Published in final edited form as:
Lancet Neurol. 2012 September ; 11(9): 814–826. doi:10.1016/S1474-4422(12)70188-6.

Impaired Consciousness in Epilepsy

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Abstract

Consciousness is essential to normal human life. In epileptic seizures consciousness is often transiently lost making it impossible for the individual to experience or respond. This has huge consequences for safety, productivity, emotional health and quality of life. To prevent impaired consciousness in epilepsy it is necessary to understand the mechanisms leading to brain dysfunction during seizures. Normally the “consciousness system”—a specialized set of cortical-subcortical structures—maintains alertness, attention and awareness. Recent advances in neuroimaging, electrophysiology and prospective behavioral testing have shed new light on how epileptic seizures disrupt the consciousness system. Diverse seizure types including absence, generalized tonic-clonic and complex partial seizures converge on the same set of anatomical structures through different mechanisms to disrupt consciousness. Understanding these mechanisms may lead to improved treatment strategies to prevent impaired consciousness and improve quality of life in people with epilepsy.

Introduction

Imagine that at any moment you might suddenly become unconscious and lose control of your behavior. This is the burden carried by many people with epilepsy who face their lives each day not knowing when all their plans and activities will be devastated by seizures. Uncontrolled seizures are the most important factor determining impaired quality of life in epilepsy [1, 2], and this is particularly true for seizures that disrupt consciousness. When consciousness is lost patients may be injured, lose work or school productivity, suffer social stigmatization or lose their lives. Because of the enormous importance of impaired consciousness in epilepsy, there has been a growing interest in directly investigating this problem. Understanding impaired consciousness in epilepsy may lead to improved treatments for patients with epilepsy as well as for other disorders of consciousness.

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Search Strategy and Selection Criteria

Material covered was based on PubMed search using the terms “epilepsy” and “consciousness” and then selecting original research articles in which the primary focus was evaluating consciousness or mechanisms of impaired consciousness in epilepsy. In addition, references listed in prior review articles on this topic were included if they met the same criteria.

Contributors and Conflicts of Interest

H.B. wrote the manuscript while supported by NIH R01NS055829, R01NS066974, R01MH67528, R01HL059619, P30NS052519, U01NS045911, Donaghue Foundation Investigator Award, and the Betsy and Jonathan Blattmachr Family, and has no conflicts of interests to report.

Not all seizures cause impaired consciousness. In some localized seizures, patients may retain the ability to interact with their surroundings, answer questions and commands, and recall events normally despite ongoing focal motor, sensory or autonomic seizures. Seizures that do impair consciousness appear very diverse in terms of behavior, physiology and patient demographics. They include absence seizures—brief staring episodes seen most commonly in young children; generalized tonic-clonic seizures—dramatic convulsive attacks with profound unresponsiveness; and complex partial seizures—with staring and automatic repetitive movements (Table 1). Until recently it has been unclear what these three seizure types have in common to explain the impairment of consciousness.

Rapid advances in neuroimaging technology and physiological studies from human patients and animal models have provided fundamental new insights into impaired consciousness in epilepsy. It is now clear that despite their differences, all three seizure types converge on a common set of structures including the fronto-parietal association cortex and subcortical arousal systems in the thalamus and upper brainstem (Table 1). Involvement of these anatomical structures may be crucial for impaired consciousness in epilepsy, and is also seen in other disorders of consciousness [3, 4].

Here we will place epilepsy in the context of other consciousness disorders, reviewing first general mechanisms of consciousness, and then discuss absence, generalized tonic-clonic and complex partial seizures in turn. For each seizure type we will review recent behavioral, electrophysiological and neuroimaging studies, as well as insights gained from experimental animal model systems. Finally, we discuss implications for patient quality of life, future directions for additional investigation, and potential therapies to reduce impaired consciousness in epilepsy.

Defining Consciousness

There are two main schools of thought on defining consciousness. In one approach, certain aspects of consciousness called “qualia” are considered inaccessible to third-person investigation, and can only be described through first-person experience [5, 6]. Note that in this approach *by definition* some aspects of consciousness cannot be explained based on external observations, and are therefore outside the domain of scientific research. In another approach, no *a priori* limits are set on the potential domain of scientific investigation, and the best explanation for first-person experience is included as a possible subject of empiric study [7, 8]. According to this second approach all aspects of consciousness may be better understood through scientific investigation, though of course much work remains to be done.

Regardless of which of these alternatives is preferred, most philosophers and scientists agree that the term “consciousness” applies to a broad *collection of processes* of which qualia are just one part. From a neurological perspective most or all of these processes are implemented through specific brain networks. Plum and Posner introduced a classic distinction between brain systems that regulate the *level of consciousness* and those that provide the *content of consciousness* [9, 10]. The content of consciousness can be viewed as the substrate—it is what we are conscious of, and includes all of the hierarchically organized sensory and motor systems, memory, and emotions/drives. The brain networks serving the content of consciousness are the subject of most research in neuroscience. The level of consciousness determines whether we are awake, attentive and aware (mnemonic: AAA) of the content of consciousness. In analogy to sensory, motor and other cortical-subcortical brain systems we can refer to the specialized structures involved in regulating the level of consciousness as the “consciousness system” [11, 12].

The Consciousness System

Much has been learned about the brain systems controlling the level of consciousness over the past 100 years. In the early 20th century, based on human brain disorders [13, 14] and experimental animal models [15, 16], it became apparent that both cortical and subcortical structures play crucial roles. New techniques since then have provided a wealth of information about structures controlling the level of consciousness [17]. We term this specialized cortical-subcortical network the "consciousness system" [11, 12] (Figure 1), and now briefly discuss its anatomy, physiology and behavioral roles.

The cortical components of the consciousness system are the higher order association cortex (Figure 1). These include the medial frontal, anterior cingulate, posterior cingulate and medial parietal (precuneus, retrosplenial) cortex on the medial surface (Figure 1A), and the lateral frontal, orbital frontal, and lateral temporal-parietal association cortex on the lateral surface (Figure 1B). It is likely that portions of the insula (not shown) also participate. Note that individual cortical components play important and well-studied roles in specific cognitive functions in the dominant and non-dominant hemispheres [18, 19]. The cortical components of the consciousness system also subsume the recently described default mode network important for internally-directed processing [20] as well as other cortical networks important for externally-oriented attention [21-24]. Since we have defined consciousness as a *collection* of diverse processes it is appropriate that the cortical components of the consciousness system are not homogenous. Taken as a whole the bilateral higher order association cortices exert powerful control on the overall level of behavioral arousal, attention and awareness, and interact strongly in a reciprocal manner with subcortical arousal structures [17].

The subcortical components of the consciousness system include the basal forebrain, hypothalamus, thalamus and upper brainstem activating systems (Figure 1A). Portions of the basal ganglia, cerebellum and amygdala may also participate (not shown). Subcortical arousal systems contain numerous parallel neurotransmitter systems (including acetylcholine, glutamate, gamma amino butyric acid (GABA), norepinephrine, serotonin, dopamine, histamine and orexin) that act together to maintain the level of consciousness [17, 25-27]. Again, because of the diversity of these systems, each with distinct functional roles, subcortical arousal structures should be considered as parallel forces contributing to the overall collection of conscious processes.

The key to unlocking consciousness lies not just in "where," but "how". Equally important to the anatomy, is the physiology of how these regions interact to form the circuit of consciousness. In recent years oscillations [28-30], connectivity [31-33] and integration [34, 35] have come to the forefront of research. However, the physiological mechanisms of consciousness remain very much an open question. Disorders of consciousness including epilepsy disrupt this physiology through abnormal increases, decreases, or altered patterns of neural activity.

