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Seizing upon Mechanisms for Impaired Consciousness

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Transient loss of consciousness associated with focal temporal lobe seizures is a complex phenomenon with life-threatening repercussions. In this issue of *Neuron*, Motelow et al. (2015) describe decreased cholinergic drive and suppressed subcortical arousal in seizures as a novel mechanism for impaired cortical function.

The controversial subject of consciousness dates back at least as far as the philosophical theories of Descartes in the 17th century. However, recent advances in neuroscience techniques to measure neural activity in both human and animal models have begun to shed new light on this ancient affair. Consciousness comprises the state of wakefulness, awareness, or alertness in which sentient beings function while not asleep. Although the exact mechanisms that mediate consciousness are poorly understood, studies correlating brain activity with states of consciousness have identified widespread bilateral cortical networks and subcortical arousal systems as key players. In temporal lobe epilepsy (TLE), complex-partial seizures are those associated with impaired consciousness both during and after the seizure, unlike simple-partial seizures, which do not disrupt consciousness. Investigators have long been bewildered as to how a focal seizure confined to the temporal lobe, a brain region not typically thought of as essential for consciousness, can nevertheless profoundly impair consciousness. Clearly other structures are involved.

Impaired consciousness, such as during deep sleep or coma, typically produces cortical slow-wave activity, increased cerebral blood flow, and reduced metabolism (Steriade et al., 1993; Cowan and Wilson, 1994; Haider et al., 2006). Similarly, impaired consciousness in complex-partial seizures is highly correlated with ictal and postictal slow-wave activity and abnormal increased cerebral blood flow in the upper frontal and parietal neocortices (Lieb et al., 1991; Blumenfeld et al., 2004a, 2004b), as well as brainstem and medial diencephalon (Lee et al., 2002; Blumenfeld et al., 2004b; Tae et al., 2005). Consistent with the results of electrophysiological and neuroimaging studies in human TLE, impaired consciousness (as measured by behavioral arrest) in rat during partial limbic seizures is associated with slow-wave activity, reduced neural activity, and decreased metabolism in the frontal cortex (Englot et al., 2008). Animal models of TLE have allowed detailed mechanistic study of the role of *subcortical* structures in impaired consciousness. For example, stimulation of the septum results in the appearance of cortical slow waves and behavioral arrest, whereas fornix lesions blocked seizures from reaching subcortical structures such as the septum and thalamus (Englot et al., 2009) and prevented cortical slow waves and the associated behavioral changes during seizures. Englot et al. concluded that activity in subcortical structures, in particular the septum, is required for ictal neocortical slow activity and behavioral arrest in partial seizures. Together, these previous animal studies have documented a remarkable correlation between reduced neural activity in the frontal cortex and subcortical structures and the impaired consciousness during complex partial seizures. However, the specific circuit mechanisms underlying impaired consciousness in complex partial epilepsy have been elusive, with the answer to the following question still unresolved: how might seizure activity in the temporal lobe lead to activation of these subcortical structures and result in neocortical dysfunction and impaired consciousness?

Various hypotheses for loss of consciousness during complex partial seizures have been proposed. One suggests that seizure-related impairment results from spread of ictal activity to bilateral temporal lobes (Inoue and Mihara, 1998). An alternate view is the "network inhibition hypothesis," which suggests that seizures spread from the temporal lobe to activate inhibitory subcortical structures that in turn deactivate frontal cortical regions necessary for the normal conscious state (Norden and Blumenfeld, 2002). However, this hypothesis relies on an unidentified major inhibitory component(s) within the poorly understood consciousness network and is based in part on a correlative, not causative, link between slow-wave activity and impaired consciousness.

