Temporal Lobe Seizures

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Moran Furman and Hal Blumenfeld

Abstract

Focal temporal lobe seizures often cause loss of consciousness. Whereas abnormal function of the temporal lobe is expected to cause memory loss, it is unclear why it should impair consciousness. Recent advances in neuroimaging, behavioral, and electrophysiological techniques spanning both human patients and animal models have revealed new and exciting insights into this old question. Impaired consciousness in temporal epilepsy (TLE) is correlated with large-amplitude slow electroencephalogram (EEG) activity and decreased metabolic activity in the frontal and parietal association cortices, similar to other states of impaired consciousness such as sleep, coma, and deep anesthesia. According to the "network inhibition hypothesis," supported by imaging and electrophysiological data, cortical dysfunction during temporal lobe seizures results from inhibition of subcortical arousal structures which are required for maintaining the cortex in an alert and awake state. Advances in our understanding of impaired consciousness in epilepsy will hopefully pave the way toward novel treatments to prevent this profoundly debilitating side effect of seizures.

M. Furman
Department of Neurology, Yale University School of Medicine,
15 York Street, New Haven, CT 06520, USA
e-mail: moran.furman@yale.edu

H. Blumenfeld (✉)
Departments of Neurology,
Neurobiology and Neurosurgery
Clinical Neuroscience Imaging Center (CNIC),
Yale University School of Medicine,
333 Cedar Street, New Haven, CT 06520, USA
e-mail: hal.blumenfeld@yale.edu

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4.1 Altered Consciousness in Epileptic Seizures

Epileptic seizures are episodes of excessive, highly synchronized neural discharges in the brain. Epilepsy is one of the most common neurological disorders, affecting roughly 1 % of the population (Kobau et al. 2008). In the public's mind, epilepsy is often associated with *grand mal* or *generalized tonic-clonic seizures* and the dramatic convulsions that accompany them (Chap. 7). In reality, however, epileptic seizures are very diverse in terms of their physiological and behavioral markers. *Absence seizures*, for instance, are brief episodes of unresponsiveness, characterized by generalized 3–4 Hz spike-wave discharges on the EEG and seen most commonly in young children (Chap. 6). Despite their differences, generalized tonic-clonic seizures and absence seizures share an important and debilitating side effect: impaired consciousness. A third class of epileptic seizures causing impaired consciousness is *complex partial seizures*, involving focal seizures most commonly originating from the temporal lobe and characterized behaviorally by staring and automatic repetitive movements. Impaired consciousness in temporal lobe epilepsy (TLE) is the focus of this chapter.

A key idea emerging from recent neuroimaging studies is that despite the limited spread of temporal lobe seizures, altered consciousness in TLE results from abnormal activity in widespread brain networks. In addition to imaging, intracranial EEG studies have elucidated important aspects of the pathophysiology of impaired consciousness in epilepsy (see also Chap. 8); and neurostimulation techniques, including optogenetics, would hopefully lead to mechanistic, microcircuit-level insights into impaired consciousness in epilepsy and pave the way to novel therapeutic strategies for this debilitating side effect of seizures (Tønnesen et al. 2009; Fisher et al. 2010; Kahane and Depaulis 2010; Lega et al. 2010; Kokaia and Ledri 2012).

4.2 Behavioral Correlates of Loss of Consciousness During Complex Partial Seizures

Epileptic discharges in the mesial temporal lobe evoke a wide range of behavioral and cognitive symptoms. These symptoms include amnesia for the event, fear, autonomic changes, neuroendocrine changes, a rising epigastric sensation, dystonic posturing of the limbs, and automaton-like movements referred to by Penfield as "automatisms" (Marks and Laxer 1998; Bauer 2001; Park et al. 2001; Quigg et al. 2002; Janszky et al. 2003; Engel and Pedley 2008). Since many of these symptoms relate to functions attributed to the temporal lobe/limbic system, their occurrence during mesial temporal lobe seizures may be expected. Surprisingly, however, mesial temporal lobe seizures often cause, in addition to the abovementioned symptoms, behavioral unresponsiveness and impaired consciousness (Bagshaw and Cavanna 2011; Blumenfeld 2012).