To test the behavioral level of consciousness clinically or experimentally, it is necessary to evaluate *alertness, attention and awareness.* (1) Basic alertness, which distinguishes coma or sleep from the awake state can be evaluated based on the presence of behaviorally meaningful responses to simple questions, commands, or aversive stimuli. (2) Attention is often tested by the ability to carry out a sequence of tasks or to detect stimuli among distractors. (3) Awareness can be evaluated based on verbal or nonverbal report of experience. This returns us to the dichotomy already mentioned where some posit that awareness or qualia cannot truly be studied by external means, while others hold that report of experience is sufficiently close to qualia to provide useful information for further study.

Deficits in consciousness

Disorders of consciousness can be mild or severe depending on the degree of impairment in brain systems important for the content or level of consciousness. If the content of consciousness is altered by disruption of multiple brain areas involved in sensory-motor functions, memory, or emotion and drives, consciousness is severely impaired. An example is diffuse anoxic brain injury. More discrete lesions affecting specific contents of consciousness lead to states where fully normal consciousness is not possible, yet the deficits are more circumscribed. For example, damage to visual cortex impairs visual perception, to language cortex impairs linguistic processing, to medial temporal cortex disrupts recent memory, yet these patients have relatively preserved consciousness in other domains. Therefore, focal lesions affecting discrete aspects of consciousness are usually not considered among the typical disorders of consciousness.

In contrast when the level of consciousness is impaired there are deficits in virtually all the contents of consciousness. Decreased level of consciousness is seen in the classic disorders of consciousness such as coma, syncope, vegetative state, sleep disorders, encephalopathy and seizures [3, 4, 36]. These disorders affect the consciousness system (Figure 1). Interestingly, the impact of depressed level of consciousness is often greater for tasks requiring more complex information processing. For example higher order executive function, abstract language processing, writing, logic, arithmetic, working memory, and emotional judgment are usually much more severely impaired than simple sensory-motor tasks [18, 19]. This is consistent with the anatomy of the consciousness system (Figure 1), weighted more heavily to higher-order information processing; while in contrast, the content of consciousness is weighted toward specific sensory-motor, limbic or mnemonic functions.

Impaired consciousness in epilepsy is similar to other disorders of consciousness [37] except that the deficits are transient. For example, in generalized tonic-clonic seizures patients are deeply unresponsive to all external stimuli and transiently resemble comatose patients. One interesting difference is that the eyes are typically open in tonic-clonic seizures, unlike coma [10]. In absence and complex partial seizures, the eyes are also open and responses to external stimuli vary from no response to impaired or abnormal simple responses [38, 39], similar to a transient vegetative or minimally conscious state [37].

One important cautionary note is that sensorimotor deficits together with amnesia may produce behavioral unresponsiveness mimicking impaired consciousness[40, 41]. Recent functional neuroimaging studies provide a new means to evaluate the internal state of patients with epilepsy and other disorders of consciousness. As we will discuss in the sections that follow, absence, generalized tonic-clonic and complex partial seizures differ in many ways, yet all converge on the same set of anatomical structures to produce dysfunction in the consciousness system (Figure 1).

Absence Seizures

First described in the medical literature as early as 1705 [42], in absence seizures the patient is metaphorically “absent” for a brief period, meaning that normal consciousness is temporarily lost. Seen most commonly in childhood absence epilepsy (CAE), absence seizures also occur in other epilepsy syndromes including adolescent and adult forms. The signature of absence seizures is generalized 3-4 Hz spike-wave discharges on EEG along with brief episodes of unresponsiveness. Despite being classified as a form of generalized epilepsy, recent work suggests that absence seizures preferentially involve selective bilateral cortical and subcortical networks [43, 44], which may help explain specific deficits in consciousness.

Behavioral studies of absence seizures have used a variety of tasks during and between electrographic seizures (for original references back to 1950s see recent reviews [45, 46]). Interestingly, the degree of impairment depends on the task. More severe deficits are seen when a verbal response or complex decision is required, while simpler repetitive actions can continue at times right through absence attacks (Fig 2A). This resembles other disorders of consciousness which, as we have already mentioned, most severely impair tasks requiring higher-order information processing. In absence seizures, deficits typically begin and end abruptly with the EEG discharge (Fig 2). There may be some recovery of function towards the end of seizures, and function is also sometimes initially spared resulting in a U-shaped curve of deficits (Fig 2A). In the immediate pre-ictal or post-ictal periods, more subtle impairment has been reported by some authors, but this has been disputed by others. However, there is broad agreement that patients with CAE often have chronic deficits in attention during the interictal period even when no seizures are present [47-50]. Another important behavioral feature of absence seizures is variability in the deficits in consciousness from one seizure to the next, even within the same patient (reviewed in [45], see also [39]). By comparing EEG or neuroimaging in absence seizures with impaired vs. spared behavioral responses, it may be possible to determine the physiological and anatomical basis of impaired consciousness.

The EEG of absence seizures shows a characteristic bilateral 3-4 Hz spike-wave discharge, usually lasting less than 10 seconds, with relatively abrupt onset and end (Fig 2B). The voltage distribution of the discharges has been investigated by conventional EEG [51, 52], high-density EEG [53] and magnetoencephalography (MEG) [54] usually demonstrating a midline frontal amplitude maximum. These findings support the notion that absence seizures are not truly generalized, but involve specific brain regions most intensely involved. Several EEG features have been associated with more severe behavioral unresponsiveness, including spike-wave amplitude, duration, rhythmicity, frontocentral distribution, and “generalization” (reviewed in [45]). However since others have found no relation to EEG features, this remains a topic of potentially important investigation. Even effects of seizure duration are controversial since behavioral deficits are not obvious in seizures lasting less than 3 seconds [55, 56] yet even brief < 1s spike-wave episodes do cause behavioral deficits when evaluated by careful testing [39, 57].

Functional neuroimaging in absence seizures was initially performed with lower-resolution techniques (reviewed in [44, 45]), but in recent years has been based mainly on functional magnetic resonance imaging (fMRI). Simultaneous EEG-fMRI studies in patients with absence epilepsy have found fMRI changes in all components of the consciousness system during seizures. Notably, most studies describe (1) increases in the thalamus, (2) decreases in the medial frontal, medial parietal, anterior/posterior cingulate, and lateral parietal cortex, and (3) a mixture of increases and decreases in the lateral frontal cortex [39, 58-61]. fMRI increases have also been reported in primary motor, somatosensory, visual and auditory cortex as well as the cerebellum; and decreases are often observed in the basal ganglia and pons [39, 62, 63]. Only a few studies have attempted to relate fMRI changes in absence seizures to impaired behavioral performance [39, 64, 65] with results so far suggesting more extensive fMRI changes when behavior is impaired, although sample sizes have generally been too small to draw strong conclusions.

One important challenge is the fact that most fMRI studies oversimplify the hemodynamic response function relating fMRI to brain activity. It was recently found that fMRI increases may begin in the medial frontal and parietal cortex up to 10 seconds before onset of absence seizures on the EEG (Fig 3) [62, 66, 67]. This is followed by a complex sequence of increases and decreases with different time-courses in cortical and subcortical structures, most of which do not follow the standard hemodynamic response function used for conventional

fMRI analyses. Therefore, better analysis approaches are needed to detect these important aspects of fMRI changes during absence seizures that could be related to impairment of consciousness.

