

## An unaware agenda: interictal consciousness impairments in epileptic patients

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### Abstract

Consciousness impairments have been described as a cornerstone of epilepsy. Generalized seizures are usually characterized by a complete loss of consciousness, whereas focal seizures have more variable degrees of responsiveness. In addition to these impairments that occur during ictal episodes, alterations of consciousness have also been repeatedly observed between seizures (i.e. during interictal periods). In this opinion article, we review evidence supporting the novel hypothesis that epilepsy produces consciousness impairments which remain present interictally. Then, we discuss therapies aimed to reduce seizure frequency, which may modulate consciousness between epileptic seizures. We conclude with a consideration of relevant pathophysiological mechanisms. In particular, the thalamocortical network seems to be involved in both seizure generation and interictal consciousness impairments, which could inaugurate a promising translational agenda for epilepsy studies.

**Key words:** epilepsy; interictal period; consciousness impairments; therapy; thalamocortical network; interictal epileptic discharges

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## Introduction

Before the birth of modern neuroimaging, the classification of epilepsies was based on behavioral observations. The first publications of the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) relied mainly on genetic and molecular profiling. Conversely, the ILAE report published in 2010 described epilepsy as a brain-network-level disorder (Berg et al., 2010). In this classification, generalized epilepsy is considered to result from rapid seizures that engage distributed networks bilaterally. By contrast, focal epilepsies are associated with seizures limited to a specific cerebral location (e.g. right frontal lobe, left occipital lobe). Recently, a new classification has been suggested based on the various types of consciousness alterations that occur during seizures (e.g. auras with illusions or hallucinations, focal seizures with impaired awareness, epileptic delirium, and epileptic coma) (Luders et al., 2014). A full-blown elaboration of such a taxonomy calls for the identification of specific semiological profiles and distinct pathophysiological mechanisms. In some cases however, one patient with a single type of epilepsy (in particular, generalized tonic-clonic seizures) can suffer from more than one type of seizure. In fact, only in rare exceptions does a patient have only one type of epilepsy. Much like existing classifications, this proposal highlights clinical manifestations during ictal periods and associated abnormal activity recorded with imaging and electrophysiological (electroencephalographic, EEG) techniques. However, epilepsy may impact brain function globally and consciousness as a particular domain, even during the interictal period. Here we consider two possible underlying mechanisms. First, epileptiform discharges during seizures may induce stable changes in cortical-subcortical connectivity, impairing the function and structure of networks that underlie consciousness. Second, the occurrence of interictal spikes may produce changes in normal oscillatory activity generated by thalamocortical (TC) networks, which are critical to regulate states of consciousness. Below we review various sources of evidence to characterize the stable and interictal impact of epilepsy on consciousness.

## Consciousness Impairments in Epilepsy

Wakefulness usually grants awareness, but this may not be the case in a pathological state. During sleep, coma, and anesthesia, the levels of awareness and wakefulness decline simultaneously. However, sometimes they become disassociated (Laureys et al., 2004). This is the case during epileptic seizures (Cavanna, 2014), such as absence seizures and focal seizures with impaired consciousness. In some types of epilepsy, such as focal epilepsies involving somatosensory, visual, or cognitive impairments, awareness can be affected without compromising wakefulness (Cavanna et al., 2008). Consciousness is usually assessed behaviorally in clinical research; however, this approach to testing may lead to misdiagnosis (e.g. locked-in syndrome, minimally conscious states). Moreover, since cognitive test performance usually depends on arousal level, the distinction between cognitive impairments and consciousness impairments is neither straightforward nor fully understood. In order to increase objectivity and efficiency, the assessment of conscious awareness need to be complemented with electrophysiological and neuroimaging studies. The neural signatures of the levels of consciousness can be studied neurophysiologically from neurons to whole brain; and neural markers of conscious awareness by cognitive neuroscience. Notably, as we show below, the

specific toolkits used to study epilepsy in each of these disciplines yield overlapping results.

