In a sample of 97 patients with epilepsy, time to full recovery was more than 60 minutes for almost 40% of patients (T1).

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.[74] They showed that mean duration of postictal scalp EEG changes after focal seizures was 275 seconds, ranging from 7 seconds to >40 minutes (T1).[66,74] Others reported postictal periods of 45 minutes after generalized convulsions,[75] defining postictal duration as recovery of consciousness and motor function. The postictal state ranged from 2 minutes to 2 months based on symptom presentation, that is, postictal headache/confusion and postictal psychosis, respectively (T1-T3).[4]

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).[29] 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).[75] 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).[76] Furthermore, postictal slowing was shorter for frontal lobe seizures than temporal lobe seizures (T2).[76]

The various differences in definitions for the postictal state further illustrate the demand for adapting the definition for an accurate estimation of its duration.[4] A definition based solely on responsiveness[73] or recovery of motor function[75] questions the validity of results. We, and others, argue that the widely used criteria based on clinical observation alone[12] are too crude to provide an accurate measure of the full postictal state.[6]

6 | DIFFERENTIATION BETWEEN THE ICTAL, INTERICTAL, AND POSTICTAL STATES

Differentiation between the ictal, interictal, and postictal states remains challenging.[77] 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.[6,78] Marking the end of a seizure based on clinical manifestations can be therefore difficult.[78] Continuous EEG recordings may have additional value in determining the postictal state, as this helps to identify that the ictal EEG characteristics have vanished.[68] Quantitative EEG measures may aid in determining boundaries of the postictal state. In particular in the treatment of a nonconvulsive status, continuous EEG monitoring is nearly mandatory to assess transition to the postictal state and if treatment is satisfactory.[12]

Pragmatically, patients should show recovery of neurological deficits within 30-60 minutes (T1); otherwise, a nonconvulsive status must be considered.[12] Recently, various EEG criteria for nonconvulsive status epilepticus were reported as the "Salzburg consensus criteria."[79]

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).[66] 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.[80] Furthermore, in some critically

TABLE 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)[82]
Deactivation default mode network	SPECT	Epilepsy with spontaneous secondarily generalized tonic-clonic seizures	Blumenfeld et al (2009)[83]
Dysregulated cerebral blood flow			
Hypoperfusion (lateral temporal lobe, hippocampus)	SPECT, ASL-MRI, PWI, CT	Temporal lobe epilepsy, focal epilepsy	Koepp et al (2010)[10], Farrell et al (2016)[88], Gaxiola-Valdez et al (2017)[85], Li et al (2019)[84]
Hyperperfusion (parahippocampal gyrus)	PWI	(Extra-) temporal lobe epilepsy	Leonhardt et al (2005)[89]
Hyperperfusion (right temporal lobe, basal ganglia)	SPECT	Epilepsy after encephalitis (during postictal psychosis)	Yasumoto et al (2015)[87]
Hyperperfusion (left parahippocampal gyrus, bilateral fusiform gyri, left middle temporal gyrus)	ASL	Idiopathic epilepsy	Chen et al (2016)[90]
Dysregulated diffusion			
Decreased diffusion around seizure foci	DWI	Focal status epilepticus	Koepp et al (2010)[10]
Increased diffusion in underlying white matter			

Note: Abbreviations: ASL-MRI, Arterial spin labelling magnetic resonance imaging; CT, computed tomography; DWI, diffusion-weighted imaging; MR, magnetic resonance; PWI, pefusion-weighted imaging; SPECT, single photon emission computed tomography.

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."[81] 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 antiepileptic medication is generally advised.[77] Despite these limitations, EEG remains the most valuable tool for differentiating between the ictal and postictal states.[6]

7 | NEUROIMAGING AND BIOCHEMISTRY

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). The extent and duration of postictal EEG suppression (T1) in the delta frequency range was correlated with hippocampal atrophy in patients with TLE: Postictal delta power was lower on the right side if hippocampal atrophy on the ipsilateral site was also worse.[82] Deactivation of the default mode network (DMN) may persist after a seizure in epileptic patients (T1-T2).[83] Cortical areas that were found to generate slow waves partly overlap with regions involved in the DMN.