How is ictal unconsciousness measured and characterized? Until recently, epileptic unconsciousness was characterized mainly through retrospective and nonstandardized methods (Bell et al. 1998; Inoue and Mihara 1998; Lee et al. 2002;

Lux et al. 2002; Blumenfeld et al. 2004a, b; Guye et al. 2006). In the last years, a number of studies have made important steps toward more systematic characterization of impaired consciousness during seizures. Cavanna and colleagues (2008) developed a scale of ictal alternations of consciousness, the "Ictal Consciousness Inventory" (ICI). ICI is based on a 20-item self-report questionnaire that quantifies a patient's level of general awareness or responsiveness and the vividness of ictal experiential phenomena during epileptic seizures. Arthuis et al. (2009) used a consciousness seizure scale (CSS)-based video recordings of seizures. The CSS testing battery includes criteria for unresponsiveness, impaired attention, altered behavior, and amnesia, resulting in a consciousness score from 0 to 9. Recently, to allow externally based prospective testing and online monitoring during seizures, a "Responsiveness in Epilepsy Test" (RES-I) was proposed (Yang et al. 2011; McPherson et al. 2012). This testing battery was derived from the JFK Coma Recovery Scale-Revised (Giacino et al. 2004) and modified to enable testing within the typical 1–2 min time frame of seizures (Afra et al. 2008). To accomplish this, RES-I testing begins with higher-level questions and commands, proceeds adaptively to more basic sensorimotor responses depending on patient performance. RES-I continues postictally with memory testing. A major challenge in developing standardized ictal behavioral testing is the rapidly changing time course of behavioral impairments during seizures. The adaptive nature of the RES-I testing procedure was intended to maximize information obtained in the shortest time possible. However, adaptive testing schemes require highly trained and skilled testing personnel. To overcome this limitation, a modified and simplified nonadaptive testing scheme was recently developed (RES-II) (Bauerschmidt et al. 2013). RES-II has been designed to be faster and less error prone to administer while retaining the diverse range of cognitive and sensorimotor functions evaluated.

Testing batteries such as RES, combined with inpatient continuous video/EEG (cVEEG) monitoring, will help to identify brain networks underlying specific components of impaired consciousness in seizures.

4.3 Human Imaging of TLE

The temporal lobe has long been implicated in functions such as memory and semantic processing, but not in maintaining consciousness or alertness (e.g., Milner 1972). Why then do focal temporal lobe discharges often impair consciousness? A number of studies proposed that temporal lobe seizures impair consciousness when seizure activity spreads from the ipsilateral mesial temporal lobe to involve the bilateral temporal cortex (Gloor et al. 1980; Pedley 1992; Bancaud et al. 1994). However, even bilateral temporal lobe dysfunction is not expected to cause, by itself, loss of consciousness. If so, perhaps bilateral temporal lobe seizure activity is *correlated* with impaired consciousness rather than directly mechanistically linked to it (Englot et al. 2010). In particular, bilateral temporal seizure spread could mark the disruption of other downstream bilateral networks directly involved in

consciousness. Examining this hypothesis requires monitoring widespread changes in brain activity during seizures.

Imaging techniques such as fMRI or O-15 PET are not usually feasible for use during seizures in humans, due to safety concerns as well as methodological difficulties such as movement artifacts. In contrast, single photon emission computed tomography (SPECT) has the unique ability to take a "snapshot" of cerebral blood flow (CBF) during seizures, by injecting the SPECT radioisotope at the time of the seizure and carrying out the imaging at a later time point. Using SPECT imaging during complex partial seizures, a number of studies revealed abnormal increases in CBF in the upper brainstem and medial diencephalon and decreases in frontoparietal cortical regions (Lee et al. 2002; Van Paesschen et al. 2003; Blumenfeld et al. 2004a; Tae et al. 2005; Hogan et al. 2006; Van Paesschen et al. 2007). Furthermore, CBF increases in the medial thalamus are directly correlated with CBF decreases in the frontoparietal cortex during temporal lobe seizures (Fig. 4.1; Blumenfeld et al. 2004a). These findings raise the intriguing possibility that temporal lobe seizures impair consciousness not because of abnormal discharges in the temporal lobe itself but by affecting subcortical arousal systems, including the upper brainstem and medial diencephalon (Penfield and Jasper 1954; Blumenfeld 2002). The involvement of subcortical structures in impaired consciousness during complex partial seizures as suggested by altered CBF has been also confirmed by direct electrical recordings (Guye et al. 2006; Arthuis et al. 2009).