## Interictal epileptiform discharges

The most widely used technique to diagnose epilepsy is EEG. EEG recordings during seizure onset consistently reveal spikes, such as the spike and wave discharges (SWDs) generated by TC networks. While such discharges usually disappear after the seizure, abnormal activity may be still present between seizures in the form of interictal epileptiform discharges (IEDs) (Keller et al., 2010), also called subclinical epileptiform activity. The electrophysiological, psychiatric, cognitive, or behavioral manifestations that are temporarily close to the seizure take place during the peri-ictal period. This includes the pre-ictal period (i.e. symptoms preceding the ictus), the ictal period (i.e. manifestations during the seizure), and the post-ictal period (i.e. symptoms following the ictus) (Mula and Monaco, 2011). When there is no clear temporal relationship between the abnormal activity and the peri-ictal period, the aforementioned activity may be classified as inter-ictal phenomena. A study on a large sample of patients ( $n = 129$ ) did not find an association between the presence or absence of IEDs or IED frequency and seizure frequency (Selvitelli et al., 2010). Moreover, a large number of pre-surgical studies on the functional interactions between epileptogenic and irritative zones (i.e. areas that generate abnormal interictal events/potentials, but are not directly recruited during a seizure discharges) indicate that: (i) the irritative area does not correspond to and is usually larger than the epileptogenic/seizure onset zone, (ii) interictal discharges show no coherent relationship with seizure discharges, in terms of location and activation patterns, (iii) the rate of interictal discharges can either increase or decrease just ahead of a seizure, and (iv) in most cases the electrographic pattern of seizure onset is completely different from the activity recorded during interictal discharges (Fisher et al., 2014). Hence a distinction can be made between pre- and post-ictal consciousness impairments, on the one hand, and interictal ones, on the other.

IEDs involve large intracellular depolarization leading to transitory cognitive impairment (Holmes and Lenck-Santini, 2006; Tassinari and Rubboli, 2006). The impact of interictal epileptiform activity is reflected also in reaction time impairments. For example, in a study based on driving simulators (Krestel et al., 2011), epileptic patients had slower reaction times during generalized IEA compared relative to unremarkable EEG periods. Also, the occurrence of frequent IEDs can affect global cognitive function in children without seizures during formal testing (Nicolai et al., 2012), suggesting that the type of association between frequent epileptiform activity and cognitive function is comparable to the association between short non-convulsive seizures and cognitive function. Another study (Ebus et al., 2012) showed that children with diurnal IEDs (at least one spike or spike and wave complex per 10 s of EEG) featured impaired central information processing speed, short-term verbal memory, and visual motor integration. The aforementioned effect was seen independently of other EEG- and epilepsy-related characteristics, and independently of epilepsy syndrome diagnosis. Cognitive impairments seen in children during IEDs are also present in adults (Lv et al., 2013; Liu et al., 2016). Moreover, interictal epileptiform activity can disrupt auditory, somatosensory, motor, and visual function (Fisch, 2003). Crucially, in seizure-free patients and patients with infrequent seizures, pharmacological suppression of IEDs improves scores in attentional tasks (Pressler et al., 2005). If the cognitive functions involving

attention require conscious awareness, then those cognitive impairments may be tentatively related to underlying consciousness impairments.

Additional evidence comes from research into the P300 complex. The P3b event, which belongs to this complex, is an event-related potential proposed to index consciousness in different populations (Bekinschtein *et al.*, 2009; Chennu and Bekinschtein, 2012). An EEG study revealed larger P300 mean latency for patients with frequent IED, compared to patients with infrequent IED and controls (Mohammed *et al.*, 2012). In this report, treatment of IEDs using anti-epileptic drugs reduced mean P300 latency with a concomitant increase in cognitive performance. Moreover, a recent investigation showed that patients with a larger P300 latency compared with controls tended to present loss of consciousness (Li *et al.*, 2015). While EEG recordings of IEDs provide useful information to diagnose epilepsy, such discharges may not be apparent in some patients because of methodological limitations such as insufficient sampling, deep seating of the epileptic focus, tangential dipoles, or insufficient amounts of cortex for signals to propagate to the scalp (Pillai and Sperling, 2006). Alternative techniques, such as intracranial EEG, should be used to further investigate interictal discharges. Since electrical brain activity remains abnormal after seizure cessation, the study of consciousness impairments in epilepsy should be extended to the interictal phase.

## Types of epilepsy featuring interictal consciousness impairments

### *Idiopathic generalized epilepsy*

The term idiopathic generalized epilepsy (IGE) comprises a group of epilepsy syndromes with a non-focal onset mechanism and no identifiable cause other than a genetic predisposition (Sullivan and Dlugos, 2004). In the interictal state, patients with IGE show slower psychomotor response and decreased sustained visual attention when compared with controls (You, 2012). Furthermore, they may exhibit “phantom absences”, namely, short (2–4 s) absence seizures without concomitant clinical features (Rubboli *et al.*, 2009). Although these types of epilepsy do not typically affect the patients’ everyday functioning, they can cause momentary consciousness impairments. Below we describe the interictal awareness impairments of two subtypes of IGE: juvenile myoclonic epilepsy (JME) and childhood absence epilepsy (CAE).

