

FEELING OUT THE ELEPHANT IN THE ROOM: WHY DO TEMPORAL LOBE SEIZURES CAUSE UNCONSCIOUSNESS?

Remote Effects of Focal Hippocampal Seizures on the Rat Neocortex. Englot DJ, Mishra AM, Mansuripur PK, Herman P, Hyder F, Blumenfeld H. *J Neurosci* 2008;28(36):9066–9081. Seizures have both local and remote effects on nervous system function. Whereas propagated seizures are known to disrupt cerebral activity, little work has been done on remote network effects of seizures that do not propagate. Human focal temporal lobe seizures demonstrate remote changes including slow waves on electroencephalography (EEG) and decreased cerebral blood flow (CBF) in the neocortex. Ictal neocortical slow waves have been interpreted as seizure propagation; however, we hypothesize that they reflect a depressed cortical state resembling sleep or coma. To investigate this hypothesis, we performed multimodal studies of partial and secondarily generalized limbic seizures in rats. Video/EEG monitoring of spontaneous seizures revealed slow waves in the frontal cortex during behaviorally mild partial seizures, contrasted with fast polyspike activity during convulsive generalized seizures. Seizures induced by hippocampal stimulation produced a similar pattern, and were used to perform functional magnetic resonance imaging weighted for blood oxygenation and blood volume, demonstrating increased signals in hippocampus, thalamus and septum, but decreases in orbitofrontal, cingulate, and retrosplenial cortex during partial seizures, and increases in all of these regions during propagated seizures. Combining these results with neuronal recordings and CBF measurements, we related neocortical slow waves to reduced neuronal activity and cerebral metabolism during partial seizures, but found increased neuronal activity and metabolism during propagated seizures. These findings suggest that ictal neocortical slow waves represent an altered cortical state of depressed function, not propagated seizure activity. This remote effect of partial seizures may cause impaired cerebral functions, including loss of consciousness.

COMMENTARY

The biological basis of consciousness is a mystery—for centuries, debated by philosophers and neuroscientists alike. In a clinical context, loss of awareness is assumed to require diffuse brain dysfunction, involving either bilateral cerebral hemispheres or the reticular activating system. A notable exception to this rule are patients with temporal lobe epilepsy who may lose consciousness despite clear evidence from EEG and ictal SPECT that the seizures remain localized to one temporal lobe. One promising hypothesis is that focal hippocam-

pal seizures can somehow cause a diffuse disruption of cerebral function that may not be apparent on routine scalp EEG. This idea is supported by ictal SPECT imaging studies showing reduced frontal lobe perfusion during temporal lobe seizures with loss of consciousness, but not during seizures with retained awareness (1). Moreover, intracranial EEG monitoring has shown nonrhythmic, bifrontal, slow activity during temporal lobe seizures (2). However, while this slowing suggests diffuse cerebral dysfunction, neocortical seizures sometimes can have a similar disorganized appearance, particularly when the recording electrode is not placed immediately adjacent to the seizure focus. In an effort to discover how temporal lobe seizures produce loss of awareness, Englot et al. used a variety of complementary methods in rodent models of epilepsy to argue that

hippocampal seizures disrupt bilateral frontoparietal cortical function.

The authors build on previous patient and animal studies by defining two distinct electrographic patterns that correspond to specific behavioral seizure types. Using intracranial EEG recordings of rats that were rendered epileptic following pilocarpine-induced status epilepticus, the authors found that all spontaneous seizures began with rhythmic electrical activity in the hippocampus but differed in frontal lobe involvement. Severe behavioral seizures (Racine stage ≥ 2), with head nodding, forelimb clonus, rearing, and/or falling, were all associated with rhythmic fast electrical activity that spread outside the temporal lobe as they evolved. The authors referred to these events as secondarily generalized seizures. In contrast, partial limbic seizures were defined as more subtle (Racine stage 0 or 1), with behavioral arrest and/or mouth and facial movements associated with irregular bifrontal slow activity. Because the frontal slowing was similar to patterns seen in the postictal phase or during normal sleep, the authors speculated that the activity might represent cerebral dysfunction rather than ictal involvement of the frontal lobes.

In order to explore further the significance of these electrographic changes, a model with more predictable seizures was needed. Toward that end, Englot et al. studied rats that had undergone electrical hippocampal kindling, which has the advantage of allowing predictably evoked hippocampal seizure onset and severity, while at the same time, avoiding the diffuse injury often seen after pilocarpine-induced status epilepticus. As expected, local field potential changes recapitulated the intracranial EEG findings reported in pilocarpine-treated rats. Extracellular multiple-unit activity was measured simultaneously to better assess the activity of individual neurons throughout these events. During a hippocampal seizure, the multiple-unit activity within the hippocampus switched from small individual units to large, rhythmic population spikes, suggesting a somewhat synchronous firing within groups of neurons. A very similar pattern was seen in the multiple-unit activity of the frontal lobes in the course of a secondarily generalized seizure. In contrast, during partial limbic seizures, neuronal firing in the frontal lobes persisted as single units, with periods of reduced firing that were coincident with the slow waves seen in the local field potentials. This firing pattern also was noted to be remarkably similar to the activity present in the postictal state or under deep anesthesia.