7.1.1 | SPECT

Neuroimaging studies have also identified significant changes in cerebral blood flow during the postictal state.[10,84,85] In one study, ictal hyperperfusion was followed by postictal hypoperfusion (T1).[10] Ictal hyperperfusion has been related to increased glucose and oxygen demand,[80] which sometimes also manifested postictally, leading to contradicting

findings.[86] 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).[87]

7.1.2 | DWI

With diffusion-weighted imaging (DWI), decreased diffusion in gray and increased diffusion in white matter was found in focal status epilepticus patients, presumably reflecting cell swelling of cortical neurons at the seizure foci (T2).[10] In a case study, decreased diffusion was located around seizure foci in the gray matter, with facilitated diffusion in the underlying white matter.[10] Another study in patients with epilepsy showed postictal decreased cerebral blood flow in regions as hippocampus, parahippocampal gyrus, and cortex.[10]

7.1.3 | ASL–MRI

Arterial spin labeling (ASL)–perfusion MRI provides reliable information about postictal brain perfusion and may serve as a reliable tool to identify seizure-onset zones prior to surgery.[85,88] 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 4).[10,88] Another study showed that perfusion decreased postictally in the hippocampus but in turn showed a reversed (hyper-)perfusion pattern in the parahippocampal gyrus, probably reflecting increased metabolism to restore neuronal excitability (T1-T2).[89] In a recent study using ASL-MRI in 21 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).[90] In 21 TLE patients, using ASL, postictal hypoperfusion in the lateral temporal
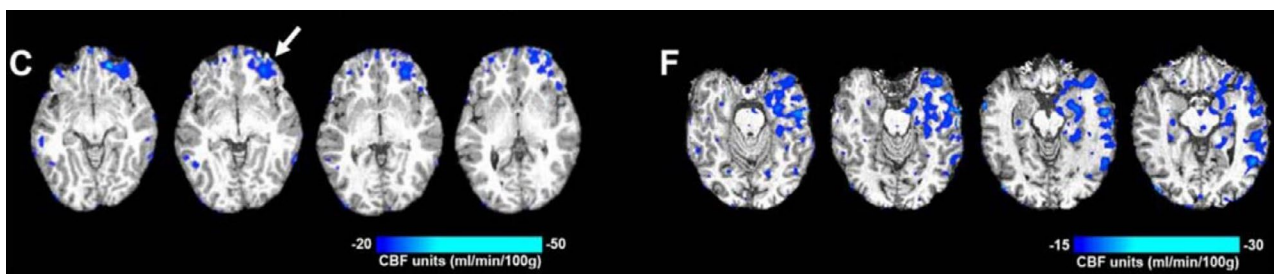

FIGURE 4 Subtraction cerebral blood flow (CBF) maps taken with arterial spin labelling magnetic resonance imaging (ASL-MRI) in a patient with frontal lobe epilepsy (C) and temporal lobe epilepsy (F). The four CBF maps show the transition from interictal to postictal state. Both patients show left hypoperfusion relative to seizure onset (left frontal with >20 mL/100 g/min, and left temporal with >15 mL/100 g/min, respectively). Figure taken from Farrell et al[88]

lobe manifested prominently, while sparing the mesial temporal lobe (T2).[85] Two patients showed postictal hyperperfusion, which might be explained by the delayed scanning time and complexity of brain network distortion.[85]

7.2 | Biochemistry

Increased blood levels of ammonia have been observed in patients with epilepsy who did not regain complete consciousness after seizure termination (T1-T2).[91] However, the level of consciousness was not recorded during the postictal state continuously but initially after the seizure and after 1 to 2 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 hyperammonemia can occur in generalized tonic-clonic but not focal seizures.[13]