*Juvenile myoclonic epilepsy.* JME is a common idiopathic epilepsy syndrome considered as a benign seizure disorder with a high genetic predisposition. Patients present symmetric, myoclonic jerks (mostly affecting the upper limbs), generalized tonic-clonic seizures, and, more rarely, absence seizures (Wandschneider *et al.*, 2012).

In generalized tonic-clonic seizures, loss of consciousness is associated with epileptiform discharges affecting several brain regions. These seizures can be subdivided into primary generalized seizures (in which the epileptogenic focus is not identified) and focal seizures (which evolve to bilateral tonic-clonic seizures featuring a well-defined epileptogenic focus). Research into the latter type via single-photon emission computed tomography (SPECT) has shown increased cerebral blood flow (CBF) during seizures in the superior medial cerebellum, the thalamus, and the basal ganglia (Blumenfeld *et al.*, 2009). Seizure propagation involves increased CBF in the bilateral frontal and parietal association cortices as well as the thalamus, suggesting that cortical-thalamic-cortical interactions are

involved in seizure spread. The large-scale effect of generalized seizures on both cortical and subcortical networks directly impacts long-range networks involved in the maintenance of conscious awareness and those subserving wakefulness.

Subjects with JME are impaired in several frontal functions, including mental flexibility, working memory, and verbal fluency (You, 2012). Additional deficits have been observed in processing speed, concept formation, and planning (Pascualichio *et al.*, 2007). Individuals with JME may also exhibit impairments of alertness and attention span, as well as sustained and divided attention (Moschetta and Valente, 2012). This condition is associated with functional and structural abnormalities in the frontal (including prefrontal) cortex and the thalamus (Wandschneider *et al.*, 2012). Molecular imaging studies reported abnormalities of the dorsolateral prefrontal cortex, indicating an underlying thalamo-frontocortical network dysfunction (Wandschneider *et al.*, 2012). Moreover, executive impairments in JME have been related with frontal lobe and thalamic dysfunction; e.g. children with JME have significant executive dysfunction associated with significantly smaller thalami (Pulsipher *et al.*, 2009). Consequently, preliminary evidence suggests that interictal consciousness impairments can consistently occur in this epilepsy type, probably due to TC dysfunction.

*Childhood absence epilepsy.* CAE affords a particularly interesting model because it specifically impairs both wakefulness and awareness, with only mild motor manifestations. In a typical absence seizure, patients stare unresponsively for less than 10s, temporarily losing time perception altogether. Although CAE is considered a form of generalized epilepsy, animal research shows that its underlying epileptiform discharges originate from specific corticothalamic networks while sparing other regions (Meeren *et al.*, 2002; Nersesyan *et al.*, 2004; van Luijtelaar and Sitnikova, 2006; Cavanna and Monaco, 2009). The mechanisms implicated in the ensuing loss of consciousness resemble those involved in transitions between wakefulness and sleep (Bagshaw *et al.*, 2014). In both cases, the subject experiences alterations of consciousness that are usually correlated with modifications in the activity of thalamic and long-range cortical networks, whose connectivity may be also altered. In fact, a resting-state functional MRI (fMRI) study in absence epilepsy showed decreased integration of the default mode network (DMN) even in the interictal phase (Luo *et al.*, 2011). Aberrant resting-state fMRI functional connectivity has also been observed in untreated CAE patients, manifested as reduced connectivity between the thalamus and the basal ganglia (Masterton *et al.*, 2012). These findings suggest that plastic changes remain after the generalized spike and wave activity that is present during seizures. As we will show below, long-term alterations of cortical and subcortical connectivity in epileptic patients can impair their awareness even in the interictal phase.

In the interictal phase, CAE patients may show impaired global cognitive function, including attention problems (Caplan *et al.*, 2008) and disorders of conduct, perception, and more complex mental functions (Pavone *et al.*, 2001). Interictal SWDs related to subclinical EEG discharges appear to be synchronized with transient cognitive impairments (Aarts *et al.*, 1984). Moreover, children exhibiting no seizures during the interictal phase showed figure recognition tests deficits (Nicolai *et al.*, 2012). Yet, it is unclear why epileptiform EEG discharges affect the patients’ cognitive functioning, but it may be surmised that focal discharges disrupt central information processing as

occurs in subtle seizures. Therefore, seizure-like activity during the interictal phase of CAE may be related with consciousness impairments.