If subcortical arousal systems are indeed implicated in loss of consciousness during limbic seizures, one would expect, physiologically, a transition of cortical activity into a sleep-like state, characterized by slow-wave oscillations in the EEG (Steriade et al. 1993; Haider et al. 2006). Notably, large-amplitude 1–2 Hz slow-wave activity has indeed been observed in the frontal and parietal neocortices during and immediately following complex partial seizures (Lieb et al. 1991; Blumenfeld et al. 2004b) but not during simple partial seizures, in which consciousness is intact (Englot et al. 2010). As can be seen in the intracranial EEG data shown in Fig. 4.3 (*right panels*), slow-wave activity recorded from the frontoparietal association cortex (*bottom*) contrasts with the fast polyspike activity in the temporal lobe (*top*), indicating (1) lack of seizure activity in the frontoparietal cortices and (2) a transition of the neocortex to a sleep-like, depressed state. The transition of the frontoparietal network into slow-wave activity during complex partial seizures is further supported by animal studies (Englot et al. 2008, 2009). As described later in this chapter, these animal models have provided direct, mechanistic evidence for the remote effect of the temporal lobe on frontoparietal cortices during complex partial seizures.

It is also possible that apart from or in addition to neocortical slow-wave activity, other mechanisms play a role in impaired consciousness in TLE. In particular, Arthuis et al. (2009; see also Chap. 7) have argued for a role of synchronization between brain structures that are critical for awareness, particularly the thalamocortical loop, in ictal unconsciousness. More generally, these findings relate to the "global workspace" theory of consciousness (Dehaene et al. 2003; Baars 2005), in which information becomes consciously available via synchronized