Animal models have long provided fundamental insights into the pathophysiology of absence seizures [68-71]. One favorite and long-standing dispute is the relative importance of cortex vs. thalamus in absence seizure generation. The most recent trend based on rodent models has been to favor a cortical origin. However, since all agree that both cortex and thalamus usually participate in spike-wave seizures, and that spike-wave activity can be generated by many different causes in various disorders and species, this debate is unlikely to be fully resolved any time soon. Another important point supported by animal models is the focal nature of bilateral spike-wave seizures [43, 44]. Electrical recordings and fMRI from rodent absence seizure models show focal bilateral cortical activation in the peri-oral and whisker barrel somatosensory cortex while other regions are relatively spared [43, 72-75]. Corresponding specific thalamic somatosensory relay and reticular thalamic nuclei are also involved while other thalamic nuclei are relatively spared by spike-wave. These findings support the notion of focal bilateral network involvement leading to deficits in specific aspects of consciousness during absence seizures [46, 76]. Finally, animal models have been important for validation of neuroimaging studies, since fMRI signals are only indirectly related to underlying neuronal activity [77]. Direct electrical recordings under the same conditions as fMRI have confirmed that cortical and thalamic fMRI increases correspond to increased neuronal activity in the same regions [73, 74, 78]. However, the neuronal basis of fMRI decreases during spike-wave seizures is less certain. Paradoxical fMRI decreases with increased neuronal activity are observed in the basal ganglia [78], and the neuronal basis of fMRI decreases in the cortex during spike-wave seizures requires further investigation.

Generalized Tonic-Clonic Seizures

Much of the stigma of epilepsy arises from the terrifying appearance of generalized tonic-clonic, or *grand mal* seizures. In these convulsive episodes consciousness is deeply impaired, both during seizures and for a variable postictal period. Despite being classified as generalized events, recent evidence again suggests preferential focal involvement of the consciousness system (Figure 1), which may explain the profoundly impaired consciousness in generalized tonic-clonic seizures.

Behavior in generalized tonic-clonic seizures progresses through a series of characteristic stages [79-82]. The beginning of the seizure may be focal as in localized seizures with secondary generalization, or may be generalized from the outset in primary generalized epilepsy. Although all patients do not exhibit every phase, the typical sequence is localized or bilateral clonic activity which may precede the tonic phase, a transitional vibratory phase, bilateral clonic activity, and finally postictal lethargy. Usual duration of the convulsive seizure is about two minutes. Patients are profoundly unresponsive during and following generalized tonic seizures, even to relatively basic tasks such as ball grasp, visual tracking or blink to visual threat [38] and are amnestic to events around the time of the seizure. Notably, there are exceptional cases where patients retain consciousness during generalized tonic-clonic seizures and can accurately describe the experience afterwards [83-85]. It has been proposed that these represent bilateral frontal lobe seizures which spare other brain regions necessary for loss of consciousness, though this has not been definitively proven.

The EEG in generalized tonic-clonic seizures exhibits widespread low-voltage fast or polyspike activity during the tonic phase, followed by polyspike-and-wave activity in the clonic phase, and generalized suppression postictally. Focal seizures with secondary generalization may show some EEG asymmetry even during the generalized phase [86, 87].

Intracranial EEG has demonstrated that generalized tonic-clonic seizures are not truly generalized, but may spare some brain regions [88].

Imaging of generalized tonic-clonic seizures is challenging, because patient movement during seizures creates artifact and safety risk. Single photon emission computed tomography (SPECT) has the advantage of allowing injection of radiotracer during the seizure, but imaging occurs over 45 minutes later once the patient is medically stable and no longer moving [89-91]. This imaging maps cerebral blood flow at the time of the earlier tracer injection. SPECT imaging from partial seizures with secondary generalization [81, 82, 92-95], as well as in tonic-clonic seizures induced by electroconvulsive therapy [87, 93, 96-99] has shown dramatic changes in the consciousness system. In particular, increases are seen in the bilateral lateral frontal and parietal cortex, medial parietal cortex, thalamus and upper brainstem, while decreases are seen in the medial frontal and cingulate cortex during seizures. Positron emission tomography (PET) blood flow imaging has generally agreed with these findings [100]. In the postictal period, cerebral blood flow decreases are seen in medial and lateral fronto-parietal association cortex [82, 99]. Interestingly, the cerebellum shows progressive increases in activity (measured by blood flow) in the late ictal and postictal period [82]. Because cerebellar Purkinje cells have a powerful inhibitory output to the deep cerebellar nuclei which in turn project to the thalamus, it was proposed this may reduce activity in the forebrain, participating in seizure termination and in post-ictal suppression. In support of this hypothesis, analysis of cerebellar activity during and following tonic-clonic seizures showed a strong correlation with *decreased* activity in the fronto-parietal consciousness system structures (Fig 4) [82]. The neural mechanisms for these changes require further investigation. For example, it is unclear why the thalamus and upper brainstem show increased activity (Fig 4), since reduced output from deep cerebellar nuclei is expected to decrease activity in the thalamus.

Animal studies using direct electrical recordings in cats have similarly shown progressively increasing cerebellar neuronal activity in the late ictal and post-ictal periods of generalized tonic-clonic seizures, proposed to depress activity in the forebrain [101]. This mechanism may play an important role in reduced cerebral function and impaired consciousness. An additional conclusion from animal models, using-high field fMRI in rats again supports the finding of focal bilateral changes in “generalized” tonic-clonic seizures [102], and the role of focal network dysfunction in ictal impairment. Studies using both neuroimaging and direct electrical recordings in rat generalized tonic-clonic seizures have shown good agreement between fMRI and neuronal activity in the neocortex, but a paradoxical dissociation in the hippocampus, providing a cautionary note to the interpretation of indirect neuroimaging signals [103].

Complex Partial Seizures

Partial seizures can disrupt the content or level of consciousness. Traditionally, partial seizures with focal changes but without a decrease in overall level of consciousness have been classified as simple partial, while those with impaired level of consciousness are called complex partial [104]. As we have already discussed, dysfunction affecting isolated aspects of the content of consciousness is not usually considered a disorder of consciousness. For example, simple partial seizures can cause focal motor twitching, focal limb tingling, selective emotional, language or visual changes while consciousness remains relatively preserved in other domains. More interesting to consider are focal seizures which affect selective aspects of higher-order processing or memory. For example, focal seizures may cause déjà vu, amnesia, hallucinations, “forced thinking,” or altered self-perception [105, 106] in which specific aspects of consciousness are impaired. Such seizures may or may not also cause deficits in the overall level of consciousness[107, 108].

Altered level of consciousness, evidenced by decreased overall arousal and responsiveness, is the defining feature of complex partial seizures. Complex partial seizures most commonly arise from the temporal lobe, have a high prevalence, and an enormous impact on patient quality of life [109, 110]. The recent ILAE Commission Report has renamed these events focal seizures with impaired consciousness/responsiveness [111] though here we retain the briefer and older term, complex partial seizures [104]. One important puzzle, discussed further below, is the mechanism by which focal seizures can affect the overall level of consciousness.

Behavioral changes in complex partial seizures include an arrest of ongoing activities, staring, and unresponsiveness to questions and commands, often accompanied by "automatisms" such as lip smacking, chewing, or repetitive semi-purposeful limb movements [14, 112, 113]. Typical duration is one to two minutes. Unlike generalized tonic-clonic seizures, simple responses are preserved in over half of complex partial seizures, including grasping a ball or visual tracking [38]. Like in absence seizures, tasks that require meaningful higher-order processing such as verbal responses, command following, or decision making are profoundly impaired. This eyes-open state of impaired higher function with preserved automatic behaviors resembles parasomnias such as sleep walking seen during slow wave sleep. Most testing has been biased towards verbal responsiveness, however efforts have been made to introduce non-verbal testing items as well [114-116]. The time course of in complex partial seizures is often characterized by relatively spared function towards the beginning of seizures, followed by decreased responsiveness which may persists for several minutes into the postictal period. Patients are usually amnestic for events around the time of complex partial seizures.