#### Focal epilepsies

Focal seizures with impaired awareness are usually triggered by epileptiform activity in the temporal or frontal lobe, which then spreads to other cortical areas and impairs long-range cortical networks such as the DMN and the fronto-parietal networks. Studies using fluorodeoxyglucose-positron emission tomography (FDG-PET) reported frequent occurrence of thalamic hypometabolism during the interictal phase in mesial temporal lobe epilepsy (mTLE) patients. The relative reduction in metabolism of the left side of the thalamus correlates with lower scores for recall of logical prose (Rausch et al., 1994). The prevalence of thalamic hypometabolism suggests a pathophysiological role for the thalamus in the initiation or propagation of temporal lobe seizures or even in the interictal cognitive dysfunction of temporal lobe epilepsy (TLE) (Henry et al., 1993). A study comparing the ictal and the interictal phases via SPECT images showed thalamic CBF differences, consistent with a role for the thalamus and upper brainstem in consciousness mechanisms during the ictal phase. The distribution of blood flow changes during seizures with consciousness impairments was assessed by subtraction (ictal-interictal) SPECT co-registered to magnetic resonance imaging (MRI). Impairments of consciousness during the ictal phase showed a strong association with secondary hyperperfusion in the thalamic/upper brainstem region, with 92% of the patients exhibiting complete breakdown of consciousness, 69% falling within the uncertain consciousness level group, and 11% presenting no impairments (Lee and Park, 2002). One of the limitations of this study is the low temporal resolution of the SPECT technique, as the timing of radioisotope injection plays a critical role to correctly assess the ictal and inter-ictal phases. Consequently, the subtraction method alone does not clarify whether these findings reflect an ictal dysfunction or a combination of ictal and interictal abnormalities.

Another study using SPECT and video/EEG monitoring during temporal lobe seizures with loss of consciousness showed two patterns of alterations in CBF (Blumenfeld et al., 2004). On the one hand, CBF increased in the temporal lobe, followed by increases in bilateral midline subcortical structures. On the other, it decreased in the frontal and parietal association cortices. This reduction strongly correlated with increases in midline structures, such as the mediodorsal thalamus. In terms of the inhibited network hypothesis (Norden and Blumenfeld, 2002), seizures occur when the associative cortices are affected secondarily. In this scenario, slow brain wave oscillations generated by the TC network modulate activity in the association cortices and interrupt the normal functioning of the brain mechanisms subserving attention and consciousness. In line with this view, consciousness impairments during focal seizures are correlated with large-amplitude slow EEG activity and decreased blood flow in the frontal and parietal association cortices (Englot and Blumenfeld, 2009), two regions that play critical roles in the long-range networks supporting conscious processing and responsiveness.

*Benign childhood epilepsy with centrotemporal spikes.* Patients suffering from benign childhood epilepsy with centro-temporal spikes (BCECTS) present unilateral or bilateral stereotyped focal spikes during the interictal period (Pavlou et al., 2012). Centrotemporal spikes (CTS) activated by sleep have been hypothesized to play a causal role in global cognitive disorders

(Pinton et al., 2006). Moreover, the presence of at least six anomalous EEG interictal features are related to the occurrence of a complicated evolution of BCECTS where patients suffer from educational and behavioral disturbances: (i) intermittent slow-wave focus; (ii) multiple asynchronous spike-wave foci; (iii) long spike-wave clusters; (iv) generalized 3-Hz (absence-like) spike-wave discharges; (v) atonia, myoclonia, or brief alteration of consciousness related to EEG discharges; and (vi) abundant interictal abnormalities during wakefulness and sleep (Nicolai and Kasteleijn-Nolst Trenite, 2011). Furthermore, right-sided interictal epileptiform activity in these children interferes with right hemisphere functions, compromising sustained, selective, and divided attention (Sanchez-Carpintero and Neville, 2003). Therefore, interictal epileptiform activity in this form of epilepsy also seems to involve consciousness impairments.