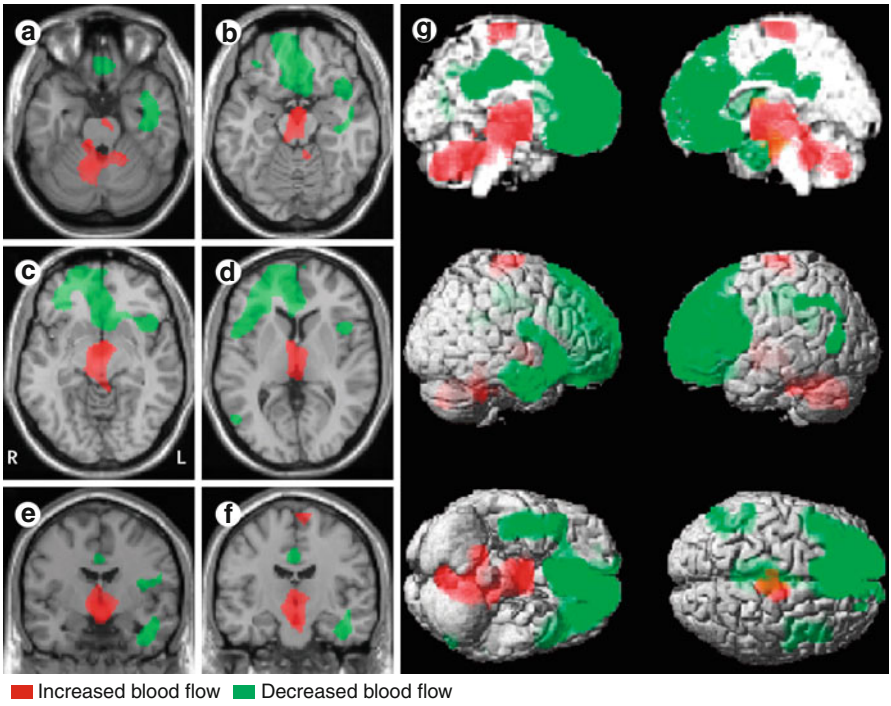

Fig. 4.1 SPECT imaging of cerebral blood flow during temporal lobe complex partial seizures. Complex partial seizures arising from the temporal lobe are associated with significant increases and decreases in cerebral blood flow (CBF) in widespread brain regions. Statistical parametric maps depict SPECT increases and decreases. Changes ipsilateral to seizure onset are shown on the *left side* of the brain and contralateral changes on the *right side* in images from ten patients. Data are from >90s after seizure onset, when consciousness was markedly impaired. At earlier times, SPECT increases were seen in the ipsilateral mesial temporal lobe (not shown). (**a**–**d**) Horizontal sections progressing from inferior to superior and (**e**, **f**) coronal sections progressing from anterior to posterior showing CBF increases in the bilateral midbrain, hypothalamus, medial thalamus, and midbrain. Decreases are seen in the bilateral association cortex. (**g**) Three-dimensional surface renderings show increases mainly in the bilateral medial diencephalon, upper brainstem, and medial cerebellum, while decreases occur in the frontal and parietal association cortices (same data as a–f). Extent threshold k = 125 voxels (voxel size 2 × 2 × 2 mm). Height threshold $p = 0.01$ (Reproduced with permission from Blumenfeld (2012), after Blumenfeld et al. (2004a))

activity within neuronal modules, often widely distributed throughout the brain. Within this framework, frontoparietal cortical slow activity during ictal unconsciousness is interpreted as preventing information processed by sensory regions from accessing awareness.

Interestingly, the networks affected during complex partial seizures largely overlap with the "default mode network" (DMN), a network of specific brain regions that are consistently activated at rest (either passive viewing or lying with eyes closed) compared to goal directed behaviors (Raichle et al. 2001; Cavanna and Trimble 2006; Cavanna and Monaco 2009; Danielson et al. 2011). Notably, cortical

slow-wave activity associated with decreased CBF and metabolism in the DMN, as observed during complex partial seizures, is commonly observed in other states of impaired consciousness including coma, encephalopathy, and deep sleep (Steriade et al. 1993; Cowan and Wilson 1994; Laureys 2005; Haider et al. 2006; Vincent et al. 2007; Laureys and Tononi 2009). However, during temporal lobe seizures, prominent slow-wave activity and decreased CBF also occur in regions not classically part of the DMN, such as lateral and orbital frontal cortex (Englot et al. 2008, 2009). As discussed next, both CBF changes and neocortical slowing associated with ictal unconsciousness have been also observed in animal models of TLE, providing insight into the mechanisms for these changes both in the DMN and other cortical networks.

4.4 Imaging in Animal Models of TLE

Animal models, particularly rodents, have been playing an important role in clarifying network mechanisms underlying loss of consciousness in TLE. Despite their more limited behavioral repertoire and lack of verbal communication, these animal models allow the application of both functional magnetic resonance imaging (fMRI) which is not feasible for routine use during complex partial seizures in humans due to safety concerns and motion artifacts and other invasive techniques which are inapplicable in humans in general.

Englot et al. (2008, 2009) have generated a rat model of TLE which recapitulates key aspects of ictal unconsciousness in human. This rat model has provided an important link for directly relating imaging data to electrophysiological recordings. Focal hippocampal seizures are initiated in the rat model using electrical stimulation or pharmacological manipulations. In acute fMRI experiments, Englot et al. (2008, 2009) found that complex partial seizures in epileptic rats were associated with BOLD signal increases in the bilateral hippocampus, as well as the thalamus and septal nuclei (Fig. 4.2). In contrast, prominent BOLD decreases were seen in downstream cortical regions such as the orbitofrontal, anterior cingulate, and retrosplenial/posterior cingulate cortices. CBV measurements in the same animals, after injection of exogenous paramagnetic contrast, closely mirrored BOLD signal alterations. Specifically, partial seizures showed increased CBV in the hippocampus, thalamus, and septal nuclei, along with decreased CBV in the orbitofrontal, cingulate, and retrosplenial cortices. These imaging results show that like in humans, partial limbic seizures in the rat have a remote network effect leading to deactivation of cortical regions including the orbitofrontal cortex, specifically in seizures involving behavioral arrest and unresponsiveness.