Scalp EEG recordings during temporal lobe complex partial seizures show rhythmic 5-7 Hz theta frequency discharges over the temporal lobe on the side of onset, which may spread to both temporal lobes, and is often accompanied by more widespread slower delta and theta frequency activity. Intracranial recordings reveal that seizures begin with periodic spiking or low-voltage fast activity in the mesial temporal structures, followed by polyspike-and wave in the theta frequency range involving the ipsilateral temporal lobe (Figure 5 B, inset). Spread to the contralateral temporal lobe is more common in seizures with loss of consciousness, although loss of consciousness can occur in some seizures where seizure activity remains unilateral [117-119]. Similarly, loss of consciousness is somewhat more common in seizures with left hemisphere onset, yet seizures with onset in the right hemisphere certainly can cause loss of consciousness as well [118] and it likely that the verbal bias in testing methods may contribute to this apparent asymmetry.

We recently proposed a "network inhibition hypothesis" to explain the puzzle of why focal seizures in the temporal lobe often cause loss of consciousness (Figure 5) [12, 118, 120-125]. Normally consciousness is maintained by reciprocal interactions between the cortical and subcortical components of the consciousness system (Figure 5A). Focal seizure activity produces abnormal polyspike discharges in the temporal lobe (Figure 5B). Known anatomical connections including the uncinate fasciculus, fornix, medial forebrain bundle, corticopontine fibers and stria medullaris, can carry abnormal seizure activity to subcortical structures, particularly to pools of GABAergic inhibitory neurons in structures such as the lateral septal nuclei, anterior hypothalamic ventrolateral preoptic area, thalamic reticular nucleus, habenula, substantia nigra pars reticulata, ventral pallidum and cerebellar Purkinje neurons (Figure 5 C). This may powerfully inhibit subcortical arousal systems in the upper brainstem, thalamus, hypothalamus and basal forebrain (Figure 5 D). Removal of subcortical arousal leads to sleep or coma-like slow wave activity in broad regions of the bilateral fronto-parietal association cortex (Figure 5 D), producing impaired consciousness.

Support for the network inhibition hypothesis has come from intracranial EEG, neuroimaging, and animal models. Intracranial EEG studies have shown neocortical slow activity in the medial and lateral fronto-parietal regions of the consciousness system (Figure 5 D, inset) [118, 126, 127]. This neocortical slow activity, in the 1-3 Hz delta or slower frequency range, continues into the post-ictal period when consciousness remains impaired [128]. In addition, bilateral neocortical slow activity is significantly more prominent in seizures with impaired consciousness compared to seizures in which consciousness is spared [118]. The slow activity is largest in the bilateral orbital, medial and lateral frontal cortex as well as in the ipsilateral parietal cortex, and is less prominent in the contralateral parietal cortex relative to seizure onset. Depressed activity in these cortical areas may serve to counterbalance excitatory inputs from entorhinal and parahippocampal regions [129] preventing seizure propagation from the medial temporal lobe into the neocortex. Depth recordings have also revealed abnormally enhanced thalamo-cortical synchrony which may contribute to impaired consciousness in temporal lobe seizures [130-132].

Functional neuroimaging in complex partial seizures, as with generalized tonic-clonic seizures, has been most readily accomplished with ictal SPECT. Multiple studies have shown relative increases in cerebral blood flow in the upper brainstem, medial thalamus, and hypothalamus (Figure 6) [133-137] associated with impaired consciousness [133, 137]. In addition, SPECT *decreases* occur in the bilateral frontoparietal association cortex in temporal lobe complex partial seizures (Figure 6) [137, 138]. Of note, the consciousness system is again involved with abnormal increases in bilateral upper brainstem/medial diencephalon, and abnormal decreases in bilateral orbital, medial and lateral frontal cortex as well as in ipsilateral medial/lateral parietal cortex. These widespread network changes are not seen in simple partial seizures with spared consciousness and SPECT changes confined mainly to the temporal lobe of seizure onset [137]. Correlation analysis of cerebral blood flow increases in the medial thalamus with the rest of the brain revealed a strong relationship with *decreases* in the bilateral fronto-parietal association cortex, again supporting the network inhibition hypothesis [137].

Animal models have been useful to investigate the neural mechanisms of depressed neocortical function and impaired consciousness in limbic seizures. Similar to human patients, rats with spontaneous hippocampal seizures exhibit behavioral arrest and neocortical slow activity, and these changes are also seen in seizures induced by brief hippocampal stimulation [125]. The neuronal basis of ictal neocortical slow activity involves alternating up and down states of neuronal firing, closely resembling coma, deep sleep or encephalopathy [125, 139, 140]. Ictal neocortical slow activity is associated with a mean *decrease* in neuronal firing, cerebral blood flow, cerebral blood volume, and cerebral metabolic rate of oxygen consumption, in contrast to hippocampal or neocortical seizure activity where *increases* are seen in all of these variables.

Ictal slow activity is therefore a unique state of depressed cortical function, distinct from fast activity typically seen in seizures, and likely arising from long-range network effects rather than direct seizure propagation. Further work with the rat model has shown that involvement of subcortical structures is necessary and sufficient for ictal neocortical slow activity and behavioral arrest, based on the following findings: (i) involved networks were mapped with high field fMRI; (ii) blocking subcortical spread of seizures by cutting the fornix prevented neocortical slow activity and behavioral arrest; (iii) stimulation of subcortical inhibitory structures involved in seizures, such as the lateral septal nuclei, replicated slow activity and behavioral arrest [124, 125]. Ongoing work has demonstrated that identified neurons involved in subcortical arousal, such as cholinergic penunculopontine tegmental neurons, are temporarily shut down during limbic seizures [141].

Clinical Consequences and Treatment Strategies

Impaired consciousness in epilepsy has an enormous impact on patient quality of life [142]. Consequences of impaired consciousness include driving hazards, other accidents and injuries such as burns, falls and drowning, impaired school and work performance, and social stigmatization [143-145]. Because seizures are unpredictable and many patients function normally in the interictal period, services and support for these transient but devastating deficits are often limited. Improved methods are needed for prospective testing during the ictal and interictal periods to better understand and predict the impact of impairments on day-to-day function [114-116, 131, 143, 146]. Another consequence of depressed arousal in the ictal and postictal periods is respiratory compromise, which may be an important cause of sudden unexpected death in epilepsy (SUDEP), mechanistically related to impaired consciousness [147]. Finally, patients' ability to accurately report their seizures to their health care providers and receive appropriate treatment is adversely affected by ictal unconsciousness. Recent work has shown that impaired consciousness during seizures is a major factor associated with under-reporting [148], with patients being unaware of 30 to 50% of their seizures [149, 150].