Similarly, increased levels of the hormone prolactin in serum have been observed after seizures, which may be due to disruption of hypothalamic function (T1).[92] However, baseline prolactin levels are ambiguous, as baseline levels are influenced by a multitude of factors (ie, sex, type of epilepsy, stress).[13] Seizures may also influence the release of gonadotropin-releasing hormone that in turn regulates gonadal sex hormones.[92] Increased levels of serum creatine kinase have been found in patients with focal and tonic-clonic seizures (T3).[93] Literature on cerebrospinal fluid lactate is
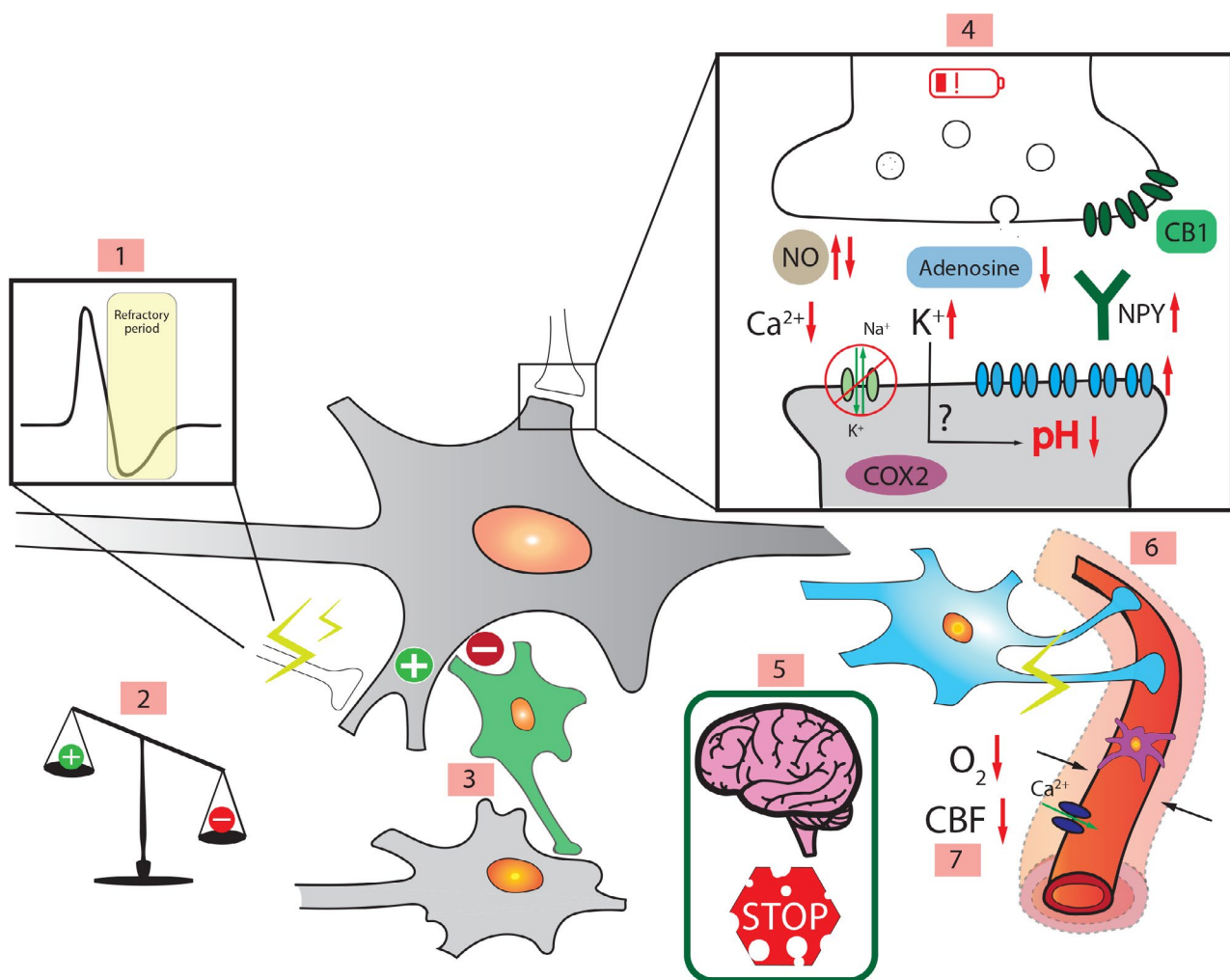

FIGURE 5 Schematic representation of pathophysiological mechanisms proposed to contribute to the postictal state. 1. Active inhibition. 2. Excitation-inhibition imbalance. 3. Inhibitory interneurons (green). 4. Intra- and extracellular mechanisms: neuronal exhaustion (red battery), neurotransmitter depletion, increased extracellular potassium, decreased extracellular calcium, 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 calcium 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 3 Overview of proposed pathophysiological mechanisms involved in the postictal state

