What Is a Seizure Network? Long-Range Network Consequences of Focal Seizures

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Abstract

What defines the spatial and temporal boundaries of seizure activity in brain networks? To fully answer this question a precise and quantitative definition of seizures is needed, which unfortunately remains elusive. Nevertheless, it is possible to ask under conditions where clearly divergent patterns of activity occur in large-scale brain networks whether certain activity patterns are part of the seizure while others are not. Here we examine brain network activity during focal limbic seizures, including diverse regions such as the hippocampus, subcortical arousal systems and fronto-parietal association cortex. Based on work from patients and from animal models we describe a characteristic pattern of intense increases in neuronal firing, cerebral blood flow, cerebral blood volume, blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) signals and cerebral metabolic rate of oxygen consumption in the hippocampus during focal limbic seizures. Similar increases are seen in certain closely linked subcortical structures such as the lateral septal nuclei and anterior hypothalamus, which contain inhibitory neurons. In marked contrast, decreases in all of these parameters are seen in the subcortical arousal systems of the upper brainstem and intralaminar thalamus, as well as in the fronto-parietal association cortex. We propose that the seizure proper can be defined as regions showing intense increases, while those areas showing opposite changes are inhibited by the seizure network and constitute long-range network consequences beyond the seizure itself. Importantly, the fronto-parietal cortex shows sleep-like slow wave activity and depressed metabolism under these conditions, associated with

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H.E. Scharfman and P.S. Buckmaster (eds.), *Issues in Clinical Epileptology: A View from the Bench*, Advances in Experimental Medicine and Biology 813, DOI 10.1007/978-94-017-8914-1_5,

impaired consciousness. Understanding which brain networks are directly involved in seizures versus which sustain secondary consequences can provide new insights into the mechanisms of brain dysfunction in epilepsy, hopefully leading to innovative treatment approaches.

Keywords
Epilepsy • Consciousness • Slow waves • Cortex • Thalamus • Sleep • Hippocampus • Pedunculopontine tegmental nucleus • Acetylcholine • Brainstem • Arousal

5.1 Introduction

Seizures are usually defined as an abnormal pattern of neuronal activity which includes excessive synchrony and high frequency firing of neurons. As in most definitions, the obvious cases are easy to recognize. However, in reality there are no distinct boundaries for precisely when neuronal activity become sufficiently synchronous or intense to be considered a seizure. The situation is complicated further by the fact that seizures occur in neuronal networks, which have both local and long-range effects. Network interactions give rise to abnormal activity in local circuits, but in some cases can also influence remote brain regions. Are these remote network changes part of the seizure proper, or are they "side effects" caused by the seizure but not directly involved in the seizure network? To answer this question it is necessary to identify characteristic features that are seen in seizure activity, and to then determine if these same features are present in the remote network regions. If similar characteristic features are present, then the remote regions are likely to be involved in propagation of the seizure itself. If the activity in the remote regions differs drastically from seizure activity, and instead resembles other well-known patterns of non-seizure brain activity (such as coma or sleep), then the activity in the remote region could be considered outside the seizure network, although influenced by it.

Temporal lobe seizures provide a concrete example of these local and long-range network phenomena. Locally, temporal lobe seizures produce high frequency rhythmic discharges. At the same time remote regions of the fronto-parietal association cortex exhibit 1–3 Hz slow wave activity resembling coma, sleep or encephalopathy [1–3]. Is this slow wave activity part of the seizure, or is it a distinct state of brain activity caused by the seizure? Here we will examine the detailed characteristics of these remote changes in neocortical networks during focal limbic seizures in both patients and in animal models, and also potential mechanisms for these phenomena. We conclude that these remote effects on neocortical networks are best considered outside the seizure network but strongly influenced by it. Analogous to post-ictal depression, which is closely related to and caused by the seizure itself but occurs at a different time, neocortical slow wave activity is closely related to and caused by focal limbic seizures but occurs in a different space.