*Temporal lobe epilepsy.* TLE may present executive function impairments and deficits in social cognition skills, such as theory of mind (Stretton and Thompson, 2012). This domain refers to the awareness of one's own mental states and those of other people, so a patient's failure on a relevant test may imply reduced awareness (Firth and Happé, 1999). Crucially, these difficulties cannot be attributed to differences in IQ between patients and controls rules, which rules out the possibility of a generalized cognitive deficit and further strengthens the finding that theory-of-mind abilities are selectively impaired in this condition (Schacher et al., 2006). Accordingly, TLE patients may also be characterized by awareness deficits, perhaps partially triggered by interictal impairments.

*Mesial temporal lobe epilepsy.* mTLE is a common focal epilepsy. Brain abnormalities in mTLE are not limited to the epileptogenic region, but they extend into widespread areas of the ipsilateral and contralateral hemispheres (McDonald et al., 2005). It is well established that mTLE patients have episodic memory impairments during the interictal phase (in particular, delayed recall deficits) (Pascalicchio et al., 2007). Left and right mTLE patients present hypoconnectivity in some lateralized regions of the DMN (angular gyri, posterior cingulum, and medial frontal cortex) and the thalamus (Doucet et al., 2013). Moreover, effective connectivity analyses show that relative to controls, patients feature a decreased driving effect from the epileptic zone to the thalamus and to the basal ganglia (Ji et al., 2013). This preliminary evidence suggests that the thalamus may play a role in the interictal dysfunctions in mTLE.

*Frontal lobe epilepsy.* Frontal lobe epilepsy (FLE) is characterized by brief, recurring seizures that arise in the frontal lobes of the brain. Frontal lobes seem to be the preferred target of ictal and interictal spreading of focal epilepsies as well as in IGEs leading to attentional deficits (van Rijckevorsel, 2006). Diffusion tensor imaging shows that FLE patients feature increased mean diffusivity in the right frontal lobe and reduced fractional anisotropy in both thalami and the right frontal lobe (Wang et al., 2011). The latter pattern correlated with patient age at seizure onset, whereas increased mean diffusivity in the left thalamus correlated with epilepsy duration. This evidence suggests that the thalamus might be an important extra-frontal structure involved in FLE and that a longer duration of epilepsy might increase thalamic abnormalities. Similar tasks requiring awareness, being affected in TLE, are also affected in FLE (Giovagnoli et al., 2011). In brief, FLE seem to feature alterations in interictal attentional states, arguably related to thalamic dysfunction.

## Pathophysiological Mechanisms Underlying Long-Term Consciousness Impairments

Epilepsy involves structural connectivity alterations in both the epileptogenic focus and cortical areas linked to it. This has been shown through various MRI techniques, such as voxel-based morphometry, MRI spectroscopy, fMRI, and diffusion tensor imaging (Braakman et al., 2012). In particular, long-range networks evince abnormal connectivity in several epilepsy types, such as FLE (Vaessen et al., 2014) and temporal lobe epilepsy (Bernhardt et al., 2015).

Consciousness impairments in epilepsy have been recently associated to abnormalities in cortical functional networks, such as the DMN, the TC network, and the fronto-parietal networks (Liao et al., 2010, 2011; Killory et al., 2011; Bor and Seth, 2012; Smallwood et al., 2012; Centeno and Carmichael, 2014), whose abnormal function is usually (though not always) correlated to consciousness impairments. Alterations in the connectivity and activation level of long-range networks seem to signal whether consciousness is impaired during epileptic episodes (Killory et al., 2011). Resting-state fMRI recordings from epileptic patients have repeatedly revealed aberrant features in networks subserving perceptual and high-level cognitive functions, while EEG-fMRI research has shown a correlation between epileptic transients (i.e. interictal spikes) and functional connectivity alterations (Centeno and Carmichael, 2014). Disturbed functional connectivity in this network has also been revealed by fMRI studies on patients during interictal periods (Liao et al., 2010, 2011). Importantly, consciousness may depend on long-range networks such as the DMN and the prefrontal-parietal network (Bor and Seth, 2012; Smallwood et al., 2012). Moreover, an EEG resting-state study in benign child epilepsy with centro-temporal spikes showed that the patients' brain networks oscillating in the  $\beta$  frequency band (i.e. brain waves associated with normal waking consciousness) exhibited reduced functional segregation (i.e. reduced clustering coefficient) and reduced integration (i.e. lower global efficiency and network degree) due to loss of both local and long-distance functional connections (Adebimpe et al., 2016). In the integrated information theory of consciousness, neurophysiological differentiation and integration of information is a key requirement for consciousness (Tononi and Koch, 2008; Tononi et al., 2016). On the other hand, in global workspace theory, conscious perception is associated with the broadcast of information by long-range parieto-frontal networks (Dehaene et al., 2006). Accordingly, and in agreement with the network inhibition hypothesis (Norden and Blumenfeld, 2002), the resulting loss of consciousness in epileptic seizures may be due to active inhibition of subcortical arousal systems that normally maintain connectivity in cortical networks such as the DMN and the prefronto-parietal networks in the waking state (i.e. upper brainstem–thalamic interactions with cortical areas) (Danielson et al., 2011). Moreover, the active inhibition of arousal systems by seizures in certain cortical regions may lead to cortical deactivation in other cortical regions supporting long-range networks, such as the fronto-parietal network.