Recordings from the hippocampus, septum, and medial thalamus demonstrate fast, polyspike activity associated with increased neuronal firing during hippocampal seizures, whereas frontal cortex showed slow oscillations with decreased neuronal firing (Englot et al. 2008, 2009). Notably, transecting the fornix, the major route from hippocampus to subcortical structures, abolished the cortical slowing and

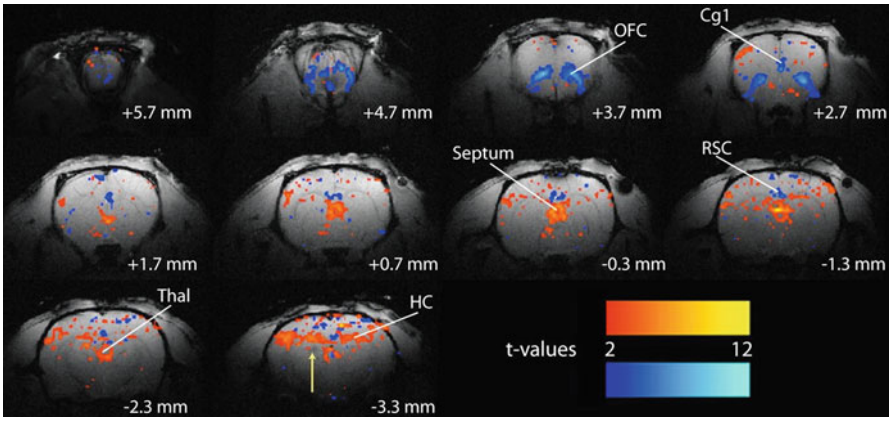

Fig. 4.2 BOLD changes during electrically stimulated partial limbic seizure in the rat. During partial limbic seizures, BOLD fMRI signal increases are observed in the hippocampus, thalamus, and septal nuclei. Prominent BOLD decreases are seen in the orbitofrontal, anterior cingulate, and retrosplenial/posterior cingulate cortices. The *arrow* indicates the hippocampal electrode artifact. *t*-maps are shown for the first 30s of seizure activity (ten consecutive fMRI images acquired every 3 s) versus 30s baseline and are superimposed on high-resolution anatomical images. Slices are shown from anterior to posterior, with approximate coordinates relative to bregma (Paxinos and Watson 2007). *Color bars* indicate *t*-values for increases (*warm colors*) and decreases (*cold colors*). The display threshold is $t=2$. *Cg1* anterior cingulate cortex, *HC* hippocampus, *OFC* orbitofrontal cortex, *RSC* retrosplenial/posterior cingulate cortex, *septum* septal nuclei, *Thal* thalamus (Reproduced with permission from Englot et al. (2008))

behavioral arrest during seizures. Thus, propagation of seizure activity into adjacent subcortical structures appears to be crucial for mediating the remote effect of the hippocampus on the neocortex. Furthermore, stimulation of the septal area, but not hippocampus or medial thalamus, in the absence of seizure activity resulted in cortical deactivation with slow oscillations and behavioral arrest, resembling changes seen during limbic seizures. As discussed further below, these findings suggest that hippocampal seizure activity propagates into subcortical inhibitory structures, including the lateral septum, that in turn inhibit neural activity in brainstem arousal structures such as the pedunculopontine tegmental nucleus (PPT), which are crucial for maintaining the cortex in an awake state.

To further examine the subcortical networks involved cortical dysfunction during seizures, Motelow et al. have recorded from identified single units in the PPT (Motelow et al. 2012). Intriguingly, cholinergic neurons, but not other types of neurons of the PPT, were suppressed during hippocampal seizures. Since cholinergic PPT neurons are part of the subcortical arousal system which maintains the cortex in an awake and alert state, inhibition of these neurons during seizures is likely to be mechanistically linked to ictal dysfunction of the neocortex. Advances in molecular-genetic tools (Witten et al. 2011) and optogenetic stimulation techniques (Cardin 2012) pave the way for testing the role of specific neuronal pathways in mediating cortical dysfunction during seizures.