5.2 Clinical Data

Intracranial recordings from patients with temporal lobe epilepsy show characteristic low voltage fast activity evolving into rhythmic polyspike-and-wave discharges in the medial temporal lobe limbic circuits, often extending into the lateral temporal cortex (Fig. 5.1c). Simultaneously, remote regions of the frontal and parietal association cortex often show 1–3 Hz slow wave activity (Fig. 5.1d). This ictal neocortical slow wave activity has been interpreted as a propagation pattern in temporal lobe epilepsy [1]. However, several features of the fronto-parietal slow wave activity make it likely that this is a distinct,

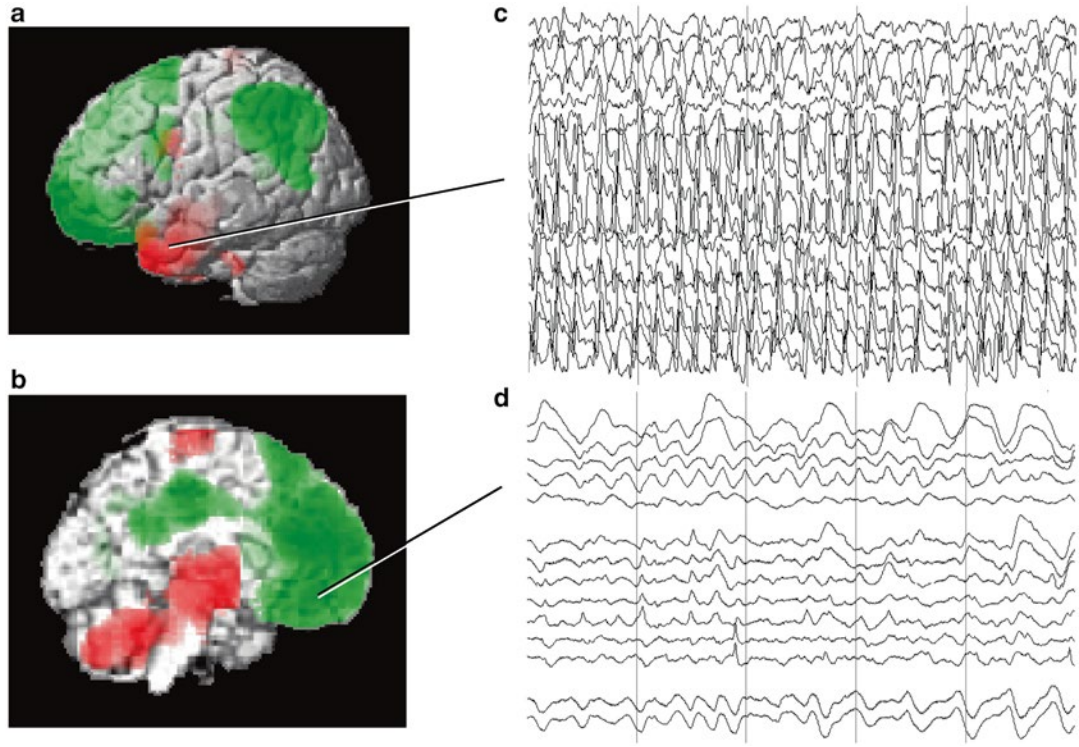

Fig. 5.1 Local and long-range network effects in temporal lobe complex partial seizures. (**a**, **b**) Group analysis of SPECT ictal-interictal difference imaging during temporal lobe seizures. CBF increases (*red*) are present in the temporal lobe (**a**) and in the medial thalamus (**b**). Decreases (*green*) are seen in the lateral fronto-parietal association cortex (**a**) and in the interhemispheric frontoparietal regions (**b**). (**c**, **d**) Intracranial EEG recordings from a patient during a temporal lobe seizure. High frequency polyspike-and-wave seizure activity is seen in the temporal lobe (**c**). The orbital and medial frontal cortex (and other regions, EEG not shown) do not show polyspike activity, but instead large-amplitude, irregular slow rhythms resembling coma or sleep (**d**). *Vertical lines* in (**c**) and (**d**) denote 1-s intervals. Note that the EEG and SPECT data were from similar patients, but were not simultaneous, and are shown together here for illustrative purposes only ((**a**, **b**) Modified from Blumenfeld et al. [2] with permission. (**c**, **d**) Modified from Englot et al. [3] with permission)

remote network effect rather than simply seizure propagation, as we discuss below.