The transition between wakefulness and sleep involves a decline of consciousness with physiological mechanisms that are related to those generating seizures in pathological cases (Kotagal and Yardi, 2008; Beenhakker and Huguenard, 2009). The relationship between sleep and seizures is further evidenced by the fact that sleep can modulate both IEDs and seizure activity (Malow, 2007). Thalamic reticular inhibitory neurons and excitatory TC neurons have been considered as

essential components of the common neuronal substrate of both spindle activity during sleep and pathological SWDs during seizures (Steriade, 2005; Leresche et al., 2012). In a recent EEG-fMRI study of CTS during wakefulness and sleep, sleep-related fMRI maps involved a wide network including the thalamus, which suggests that epileptic activity may be promoted by a sleep-related network dysfunction (Mirandola et al., 2013). Because the thalamus is involved in the coordination of cortical activity, it may be a critical contributor to the subcortical mechanisms altering consciousness-related fronto-parietal networks in epileptic patients.

### The role of the thalamus

Traditionally, the thalamus has been regarded as a relay station of information from the sensory organs to the cortex. Recent investigations at the cellular and circuit levels, however, have demonstrated that the thalamus is involved in high-level processing operations, such as controlling temporal sensory–motor associations (Groh et al., 2014, see review in Ahissar and Oram, 2015) and attention-dependent sensory selection (Wimmer et al., 2015). These functions rely on the recurrent connectivity between the thalamus, the cortex, and different inhibitory structures—in particular, the reticular thalamic nucleus (nRT). These “closed loop” circuits, together with the electrophysiological properties of TC and reticular neurons, are proposed to contribute to synchronized oscillatory activity that characterize slow wave sleep (SWS) and some forms of epilepsy (for a review, see Blumenfeld, 2005; Steriade, 2005; Beenhakker and Huguenard, 2009). The EEG hallmark of CAE and other forms of GIE are SWDs. The hypothesis that these correspond to aberrant sleep spindles is supported by a clinical correlation between sleep and 2- to 3-Hz SWDs (Kellaway, 1985), by *in vivo* studies on different animal models (Steriade and Contreras, 1995; Kostopoulos, 2000), by *in vitro* electrophysiological evidence (von Krosigk et al., 1993; Bal et al., 1995), and by computational research (Destexhe et al., 1996)—see Leresche et al. (2012) for a critique of this hypothesis.

Sleep spindles, characteristic of early phases of non-Rapid eye movement sleep (REM) sleep, are waxing and waning, 10–15 Hz oscillations of 0.5–3 s of duration that recur a few times per minute. A model of the generation and maintenance of spindles has been developed based on decades of research on the cellular mechanisms that initiate and sustain this brain rhythm (for reviews, see Steriade, 2005; Beenhakker and Huguenard, 2009; Luthi, 2014). Briefly, these oscillations are initiated by a high-frequency burst of action potentials in some neurons of the nRT. These bursts could be generated autonomously by intrinsic cellular mechanisms (pacemaker activity) or by the excitatory input of corticothalamic projections. The inhibitory output of nRT neurons, in turn, activates GABAA and GABAB receptors on TC neurons, inducing the transient hyperpolarization of their membrane potential. This hyperpolarization de-inactivates the low-threshold calcium current IT, inducing the rebound discharge of a low-threshold calcium spike which underlies burst firing in these cells (for details, see Amarillo et al., 2014, 2015). Thus, the nRT inhibitory input on TC neurons is paradoxically transformed into an excitatory output that re-excites nRT neurons, closing a cycle of the oscillation. Due to the divergent architecture of the thalamo-reticular circuit, an increasing number of nRT and TC cells are recruited during each cycle in a crescendo fashion that corresponds to the waxing phase of the spindle. The mechanisms of the waning phase and termination of the spindle are less clear.