With improved understanding of impaired consciousness in epilepsy it is hoped that better treatment strategies will become available. While the goal is always to stop seizures if possible, this cannot always be achieved, and in those cases reducing impaired consciousness could greatly improve quality of life. Behavioral measures to increase patient awareness and reporting of seizures have not been investigated but could be a potentially beneficial approach. As the mechanistic understanding of impaired consciousness in epilepsy improves it may be possible to pursue medical and surgical treatment trials to convert complex partial seizures into simple partial seizures, greatly improving patients' ability to function despite refractory seizures. Since the slow wave activity in complex partial seizures resembles deep sleep, investigation of alertness-promoting agents such as modafinil [151] may be warranted. Although fornix transection can prevent slow activity and impaired consciousness in rat models [124] it is likely this would have adverse effects on memory in human patients [152] (although see also [153]). Another adverse risk is the possibility that reducing cortical depression might actually promote seizure propagation to the cortex. With further study alternative safer disconnection procedures may be found to interrupt impaired consciousness in epilepsy. Neurostimulation is a growing therapeutic area for a number of disorders including epilepsy [154, 155] and recent work suggests that stimulation of subcortical arousal systems may be beneficial in disorders of consciousness [156, 157].

Conclusions and Future Directions

Different seizures converge on the same set of anatomical structures to cause impaired consciousness. Although they differ in terms of behavior and physiology (Table 1), absence, generalized tonic-clonic, and complex partial seizures all disrupt the upper brainstem/medial diencephalon, medial and lateral fronto-parietal association cortex, which constitutes the consciousness system (Figure 1). Impaired function can occur either through direct seizure involvement of cortical-subcortical structures, or through indirect network inhibition. The consciousness system is comprised of diverse cortical components including the default mode network and other cortical regions important for heteromodal processing along with multiple parallel subcortical arousal systems, which when affected together, lead to disorders in the level of consciousness.

Absence seizures cause brief behavioral arrest with eyes open [158], and some spared basic sensori-motor responses resembling a transient minimally conscious state [159, 160]. The thalamus shows abnormal increased activity, but the exact nature and time course of cortical

changes associated with absence seizures has been more difficult to study conclusively since fMRI changes precede and outlast the electrical changes on scalp EEG by many seconds. Although fMRI suggests that absence seizures disrupt the consciousness system, further studies will be needed to precisely define the anatomical basis of impaired and spared cognitive functions in relation to the dynamic time course of neuroimaging changes. In addition, improved animal models are needed to relate and explain the observed fMRI changes based on direct recordings of underlying neuronal activity.

Generalized tonic-clonic seizures usually cause profound unresponsiveness resembling coma during the ictal and postictal periods. EEG and SPECT imaging studies suggest that like absence seizures these so-called “generalized” seizures affect focal bilateral regions most intensely, including the consciousness-system subcortical arousal structures and higher-order association cortex. Interestingly, late-ictal and postictal cerebellar activity may be related to suppressed activity in the forebrain, and the mechanisms for this should be investigated further in animal models with an eye towards potential improved human therapy.

Complex partial seizures produce automaton-like behavior with eyes open and simple responses resembling sleep walking, or a transient minimally conscious state [159, 160]. The puzzle of why focal temporal lobe seizure activity can cause impaired consciousness may be explained by the network inhibition hypothesis, in which temporal lobe seizures depress subcortical arousal systems, leading to deep sleep-like activity in widespread neocortical regions. Again the cortical and subcortical components of the consciousness system are involved. Exciting progress has been made, but further work is needed to fully understand the neurobiology of suppressed cortical arousal including direct electrophysiological recordings from subcortical structures during limbic seizures. In addition, the mechanisms of impaired consciousness in other seizure types including atonic, tonic, or complex partial seizures from structures outside the temporal lobe are less well known and will be another important topic of future study.

Since impaired consciousness greatly affects the ability of people with epilepsy to function normally in the world, it is hoped that further behavioral, physiological and neuroimaging studies will lead the way to improved understanding of this important consequence of epilepsy. The ability to retain full consciousness without unpredictable lapses is an achievable goal that can hopefully be reached in the near future, to greatly help people with epilepsy and improve their quality of life.

Acknowledgments

Ryan Aronberg, Andrew Bauerschmidt, Moran Furman, Jennifer Guo, Joshua Motelow, Jorge Rodriguez-Fernandez and Mark Youngblood provided helpful comments on the manuscript. This work was supported by NIH R01NS055829, R01NS066974, R01MH67528, R01HL059619, P30NS052519, U01NS045911, a Donaghue Foundation Investigator Award, and the Betsy and Jonathan Blattmachr Family.

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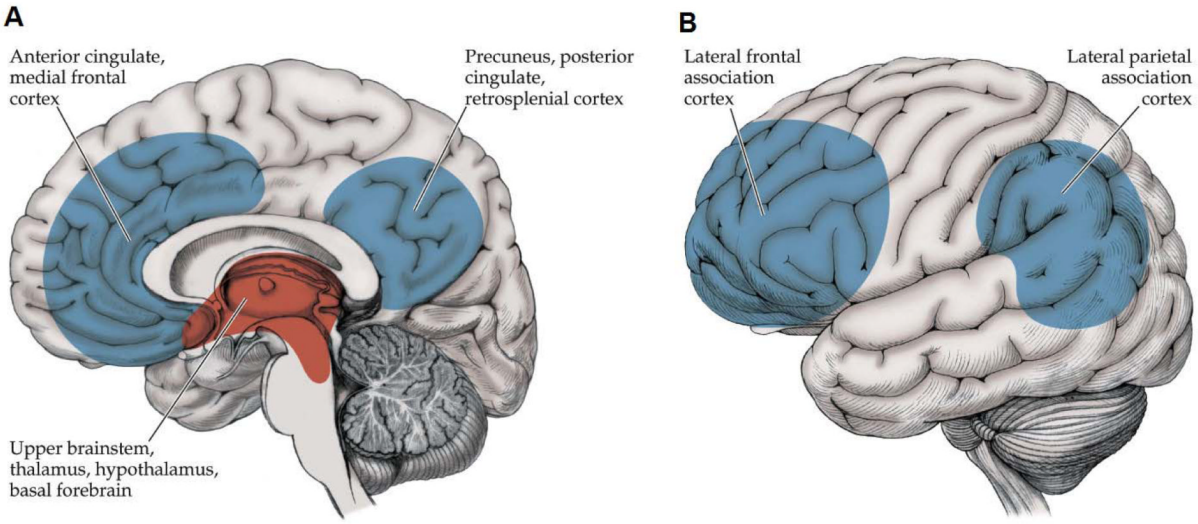

Figure 1. The consciousness system

Anatomical structures known to regulate the level of consciousness. **A.** Medial view. **B.** Lateral view. Cortical components of the consciousness system (shown in blue) include the medial and lateral fronto-parietal association cortex, anterior and posterior cingulate, precuneus and retrosplenial cortex. Subcortical components (shown in red) include the basal forebrain, hypothalamus, thalamus and upper brainstem activating systems. Note that other circuits such as the basal ganglia and cerebellum may also participate in attention and other aspects of consciousness. (Reproduced from Blumenfeld H. Neuroanatomy through clinical cases. 2nd edition. Sunderland (MA): Sinauer Associates; 2010 with permission).