While electrophysiological studies allow precise temporal and spatial resolution, those same properties make the techniques prone to spatial undersampling. To assess regional changes in brain function during a seizure, Englot and colleagues performed fMRI imaging in lightly anesthetized/paralyzed, kindled rats. Secondarily generalized seizures demonstrated increased BOLD signals in a number of areas, including

the neocortex, hippocampus, septal area, and thalamus. In contrast, while partial limbic seizures also were associated with increased BOLD signals in many of the same brain regions, there was a distinctly reduced BOLD signal in the frontal cortex that coincided with the areas of electrographic slowing. Increases or decreases in BOLD signals are generally thought to reflect the level of neuronal activity, but this may not always be the case. This interpretation is predicated on the assumption that increased neuronal activity results in increased blood flow beyond that needed for local oxygen consumption, thereby leading to areas of increased blood oxygenation. However, at times, this relationship is otherwise disrupted, possibly because the metabolic demands exceed the vascular capacity (3). Thus, to independently assess blood flow, laser Doppler flow measurements were used to confirm that there was increased frontal perfusion in secondarily generalized seizures but reduced perfusion in partial limbic seizures. By combining the fMRI and laser Doppler flow data, the authors were able to calculate regional changes in oxygen metabolism and found reduced oxygen consumption in the frontal lobes during partial limbic seizures.

The work of Englot et al. strongly suggests that ictal activity in one temporal lobe disrupts frontal lobe function bilaterally. However, the physiological mechanisms underlying these changes remain unknown, and these studies do not completely rule out a possible spread of seizure activity to the frontal lobes. Ictal spread via the midline thalamus has been described in a few animal models of temporal lobe seizures, but usually only in more severe (≥ 3 Racine stage) limbic seizures (4). Furthermore, while BOLD signal changes by themselves are subject to interpretation, previous work with interictal PET and ictal SPECT suggests a similar distribution of reduced perfusion and metabolism in temporal lobe epilepsy (1).

A vascular steal of blood flow from the frontal lobes also could explain the imaging findings and electrographic slowing, but it is unlikely for a number of other reasons. First, the two brain regions lie in different vascular territories, and there is sparing of the nearby sensorimotor areas. Second, the changes in local blood flow are actually very small compared with the brain's overall hemodynamic reserve. Furthermore, reduced BOLD signal in the frontal lobes continues to be depressed during the postictal period while temporal lobe hyperperfusion has resolved.

Another possible interpretation for the Englot et al. findings would be some form of synaptically mediated inhibition. While a classical surround inhibition is unlikely, given that nearby sensorimotor and temporal neocortical activities are unaffected, recent anatomical studies have suggested the possibility of more long-range interactions between the mesial temporal lobe and the neocortex. For example, there are direct projections from the subiculum to the anterior thalamus and other rostromedial areas via the fornix (5). In addition, smaller sets

of projections from CA1 to the anterior thalamus (6) as well as directly from CA1 to the retrosplenium, cingulate, and orbital cortex have been described recently (7). The neurochemical identity of these temporal lobe projections is unknown, so currently it is unclear whether they include inhibitory neurotransmitters or are excitatory fibers with the potential of activating local neocortical inhibitory circuits. Alternatively, projections from the temporal lobe might disrupt the tonic excitation that the cortex normally receives from certain components of the reticular activating system, such as the cholinergic neurons of the basal forebrain or the histaminergic projections from the hypothalamic mammillary bodies (6).

So, how do these physiologic changes lead to loss of awareness? The answers may lie within the specific cortical regions that are disrupted by temporal lobe seizures in both animal models and patients, primarily the dorsal mesial brain regions in the frontal and parietal lobes, including the mesial frontal, cingulate, precuneus (mesial parietal), and retrosplenium cortices as well as the dorsolateral frontal cortices (8). These brain regions continuously process both internal and external stimuli, allowing individuals to respond quickly to environment changes in the context of their current physiological and emotional state. These areas have high resting metabolic rates, which are transiently decreased during externally directed attention (9). Thus, disruption of this default-mode network is thought to interrupt the continuous monitoring of oneself and the environment that subserves normal awareness.

How do changes occurring in temporal lobe seizures compare with those found in other causes of altered awareness, such as absence epilepsy or sleep? Despite different electrographic patterns, both absence and temporal lobe seizures produce very similar fMRI changes, with reduced BOLD signal in the mesial frontal and parietal cortices and/or increased BOLD signal in the thalamus (10,11). In contrast, while Englot et al. note that the frontal electrographic activity slowing is similar during temporal lobe seizures and sleep, functional imaging changes seen with sleep are in many ways the opposite of those of partial limbic seizures. Sleep produces increased BOLD and magnetoencephalogram signals in the frontal lobes, along with reduced BOLD signals in the thalamus (11,12). So, are the electrographic or perfusion changes telling us anything about the mechanisms for loss of awareness, or are they simply epiphenomena that are specific for each model but unrelated to consciousness, per se? Given the complex network of similarities and differences, it is easy to feel like the proverbial blind man trying to determine the nature of an elephant by only feeling its leg. Part of the problem may involve overly simplistic nomenclature sometimes used in these studies. While it may be convenient to refer to changes in brain function as “activation”

or “deactivation,” these terms gloss over the fact that a brain region could have an increased electrographic or BOLD activity and still be unable to serve its normal function.

Epilepsy is a network phenomenon that involves dysfunctional activity that spreads to adjacent areas and evolves over time. The work of Englot et al. add another dimension to this issue by reporting that a focal temporal lobe seizure can disrupt bilateral frontal lobe function, without actually spreading to those areas. Their work highlights the fact that, in addition to the temporal and spatial changes, gaining a deeper understanding of epilepsy will require exploring how metabolic/physiological properties spread and evolve during a seizure. Each technique may explore limited aspects of epilepsy, but by combining areas of expertise, it may be possible to begin to comprehend the true nature of the beast. While these seemingly disparate studies may seem to compare apples and oranges, perhaps investigators are closer to comparing trunks and tails.

by Andre H. Lagrange, MD, PhD

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