Nonetheless, intrinsic mechanisms are also involved, such as the increasing calcium and cAMP-dependent activation of the hyperpolarization-activated cationic current *I<sub>h</sub>*. Note, in addition, that synaptic mechanisms such as intra-nRT GABAA-mediated inhibition could limit synchronization and even promote the desynchronization of the TC-nRT network, inducing the termination of the spindle. Sleep spindles usually occur in temporal coherence with other brain rhythms. In particular, the slow wave oscillation (< 1 Hz) that originates in cortical circuits (although similar oscillations could also be generated and sustained intrinsically in the thalamus (reviewed in [Crunelli and Hughes, 2010](#)) seems to control the temporal organization of spindles ([Steriade, 2006](#)). During the slow-wave oscillations, cortical neurons that project to the nRT and to the dorsal thalamus (corticothalamic projection) rhythmically switch between up and down states characterized by tonic firing of action potentials and silent hyperpolarization, respectively. Consistent with a cortical triggering of spindles, the occurrence of spindles is frequently associated with the cortical up state, in which the tonic firing of action potentials provides the excitatory drive that generates the initial nRT burst.

According to the aberrant spindle hypothesis, SWDs result from a failure to prevent the overall synchronization of the thalamo-reticulo-cortical circuit when it is engaged in sleep spindles. In this regard, a prominent role has been attributed to intra-nRT inhibitory mechanisms. The most compelling evidence linking spindles and SWDs comes from *in vitro* experiments performed on brain slices in which pharmacological blockade of GABAA neurotransmission in the nRT transforms autonomously generated spindling into a SWD-like oscillation ([von Krosigk et al., 1993](#); [Bal et al., 1995](#)). Compatibly, genetic elimination of the GABAA receptor subunit  $\beta 3$ , which is expressed in nRT but not in TC neurons, renders intra-nRT inhibitory transmission nonfunctional and induces a phenotype that includes absence-like seizures ([Huntsman et al., 1999](#)). Other mechanisms that could lead to the transformation of spindles into SWDs include alteration of the balance between GABAA- and GABAB-mediated nRT-TC transmission ([Destexhe and Sejnowski, 1995](#)), and conditions in which the excitatory drive of nRT neurons is increased either through cortex-nRT ([Blumenfeld and McCormick, 2000](#)) or TC-nRT pathways. Despite this large body of evidence, a definitive proof of a causal relationship between sleep spindles and SWDs is still missing (for criticism, see [Leresche et al., 2012](#)). On the other hand, several physiological and molecular studies in cats and rodents show that ion channels controlling the intrinsic excitability and synaptic connectivity of nRT and TC neurons participate in the generation and maintenance of normal sleep rhythms (not only spindles), as well as in the pathophysiology of absence epilepsy ([Noebels et al., 2012](#)). For example, genetic elimination of low-threshold calcium channels in TC neurons from mice eliminates burst firing in these cells and largely decreases (or eliminates) slow delta oscillations (1–4 Hz) characteristic of deep sleep ([Lee et al., 2004](#)). Contrary to the notion that TC neuron bursting is required for the maintenance and propagation of spindles (and perhaps SWDs), sleep spindles are unaltered in this mouse line ([Lee et al., 2013](#)). Nonetheless, these mice are resistant to the pharmacological induction of absence seizures. Contrariwise, overexpression of the same type of ion channels induces a phenotype of pure absence seizures ([Ernst et al., 2009](#)). Importantly, these manipulations also have large effects on the sleep structure of these animals ([Anderson et al., 2005](#)), indicating a link between the mechanisms of sleep and those of epilepsy. Thus, similar cellular mechanisms can be surmised to underlie the phenomenology of these physiological and

pathological states. In particular, the mechanisms involved in consciousness decline during sleep may largely overlap with those involved in the consciousness impairments in epilepsy. As mentioned above, mice lacking low-threshold calcium channels exhibit decreased slow-frequency oscillations, characteristic of non-REM sleep ([Lee et al., 2004](#)). Moreover, they take longer to fall unconscious and exhibit increased high-frequency oscillations, characteristic of wakefulness, even during unconscious states ([Choi et al., 2015](#)). Thus, the thalamus appears to be involved in controlling consciousness states both during the normal sleep-wake cycle and in pathologies compromising these states.