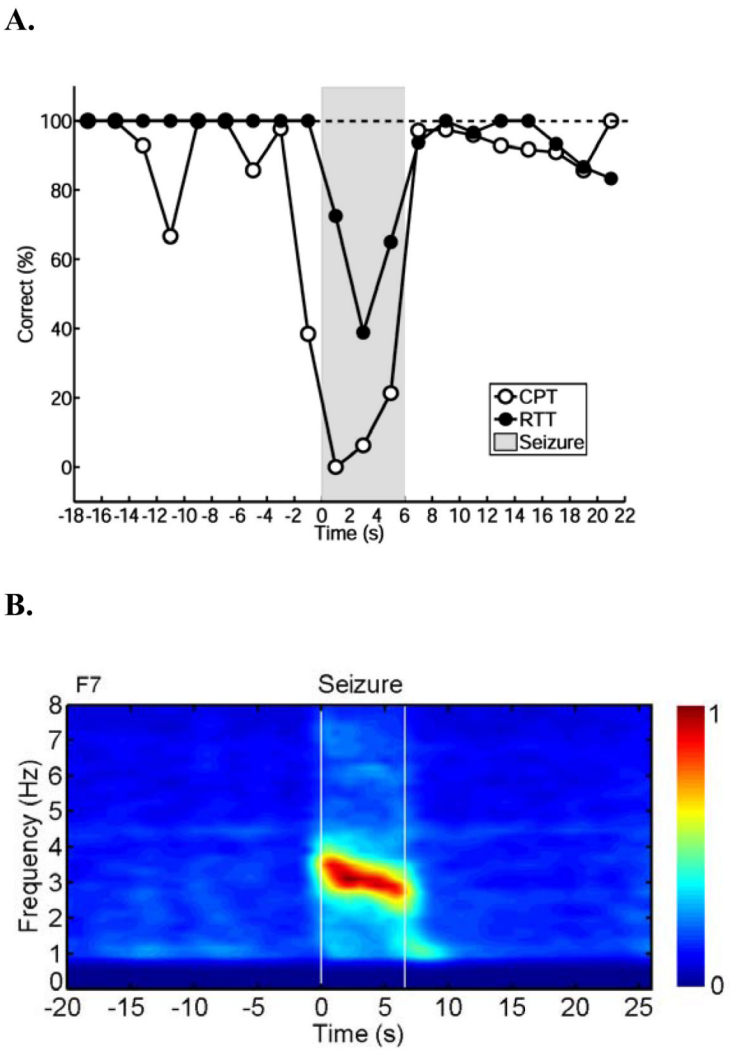

Figure 2. Absence seizures: transient behavioral and EEG changes

A. Behavioral impairment during seizures. Percent correct responses are shown over time (2s time bins) before, during and after seizures (shaded region). Performance on the more difficult continuous performance task (CPT) declined rapidly for letters presented just before seizure onset and recovered quickly after seizures end. Impaired performance on the simpler repetitive tapping task (RTT) task was more transient than on CPT, did not begin until after seizure onset, and was less severely impaired during seizures than the CPT task ($F = 15.3$, $P = 0.017$; ANOVA). Results are based on a total of 53 seizures in 8 patients.

B. EEG signal power changes abruptly at beginning and end of seizures. Average time-frequency dynamics of spike-wave discharges are shown for EEG channel F7. A total of 54 seizures (9 patients) were analyzed.

(Reproduced with permission from Bai X etal, 2010, Journal of Neuroscience 30:5884-5893.)

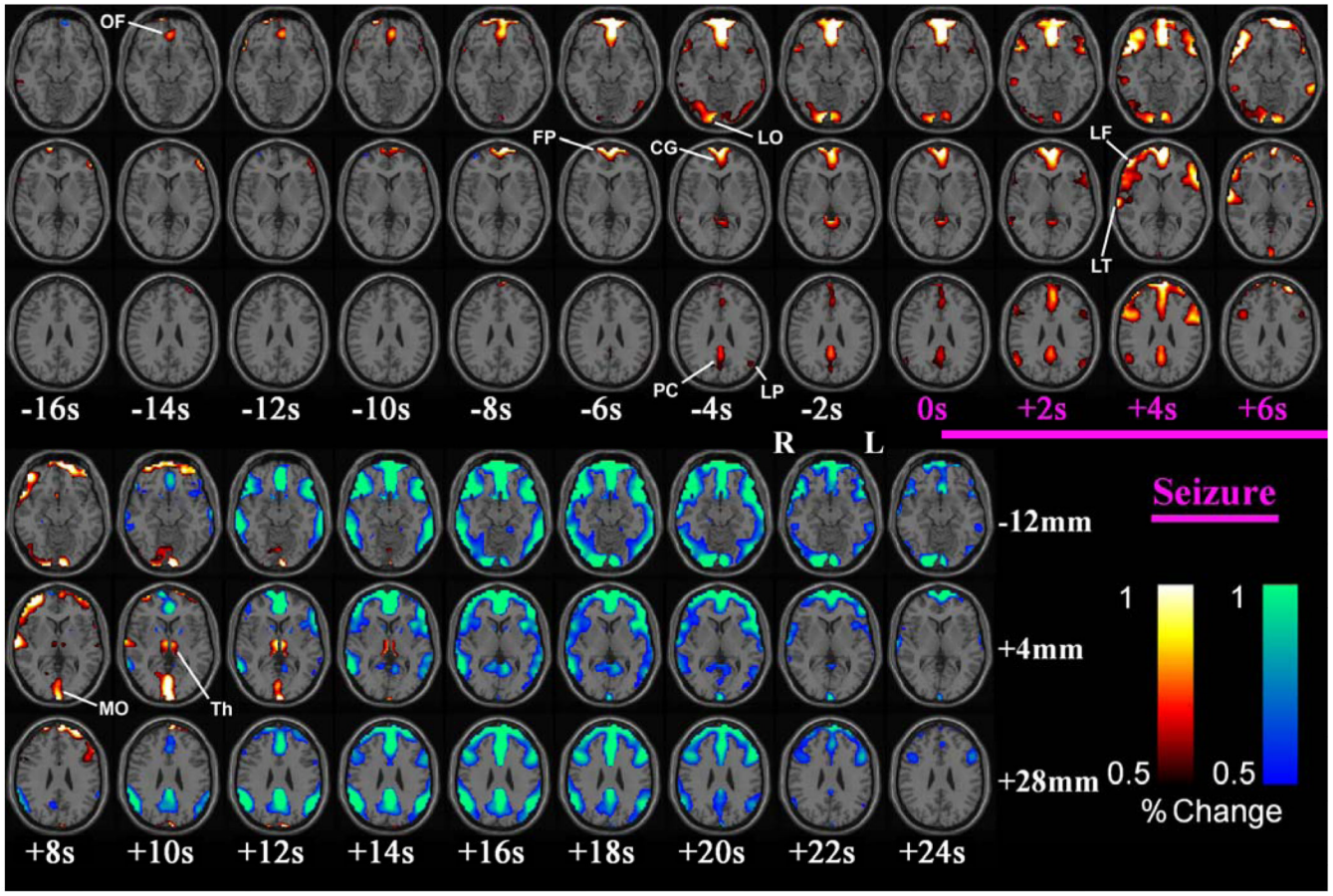

Figure 3. Absence seizures: early and late fMRI changes in cortical-subcortical networks

fMRI percent change increases (warm colors) and decreases (cool colors) are shown, with a display threshold of 0.5% The ictal time period of seizures was scaled to 6.6s (mean seizure duration), and the preictal, ictal, and postictal time periods temporally aligned across all seizures. Early fMRI signal increases were seen well before seizure onset (0s) in medial orbital frontal (OF), frontal polar (FP), cingulate (CG), lateral parietal (LP), precuneus (PC), and lateral occipital (LO) cortex. After seizure onset, fMRI increases progressed to also involve lateral frontal (LF) and temporal (LT) cortex. Following the end of seizures, fMRI increases were seen in the medial occipital (MO) cortex, and lastly in the thalamus (Th). fMRI signal decreases occurred later and continued well after seizure end, showing initial strong involvement of fronto-parietal association cortex. Data are from group analysis of 51 seizures in 8 patients. (Reproduced with permission from Bai X etal, 2010, Journal of Neuroscience 30:5884-5893.)