4.5 Recapitulation: Why Is Consciousness Impaired in Complex Partial Seizures?

The temporal lobe has long been known to support an array of cognitive functions such as memory and language but is not crucial for maintaining alertness, behavioral responsiveness, or consciousness. Why then do focal temporal lobe seizures often cause impaired consciousness?

Findings from human and animal studies reviewed above have led to the "network inhibition" hypothesis for ictal unconsciousness in TLE (Norden and Blumenfeld 2002; Blumenfeld and Taylor 2003; Blumenfeld et al. 2004a, b; Englot and Blumenfeld 2009; Blumenfeld 2012). According to the network inhibition hypothesis, ictal unconsciousness represents a depressed cortical state, resembling coma, deep sleep, or other forms of impaired consciousness. Furthermore, this depressed cortical function occurs when temporal lobe seizures propagate to neighboring structures such as the lateral septum which in turn inhibit subcortical arousal systems (Fig. 4.3). During consciousness, these subcortical arousal systems interact with the cortex to maintain alertness and responsiveness. When consciousness

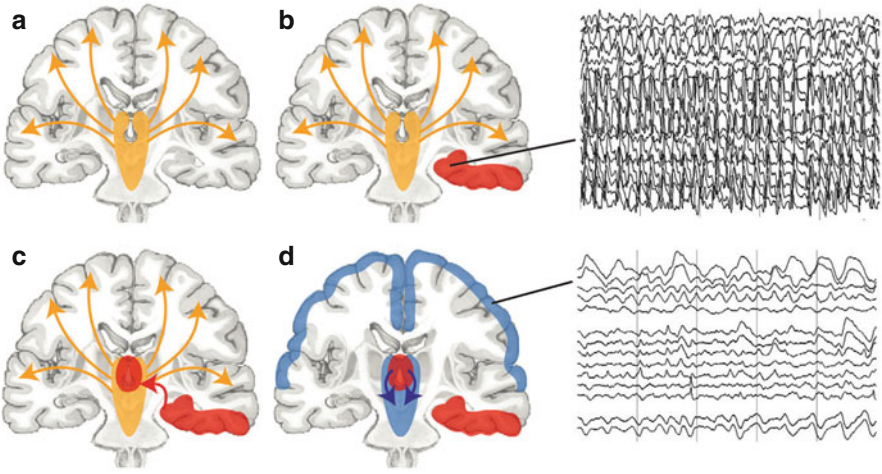

Fig. 4.3 Network inhibition hypothesis for impaired consciousness in temporal lobe complex partial seizures. (**a**) Under normal conditions, the upper brainstem and diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. (**b**) A focal mesial temporal lobe seizure. Intracranial electroencephalographic recordings (*right, upper inset*) show fast polyspike activity in the temporal lobe. If the seizure remains localized, a simple partial seizure will occur without impairment of consciousness. (**c**) Seizure activity often spreads from the temporal lobe to midline subcortical structures. Often, propagation also extends to the contralateral mesial temporal lobe (not shown). (**d**) Inhibition of subcortical activating systems leads to depressed activity in bilateral frontoparietal association cortex and to loss of consciousness. Intracranial electroencephalographic recordings (*right, lower inset*) from the frontoparietal association cortex show slow-wave activity that resembles activity during deep sleep (Reproduced with permission from Blumenfeld (2012), after Englot et al. (2010))

is impaired, the arousal systems are "shut off," resulting in a sleep-like mode of cortical activity.

Conclusions and Future Directions

Brain imaging studies have revealed network changes linked to loss of consciousness during temporal lobe seizures. In both human patients and animal models, ictal unconsciousness involves neocortical dysfunction, characterized by decreased CBF and slow-wave activity in the EEG. This transition of the neocortex into a sleep-like mode is likely to be caused by inhibition of subcortical arousal structures which are required for maintaining wakefulness and alertness. Technological advances, such as small-animal high-resolution fMRI, molecular-genetic techniques, and optogenetics, will help to mechanistically link specific brain networks to ictal unconsciousness and hopefully pave the way to new therapeutic approaches to this debilitating side effect of seizures. Understanding impaired consciousness in temporal lobe epilepsy may also shed light on more general network mechanisms contributing to other disorders of consciousness.

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