### Key Pathophysiological Mechanisms: Evidence from Therapies to Treat Consciousness Disorders

Anesthesia is intended to reduce wakefulness up to the point where pain and awareness are lost. A debate has emerged on whether consciousness breakdowns induced by anesthetic drugs originate from a disruption of fronto-parietal networks such as the DMN and the temporo-parietal network or, alternatively, from a disruption of TC connectivity ([Alkire et al., 2008](#)). Two recent studies on propofol-induced loss of consciousness ([Boly et al., 2012](#); [Barttfeld et al., 2015](#)) highlight the role of the thalamus. In the first one, mild sedation (reduction of awareness) was associated with anomalous TC activity, while complete loss of consciousness involved breakdowns in fronto-parietal connectivity. In the second, increasing concentration of propofol in blood specifically decreased the connectivity strength of fronto-parietal cortical loops; however, loss of responsiveness was indexed by a functional disconnection between the thalamus and the frontal cortex, balanced by an increase in connectivity strength of the thalamus to the occipital and temporal regions of the cortex ([Barttfeld et al., 2015](#)). Further evidence pointing to the thalamus comes from a study involving patients with consciousness disorders, evidence showed lasting recovery upon deep brain stimulation of the central thalamus by activating the TC connectivity ([Thibaut and Laureys, 2015](#)). Moreover, in patients implanted with intracortical and intrathalamic electrodes, thalamic deactivation occurring at sleep onset precedes that of the cortex by several minutes, whereas reactivation of both structures synchronizes during awakening ([Magnin et al., 2010](#)).

Furthermore, in animal studies, continuous high-frequency (100 Hz) stimulation of central thalamic areas enhances performance in awareness-related tasks (e.g. object recognition) ([Shirvankar et al., 2006](#)).

In the treatment of medically resistant epilepsy, electrical stimulation of the anterior nuclei of the thalamus ([Lim et al., 2007](#); [Fisher et al., 2010](#)) reduces seizure frequency. Although the Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trials produces a significant reduction in mean seizure frequency ([Fridley et al., 2012](#)), there is still no solid evidence regarding an improvement in arousal or cognition. Yet, relevant indications can be found in at least two studies: one report showed that anterior thalamic nucleus stimulation improves attention levels ([Hartikainen et al., 2014](#)), and the other found that cognitive function is enhanced after long-term electrical stimulation of the bilateral anterior thalamic nucleus ([Oh et al., 2012](#)). Moreover, stimulation of the intralaminar thalamic nuclei in an animal model after seizures can restore electrophysiological and behavioral indices of consciousness

(Gummadavelli et al., 2015). Finally, thalamic activation has been observed following vagus nerve stimulation (Ring et al., 2000; Chae et al., 2003; Vonck et al., 2008). Taking these findings into account, stimulation of the thalamus appears to have a direct or indirect effect on consciousness levels.

Taken together, evidence suggests that long-term therapy of epilepsy-related consciousness disorders should frame the thalamus as an important target for intervention. The delineation of specific treatments requires further research on the regulation of TC neurons' ion channels. Mutations producing ion channel abnormalities may alter neuronal firing and yield SWD complexes in seizures and interictal spikes. By reducing the occurrence of abnormal electrical brain activity, progressive enhancements of consciousness in epilepsy could become attainable. Further experimental research is critical to test this hypothesis.

### A Call for Further Assessment of Consciousness States During Interictal Periods

Consciousness impairments in epilepsy may impair the patients' overall cognitive abilities irrespective of the use of anti-epileptic drugs. The possible consequences of this hypothesis call for further research on both facets of consciousness (i.e. awareness and wakefulness) during interictal periods. Longitudinal research should also be conducted to quantify the cumulative effect of ictal epileptic discharges on consciousness levels during interictal periods. In addition, pharmacological studies with drugs aimed to restore normal thalamic activity should be considered for possible treatments of interictal consciousness disorders. Moreover, new cognitive paradigms are needed to better understand the role of thalamic activity in this condition. Further research into pathophysiological TC mechanisms may yield new avenues to predict which seizure type involves specific consciousness impairments.

### Conclusion

Interictal consciousness impairments in epilepsy have been underestimated compared to consciousness breakdowns during seizures. Our review highlights the role of the former in the alterations of structural and functional connectivity of long-range networks, most likely induced by abnormal cortico-thalamic activity. Future research should strive to determine whether each seizure type involves specific consciousness impairments during interictal phases. Deeper understanding of the underlying pathophysiological mechanisms can pave the way for new treatments relevant not just for the ictal phase, but also for the whole spectrum of epilepsy comorbidities.

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