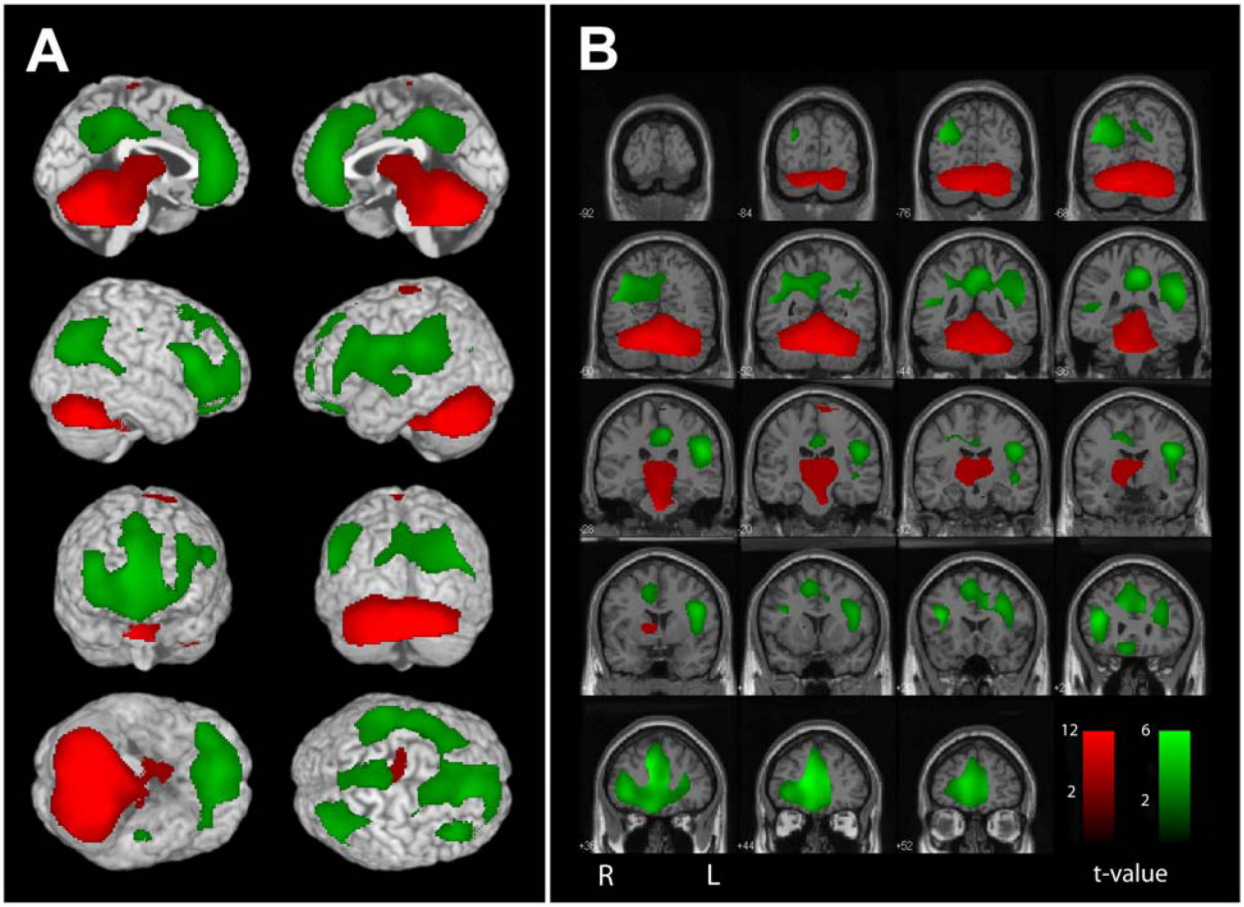

Figure 4. Generalized tonic-clonic seizures: network changes in cerebellum, thalamus and cortex
Positive (red) and negative (green) correlations are shown between cerebellum and other brain regions. **A.** Surface rendering. **B.** Coronal sections. Significant positive correlations with cerebellar blood flow changes were found in the upper brainstem tegmentum and thalamus. Negative correlations were found with the bilateral fronto-parietal association cortex, anterior and posterior cingulate and precuneus. Statistical parametric mapping (SPM) analysis was across patients (n=59) with extent threshold, k = 125 voxels (voxel size = 2×2×2 mm), and height threshold, p = 0.01.
(Reproduced with permission from Blumenfeld H et al, 2009, Brain 132:999-1012.)

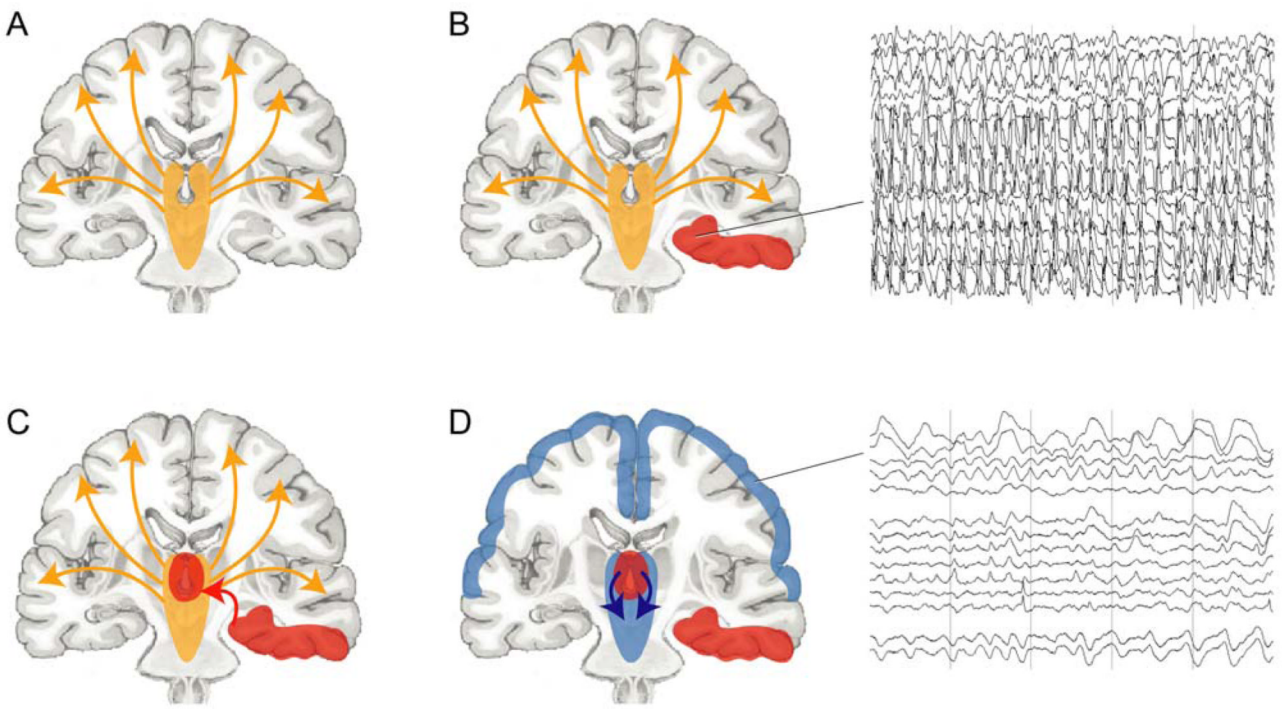

Figure 5. Network inhibition hypothesis for impaired consciousness in temporal lobe complex partial seizures

A. Under normal conditions, the upper brainstem-diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. **B.** A focal seizure involving the mesial temporal lobe. If the seizure remains confined, then a simple-partial seizure will occur without impairment of consciousness. Intracranial EEG recordings (inset) show fast polyspike activity in the temporal lobe. **C.** Spread of seizure activity from the temporal lobe to midline subcortical structures. Propagation often occurs to the contralateral mesial temporal as well (not shown). **D.** Inhibition of subcortical activating systems leads to depressed activity in bilateral fronto-parietal association cortex, and to loss of consciousness. Intracranial EEG recordings from fronto-parietal association cortex (inset) show slow wave activity resembling deep sleep. (A-D modified with permission from Blumenfeld and Taylor, 2003, *The Neuroscientist*, 9:301 – 310; B, D insets modified from Englot *et al.,* 2010, *Brain* 133(12): 3764 – 3777).