Recent work with multiunit recordings in human intracranial EEG has raised new questions about the definition of seizure activity vs. associated changes in surrounding regions. Schevon and colleagues showed that high frequency firing of neurons is highly localized in human seizures [4]. Accompanying local field potential changes measured by conventional intracranial EEG extend over a greater region, but may represent mainly synaptic activity without major changes in local firing of neurons [4]. Whether recording neuronal firing or local field potentials, at least these changes in the vicinity of seizure onset show high frequency poly-spike activity characteristic of seizure physiology. In contrast, the slow wave activity occurring in distant fronto-parietal regions during temporal lobe seizures occur at a very different frequency (1–3 Hz) from ictal temporal lobe polyspike discharges (broad band >8 Hz) (Fig. 5.1c, d) [2, 3]. Seizure activity on intracranial EEG can be defined as high frequency discharges. Although scalp EEG often exhibits rhythmic theta or delta-frequency slow waves during local seizures [5] direct recording of seizure activity with intracranial electrodes inevitably shows high frequency discharges in these same regions. Therefore, when only slow wave activity is seen in a region *without* high frequency discharges on

intracranial EEG, this likely does not represent seizures. As we discuss in the next section, detailed physiological studies from animal models further support this claim. Such slow wave activity seen in the fronto-parietal cortex during temporal lobe seizures is similar to cortical slow waves in deep sleep, coma or encephalopathy [6, 7]. In these states, cortical function and information processing is depressed, leading to impaired level of consciousness [8].

How does focal seizure activity in the temporal lobe lead to remote slow wave activity in the fronto-parietal association cortex? The anatomy and physiology of these changes differs from local "surround inhibition" described for focal cortical seizures [9, 10]. To affect distant lobes, long-range network interactions are required. Some initial clues for the mechanisms of these network changes have come from human cerebral blood flow (CBF) imaging with single photon computed tomography (SPECT) which, unlike fMRI, can be done successfully despite patient movement during seizures. As expected, ictal SPECT in temporal lobe seizures is associated with CBF increases in the temporal lobe (Fig. 5.1a). In addition, *decreases* are seen in frontal and parietal association cortex in the same regions which exhibit slow wave activity (Fig. 5.1a, b) [11–13]. Subcortical networks are also involved in temporal lobe seizures and SPECT imaging shows increases in the medial thalamus and midbrain (Fig. 5.1b) [13–16]. We found that the SPECT increases in the medial thalamus are correlated with the decrease in bilateral fronto-parietal cortex [13], suggesting a mechanistic link between subcortical changes and depressed cortical function in temporal lobe seizures. These long-range network changes in cortical and subcortical function are seen specifically in temporal lobe seizures with impaired consciousness [3, 13, 14, 17, 18]. In contrast, temporal lobe seizures without impaired consciousness are associated with localized seizure activity in the temporal lobe, without these long-range network changes [3, 13].

Based on these findings from patients, we proposed the *network inhibition hypothesis* to explain cortical dysfunction and impaired consciousness in temporal lobe seizures (Fig. 5.2) [19, 20]. Normal cortical function and consciousness is maintained by interactions between the cortex and subcortical arousal systems including the thalamus, brainstem and basal forebrain (Fig. 5.1a). Focal temporal lobe seizure activity in simple partial seizures does not have long-range network impact effects, so cortical function and consciousness are spared (Fig. 5.1b). In temporal lobe complex partial seizures, propagation to subcortical structures (Fig. 5.1c)—such as the anterior hypothalamus, lateral septum and other regions—inhibits subcortical arousal systems (Fig. 5.1d). This in turn removes cortical arousal leading to fronto-parietal slow wave activity and impaired level of consciousness. Note that according to this hypothesis, the cortical slow wave activity is not part of the seizure itself, but instead is a long-range network consequence of depressed subcortical arousal.

Further support for the network inhibition hypothesis has come from recent behavioral observations in patients [21–23]. The network inhibition hypothesis predicts that when focal seizures propagate to subcortical structures, this will cause severe and widespread cortical dysfunction. Therefore focal seizures are expected to usually be associated with either marked impairment of many cognitive functions due to depressed level of consciousness, or alternatively to spare most cognitive functions. In support of this hypothesis, we recently found that behavioral deficits in a wide range of verbal and non-verbal test items during partial seizures are bimodally distributed, such that most seizures either globally impair or spare cognition [21–24].