Mechanism	Likelihood[a]	Reference
Neuronal exhaustion	Dismissed	Fisher & Schachter (2000)[1]
Excitation-inhibition imbalance	Dismissed	Koepp et al (2010)[10]
Changes in opiate receptors	Unlikely	Fisher & Schachter (2000)[1]; Kanner et al (2010)[5]; Theodore (2010)[29]
Neurotransmitter depletion	Probable	Fisher & Schachter (2000)[1]
Neuronal (active) inhibition	Probable	Löscher & Köhling (2010)[100]; Rupprecht et al (2010)[86]
Increased extracellular potassium	Probable	Fisher & Schachter (2000)[1]
Decreased extracellular calcium and intracellular acidification	Probable	Lado & Moshé (2008)[99]
Changes in adenosine and nitric oxide concentrations	Probable	Fisher & Schachter (2000)[1]
Neurovascular decoupling	Probable	Kovács et al (2018)[107]
Dysfunction of inhibitory interneurons	Probable	Kann et al (2014)[108]; Englot et al (2010)[11]
Blood-brain barrier dysfunction and inflammation	Probable	Gorter et al (2019)[109]
Hypoperfusion and hypoxia	Likely	Farrell et al (2016)[88]; Farrell et al (2017)[22]

[a]Likelihood in this table describes the probability of a 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, underscored 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.

scarce, but shows indication of postictal increases across seizure types.[13] Most likely, all these biochemical changes seem to be epiphenomena, and are probably not involved in termination of seizures or neuronal dysfunction in the postictal state. Studies on postictal biochemistry are scarce and mostly inconclusive.

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 5 and Table 3.[1,10,94,95] T1-T3 (Figure 1) codes are used to point at the postictal time period in which mechanisms are supposed to occur.

8.1 | Neuronal exhaustion (T1)

Almost two decades ago, neuronal exhaustion was dismissed as a 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.[1]

8.2 | Neurotransmitter depletion (T1)

Direct evidence for neurotransmitter depletion is lacking.[1] 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.[96,97] This also suggests that neurotransmitter pathways are still intact if they are amenable to stimulation.[98] In addition, glutamate depletion might occur during seizures, which may continue into the interictal or postictal state.[99]

8.3 | Active inhibition and changes in ion homeostasis (T1)

Postictal symptoms may also result from active inhibition of neuronal function.[1] This hypothesis is based on the observed association between postictal refractoriness and

Treatment strategy	Current status of development	Reference
Vasoconstrictive-mediating drugs		
Paracetamol		Farrell et al (2016)[88]
Celecoxib	Animals	
Nimodipine	Human ongoing trial	NCT04028596[a,111]
Oxygen treatment	Hypothesis, not yet tested	Asadollahi et al (2018)[49]
Psychotropic medication		
Quetiapine	Humans, current treatment option	Krauss & Theodore et al (2010)[2]
Haloperidol		
Lorazepam		
Midazolam		Ohira et al (2019)[75]
Antiepileptic drugs		
Levetiracetam	Human trials	Schmidt (2010)[70]
Vagus nerve stimulation	Human trials	Vonck et al (2010)[98]
Drugs targeting BBB[b] dysfunction	Hypothesis not yet tested	Gorter et al (2019)[109]

TABLE 4 Treatment strategies targeting postictal symptoms

Note: Abbreviations: BBB, blood-brain barrier.

[a]ClinicalTrials.gov ID.

increased seizure thresholds.[100] Postictal refractoriness may result from selective neuronal hyperpolarization that inhibits activity for several minutes or longer.[1] Shunting inhibition may be involved in this process by reducing effective neuronal coupling.[99] Decreased extracellular calcium may be involved in inhibiting synaptic transmission.[99] Network inhibition of subcortical structures may be involved in impaired consciousness after temporal lobe seizures by sending inhibitory output to neocortical neurons.[7,11] Another candidate mechanism is an increased concentration of extracellular potassium following seizures that may cause a depolarization block and suppression of neural activity.[1] Other mechanisms involved in the postictal state may be important for seizure termination. Intracellular acidification (lower pH), supposedly resulting from increased extracellular potassium, seems to aid in seizure termination by reducing excitability.[99] Endocannabinoids activate CB1 receptors on presynaptic receptors, resulting in a reduction of neurotransmitter release.[101] Activation of receptors on excitatory presynaptic terminals will result in a decrease of glutamate release.[99,102,103] Neuropeptide Y has endogenous anticonvulsant effects, with high postictal expression levels hours after seizures.