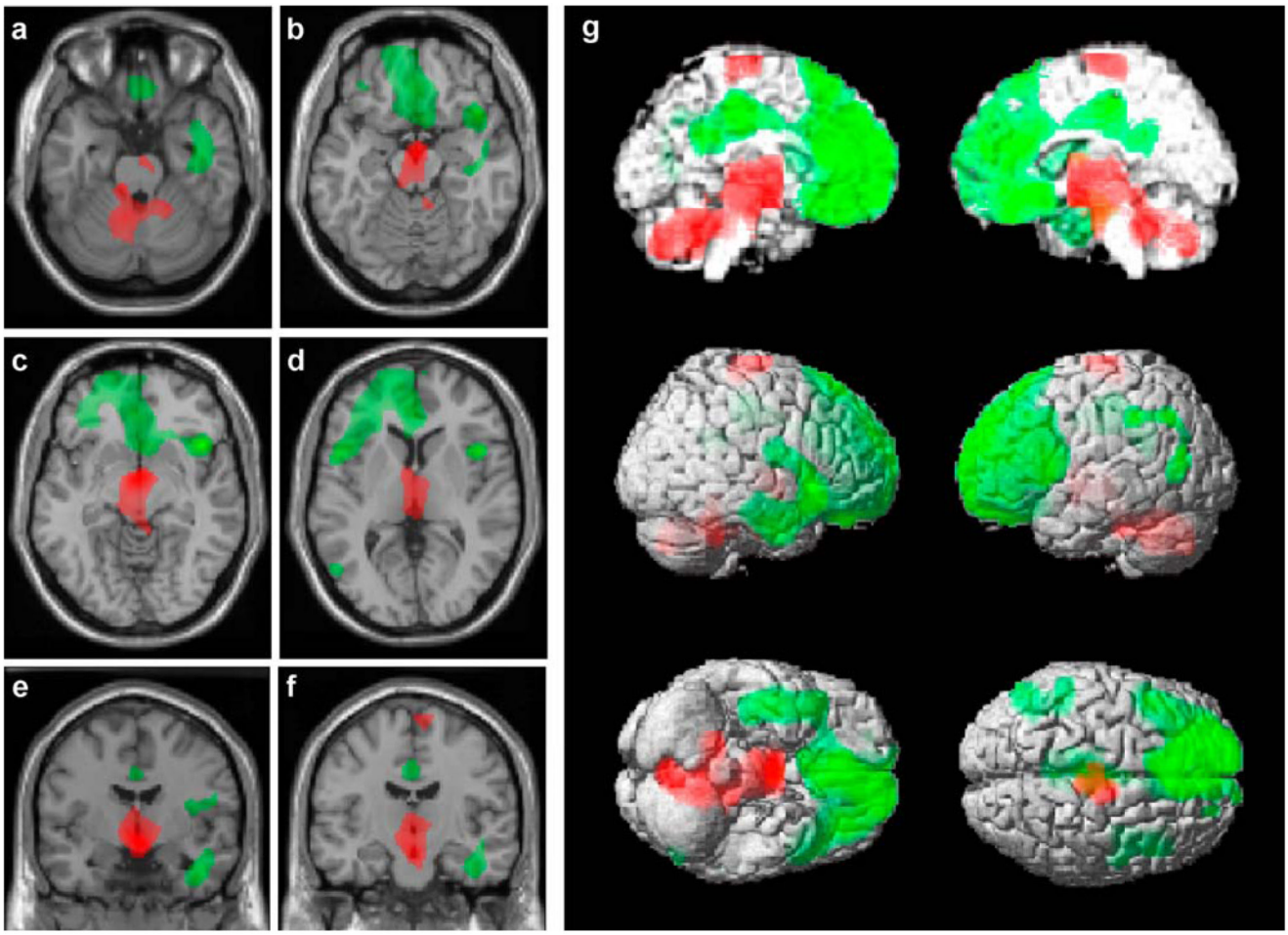

Figure 6. Complex partial temporal lobe seizures

Complex partial seizures arising from the temporal lobe are associated with significant cerebral blood flow increases and decreases in widespread brain regions. Statistical parametric maps depict SPECT increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain (combining patients with left and right onset seizures, n=10). Data are from >90s after seizure onset, when consciousness was markedly impaired. Note that at earlier times there were SPECT increases 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 blood flow increases in the bilateral midbrain, hypothalamus, medial thalamus, and midbrain. Decreases are seen in the bilateral association cortex. **G.** 3-dimensional surface renderings show increases mainly in the bilateral medial diencephalon, upper brainstem and medial cerebellum, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (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 et al, 2004, Cerebral Cortex 14:892-902.)

Table 1

Seizures and impaired consciousness: Summary of behavior, electrophysiology and neuroimaging findings

Seizure Type	Behavior	Electrophysiology	Neuroimaging
Absence seizures	Behavioral arrest typically 3-10 s with minor eyelid or hand movements and rapid return to baseline. Simple repetitive tasks can often continue during seizures.	Widespread bilateral 3-4 Hz spike-wave discharges with maximum amplitude in midline anterior frontal region and possibly precuneus. Animal models suggest focal bilateral onset with sparing of some regions.	fMRI shows increases in thalamus, but complicated early increases in some areas (e.g medial frontal cortex and precuneus) preceding EEG onset by several seconds, and later widespread fronto-parietal association cortex decreases lasting long after EEG end.
Generalized tonic-clonic seizures	Rigid tonic extension and clonic jerking of limbs usually lasting 1-2 minutes with profound unresponsiveness continuing into the post-ictal period.	High frequency polyspike discharge in tonic phase, rhythmic polyspike and wave in clonic phase, generalized suppression post-ictally. Human intra-cranial EEG shows some regions spared in “generalized” seizures.	Focal CBF increases in fronto-parietal association cortex and thalamus. Postictal CBF increases in cerebellum correlated with thalamic increases and fronto-parietal decreases. Animal model supports relatively focal bilateral cortical increases based on fMRI.
Complex partial (temporal lobe[a]) seizures	Behavioral arrest lasting 1-2 minutes commonly with oral and manual automatisms, and confusion in the post-ictal period.	High frequency discharge in medial temporal lobe, and sleep-like delta slow waves in fronto-parietal cortex. Slow waves continue postictally. Animal models suggest depressed subcortical arousal impacts cortex.	CBF increases in temporal lobe and medial diencephalon-upper brainstem with CBF decreases in fronto-parietal association cortex. Animal model shows fMRI increases in lateral septum and anterior hypothalamus; these regions may inhibit subcortical arousal.

[a]We focus here on complex partial seizures of temporal lobe origin, since less is known about the pathophysiology of impaired consciousness in complex partial seizures initiated from other cortical regions.