While human studies have provided clinically relevant correlations between physiology and behavioral changes, and suggest that ictal neocortical slow wave activity is distinct from direct seizure involvement, fundamental mechanistic studies are best performed in animal models. An experimental animal model could enable direct physiological measurements to determine if ictal neocortical slow wave activity is indeed distinct from seizure activity, and would allow further investigation of the mechanisms for this phenomenon.

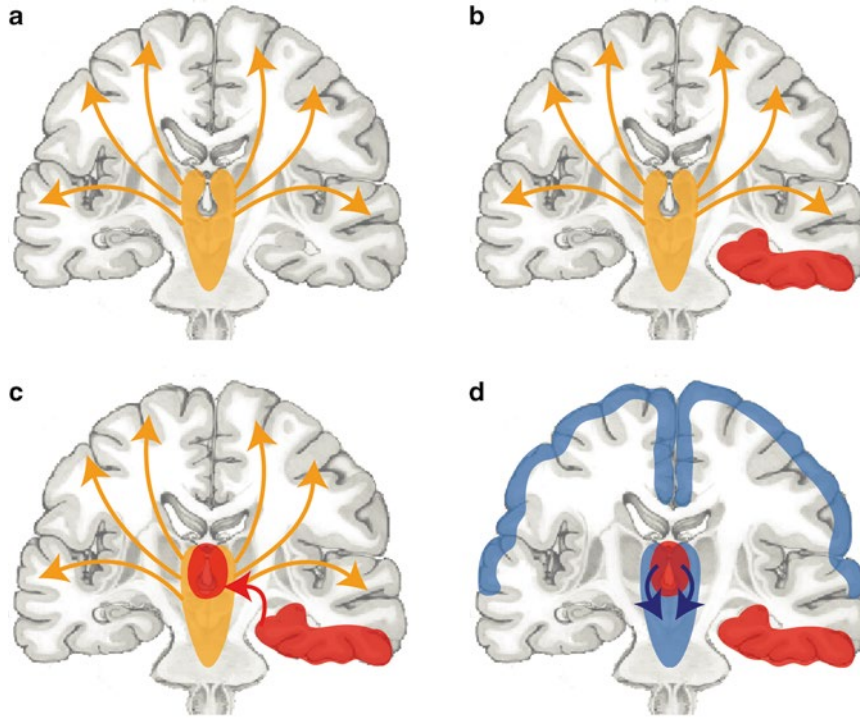

Fig. 5.2 Network inhibition hypothesis. (**a**) Under normal conditions, the upper-brainstem and diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. (**b**) A focal seizure involving the mesial temporal lobe. If the seizure remains localized, a simple partial seizure will occur without impairment of consciousness. (**c**) Seizure activity often spreads from the temporal lobe to midline subcortical structures and propagation often extends to the contralateral mesial temporal lobe (not shown). (**d**) Inhibition of subcortical arousal systems leads to depressed activity in bilateral frontoparietal association cortex and to loss of consciousness (Modified from Englot et al. [3] with permission)

5.3 Insights from an Experimental Animal Model

Rodent models of limbic seizures replicate many of the behavioral and physiological characteristics of human temporal lobe epilepsy [25–29]. We found that spontaneous focal limbic seizures in awake chronically epileptic rats following pilocarpine status epilepticus exhibited frontal neocortical 1–2 Hz slow wave activity and behavioral arrest similar to human complex partial temporal lobe seizures [30]. Ictal neocortical slow wave activity in this model resembled slow wave activity during natural slow wave sleep in the same animals. In contrast when limbic seizures secondarily generalized, recordings from the frontal cortex showed 9–12 Hz polyspike discharges characteristic of ictal activity, instead of slow waves.

Additional physiological and neuroimaging experiments were performed in an acute lightly anesthetized rat model in which seizures could be induced under controlled conditions [30]. Seizures were induced by brief 2 s stimulus trains at 60 Hz to the hippocampus under ketamine/xylazine anesthesia reduced to a stage where the cortex showed physiology near to the waking state. Under these conditions, induced partial limbic seizures produced frontal cortical slow wave activity similar to that seen in awake chronically epileptic rats. This acute model enabled detailed physiological measurements to distinguish ictal neocortical slow waves from seizure activity. Measurements from the hippocampus

during partial limbic seizures revealed dramatic increases in neuronal firing (multiunit activity), cerebral blood flow, blood oxygen dependent (BOLD) functional magnetic resonance imaging (fMRI) signals, cerebral blood volume, and cerebral metabolic rate of oxygen consumption [30]. In marked contrast, during the same seizures the frontal cortex showed *decreases* in all of these measurements along with slow wave activity. These findings provide strong evidence that ictal neocortical slow wave activity is a distinct physiological state, more closely resembling deep sleep or encephalopathy than seizure activity. Indeed, in the same animals slow wave activity under deep anesthesia induced similar changes in neuronal activity in the frontal cortex to those observed during partial limbic seizures.