8.4 | Opioid receptors (T2)

Another, more controversial, candidate mechanism relates to opiates and opioid receptors in the postictal state.[1] Increased levels of opioid receptors have been established after seizures, which last for several hours.[5,29] 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.[1]

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.[104] Nitric oxide may be involved in regulating postictal cerebral blood flow.[1]

8.6 | Hypoperfusion and hypoxia (T2)

Recently, Farrell and colleagues showed in a study in rodents and humans that postictal behavioral symptoms result from hypoperfusion and hypoxia.[22,88] After both spontaneous and electrically induced seizures in rats, local blood flow and brain tissue oxygen concentration in the hippocampus decreased dramatically for more than 1 hour, mediated by local vasoconstriction.[88] Hypoperfusion and hypoxia were positively correlated with seizure duration and severity, both in animals and humans.[88] 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.[105] This mechanism possibly acts via antagonistic effects on adenosine receptors.

Farrell and colleagues also propose that cyclooxygenase-2 (COX-2) and L-type calcium channels are involved in the induction of postictal hypoperfusion and hypoxia.[22] They showed that by administering COX-2 and L-type calcium channel antagonists prior to seizure onset, postictal hypoperfusion and hypoxia were reduced in rodents.[22,88] These experimental findings provide new insights into the mechanisms that are related to postictal phenomena.[88]

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.[106] 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.[107]

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.[88,106] Furthermore, Prager et al induced seizures with low Mg^{2+} or 4-aminopyridine, whereas 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.

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).[80] It remains unclear whether, and how, neurovascular decoupling takes place. During seizures, there is an increased metabolic demand, which ceases afterwards.[89] 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.[80] 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.[80]

In line with the hypothesis that hypoxia may exist in the postictal state is the selective sensitivity of inhibitory interneurons to hypoxia.[108] 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.[108] Abnormal activity of interneurons may compromise information processing and may explain cognitive symptoms in a postictal hypoxic state.[108]

8.8 | Blood-brain barrier (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.[106,109] MRI detected perivascular neuroinflammation and BBB disruption in animals as well as in patients with epilepsy.[109] BBB disruption after seizures may be involved in the postictal state on short timescales but this is presently unknown.

9 | TREATMENT OPTIONS

Current treatment of the postictal state consists primarily of symptom suppression and prevention of complications (Table 4).[2]

9.1 | Symptom suppression

Antiepileptic drugs (AEDs) may attenuate or shorten the postictal state; however, only one study found levetiracetam to be effective.[70] AEDs can alleviate postictal psychotic symptoms, but in turn may have anxiety- and depressive mood–promoting side effects.[2] A few case 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.[98]

9.2 | Prevention of complications

Administration of oxygen in the postictal state may counteract hypoxia.[49] Paracetamol can limit postictal headaches.[19] 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, (eg, quetiapine, haloperidol) or benzodiazepines (eg, midazolam, lorazepam), especially in cases of uncontrolled behavior and/or severe agitation.[2,75] These interventions are acceptable in these circumstances, even though some antipsychotic drugs carry an additional risk of seizure induction.[110]

9.3 | Future developments

If hypoxia caused by vasoconstriction, mediated via COX-2, is a prominent pathophysiological mechanism, as was shown in animal studies,[88] COX-2 inhibitors and calcium antagonists are candidate drugs to reduce the duration and intensity of the postictal state. 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 3).[111]

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. Furthermore, assessment of hypoperfusion in the postictal state may serve as a 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. Whether treatment of presumed postictal vasoconstriction has clinical benefit is currently studied in the SYNAPSE study.[111]

CONFLICT OF INTEREST

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

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