In this issue, Motelow et al. bridge a gap in the network inhibition hypothesis and uncover novel mechanisms by which subcortical arousal circuits are depressed during focal seizures associated with impaired consciousness. Along with increased activity in the hippocampus, anterior hypothalamus, and lateral septum, the authors report depressed activity in the frontal cortex as well as subcortical arousal structures, including intralaminar thalamus and midbrain tegmentum. It is well established that withdrawal of acetylcholine signaling plays a critical role in cortical slow-wave activity observed during sleep and in depression of thalamic and cortical activity (Marrosu et al., 1995). Motelow et al. perform in vivo juxtacellular recordings and demonstrate a decrease in firing of all recorded cholinergic neurons within the pedunculopontine tegmental (PPT) nuclei and the basal forebrain, nuclei that indirectly (via thalamus) and directly activate the cortex, respectively, during

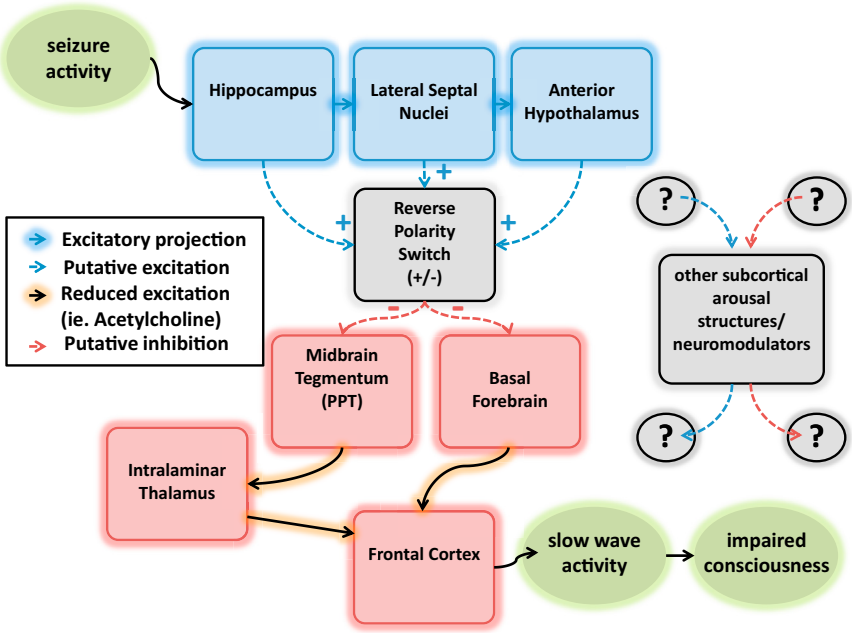

Figure 1. Adaptation of "Network Inhibition Hypothesis"
Seizure activity spreads from the hippocampus to activate lateral septal nuclei and anterior hypothalamus. Putative efferents from the aforementioned structure(s) activate an unknown reverse polarity switch, converting signal propagations from excitatory to inhibitory. Activation of the unknown reverse polarity switch results in reduced cholinergic drive from subcortical arousal structures (PPT) to intralaminar thalamus and basal forebrain to frontal cortex. The reduced cholinergic transmission directly and indirectly triggers slow-wave activity in the frontal cortex and impairs consciousness. What remains unknown are the roles of other subcortical arousal systems likely to contribute to this network.

seizure activity. Importantly, in contrast to cholinergic neurons, noncholinergic neurons in both regions displayed mixed changes in firing rates during seizures. A decrease in extracellular choline concentration measured in both the cortex and thalamus, targets of cholinergic projections from PPT and basal forebrain, was also detected during limbic seizures. These results provide the first and only solid evidence that cholinergic transmission from the subcortical arousal structures to the thalamus and cortex is impaired during seizures.

Furthermore, these results motivate new and exciting questions as to the role of the depressed cholinergic inputs to thalamus and cortex during seizures with impaired consciousness. For example, is the reduced cholinergic activity required and sufficient for the seizure-induced impaired consciousness? If so, can cholinergic activity be targeted to prevent impaired consciousness? In a very recent study, Glummadavelli et al. reduced cortical slowing and promoted behavioral arousal by electrically stimulating the downstream cholinergic targets in the intralaminar thalamus (Gummadavelli et al., 2014). Could stimulation of the PPT also reduce cortical slow-wave activity and enhance arousal?

The present study makes a critical contribution to the current network inhibition hypothesis. However, there are several key components missing in this hypothetical model. The neural basis for the "reverse polarity switch," responsible for converting the seizure-related activation of brain structures (i.e., hippocampus, anterior hypothalamus, and lateral septum) into suppression of subcortical arousal structures (i.e., PPT, intralaminar thalamus, and basal forebrain) and, ultimately, frontal cortex, remains unknown (Figure 1). Characterizing the circuit mechanism(s) responsible for the suppressed cholinergic neurons in the PPT and the basal forebrain is one possible route to unveil the identity of the reverse polarity switch (Figure 1). The lateral septal nuclei display increased neural activity during seizures and consist mainly of inhibitory neurons that send widespread projections to a plethora of subcortical structures, making it an attractive candidate for suppression of the subcortical arousal system. Although the septum has been shown to be important for neocortical slow waves and arousal during seizures, the direct downstream targets important for these activities have not been identified. Lastly, the subcortical arousal system is composed of several components, which begs the question: What other structural/neurochemical components are modulated during seizure activity, and what is their role in cortical dysfunction and consciousness?

The discovery that cholinergic depression in subcortical arousal structures is correlated with focal seizures paves the way for future experiments to dissect the processes involved in impaired consciousness. As with many studies of experimental epilepsy, future studies that elucidate mechanisms involved in cortical dysfunction and epilepsy-related impairment of consciousness will undoubtedly give insight into the basic mechanisms and circuitry involved in normal brain activity, such as consciousness itself. Although seizure prevention is the primary goal of epilepsy research, therapeutic intervention aimed to prevent comorbidities, including consciousness impairment, is a critically important goal for enhancing the quality of life for those living with epilepsy.

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Uncovering a Missing Link in Anterior Cingulate Research

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Research on human anterior cingulate cortex has long indicated a role in detecting conflict. However, efforts to find parallel effects in non-human primates were surprisingly unsuccessful. Here, Ebitz and Platt (2015) break the resulting impasse by uncovering what appear to be conflict-related signals in monkey cingulate cortex.

In order to get anything done, especially in the present technological age, it is necessary to resist distraction. If you want to buy a book online, you must struggle against having your attention hijacked by those disturbingly relevant sidebar ads. If you sit down with the resolve to finally write that paper, you may end up spending a significant portion of your time restraining the impulse to just quickly peek at your email or social media feed. Given the ubiquity of such distraction and its impact on our ability to sustain goal-directed behavior, it has been a major aim of cognitive neuroscience to understand how the brain regulates conflicts between goals and distractors.

Human neuroimaging research has consistently implicated the dorsal anterior cingulate cortex (dACC) in situations that involve conflict between a goal-directed response and a distracting alternative. For instance, if one is shown the stimulus GREEN in a red font and is asked to name the display color, this triggers greater dACC activity than when the word presented does not itself name a color (e.g., GRAIN) (Cole et al., 2009; Shackman et al., 2011). Moreover, such activity has been shown to predict subsequent increases in cognitive control, manifesting as an intensified focus on the task (in the foregoing example, an increased attention to stimulus color over word identity). Such findings led to the theory that the dACC may monitor for conflict, alongside other signals, in order to guide adaptive adjustments in control (Botvinick et al., 2001).

Over the years, a number of challenges have been raised to the notion of conflict monitoring in dACC. A majority of these have eventually been disconfirmed or else accommodated within a broader framework that still involves conflict (Botvinick, 2007; Shenhav et al., 2013). However, one formidable difficulty was raised by single-unit recording studies in monkeys, which at least initially failed to detect conflict-related signals in dACC (see Cole et al., 2009). At first, it seemed possible that the conflict responses observed in humans using fMRI and EEG might not reflect actual single-neuron spiking activity, but instead something more epiphenomenal. But no: Sheth and colleagues (2012) found conflict-related activity in the same region of human dACC using both fMRI and single-unit recordings and further showed that lesioning this region impaired conflict-related control adjustments. In view of such results, it seemed that human and monkey research might simply be incommensurable, perhaps reflecting fundamental differences in cingulate function between species.

However, recent findings have significantly altered the lay of the land. First, a study by Amemori and Graybiel (2012) offered hints of preserved conflict signaling in monkeys, showing that conflict between similarly valued choices (decision conflict) was encoded in a medial frontal region anterior to dACC. And now, as reported in the present issue, a study by Ebitz and Platt (2015) provides evidence for conflict signaling within monkey dACC itself, in a situation involving interference between goals and distractors.

Apparent Conflict Signals in Monkey dACC

In the experiment by Ebitz and Platt, monkeys performed a task that required them to saccade to a visual target on the left or right side of a computer display. On most trials, this target was accompanied by a