Further evidence supporting a physiological distinction between ictal neocortical slow waves and seizure activity was provided by secondarily generalized seizures [30]. As in the awake model, when seizures propagated to the frontal cortex, instead of slow waves the frontal cortex showed high frequency polyspike discharges. Unlike the physiological decreases seen during slow wave activity, during secondary generalized seizures the frontal cortex showed marked *increases* in neuronal firing, cerebral blood flow, BOLD fMRI signals, cerebral blood volume, and cerebral metabolic rate of oxygen consumption.

In summary, direct measurements and neuroimaging during focal limbic seizures revealed very distinct physiology for hippocampal or cortical seizure activity which generally showed marked increases in all neurometabolic functions, contrasting markedly with ictal neurocortical slow activity which showed opposite changes, with decreases in all markers of neurometabolic function. These finding support the hypothesis that ictal neocortical slow wave activity is not part of the seizure itself, but instead is a consequence arising from long-range network effects producing altered physiology in regions remote from the seizure focus.

The next step has been to identify the network mechanisms by which seizure activity in the hippocampus may produce slow wave activity in the neocortex. As we have already discussed, data from patients suggest that focal hippocampal seizures may depress subcortical arousal systems, which could lead to cortical slow wave activity resembling deep sleep or coma (Fig. 5.2). Experiments from the rat model have provided further mechanistic details to support this hypothesis [31]. fMRI mapping during focal limbic seizures demonstrated that seizure activity propagates from the hippocampus to subcortical structures including the lateral septal nuclei, anterior hypothalamus, and medial thalamus. Subsequent direct neuronal recordings confirmed increased activity in these subcortical regions during seizures. The lateral septal nuclei and anterior hypothalamus contain gamma amino butyric acid (GABA)-ergic neurons with projections to subcortical arousal structures and are thus well positioned to inhibit cortical arousal during seizures. In support of this model, electrical stimulation of these regions in the absence of seizure activity was able to reproduce cortical slow wave activity and behavioral arrest [31, 32]. Cutting the fornix, the main route of seizure propagation from hippocampus to these subcortical structures, prevented cortical slow wave activity and behavioral arrest during seizures.

Additional studies have confirmed decreased subcortical arousal during focal limbic seizures, specifically in the cholinergic arousal systems [32]. fMRI mapping during focal limbic seizures have shown decreased signals in the midbrain reticular formation, thalamic intralaminar nuclei and possibly the basal forebrain. Juxtacellular recordings from the pedunculopontine tegmental nucleus in the brainstem demonstrated decreased firing of identified cholinergic neurons during frontal cortical slow wave activity in focal limbic seizures [32]. In addition, amperometric measurements of choline signals as a surrogate marker of cholinergic neurotransmission showed decreases in both frontal cortex and intralaminar thalamus during focal limbic seizures, but not during secondarily generalized seizures. While it is likely that in addition to cholinergic arousal other subcortical arousal systems are also involved, these findings provide strong evidence that a well characterized subcortical arousal system is depressed during focal limbic seizures, resembling the decreased function seen in slow wave sleep.

5.4 Conclusions and Future Directions

Here we have examined the activity patterns in focal limbic seizures to ask the question: What is a seizure network? In this case, more specifically—which changes in activity during limbic seizures represent the seizure itself and which can be considered long-range network effects arising from, but physiologically distinct from seizure activity? Based on multi-modal measurements including direct recordings of neuronal activity, cerebral blood flow, and neuroimaging-based evaluation of neuroenergetics, we conclude that limbic seizure networks involve intense increases in activity in structures such as the hippocampus and subcortical regions including the lateral septum and anterior hypothalamus. As a long-range network consequence of this abnormal increased activity, there is also abnormal decreased activity in subcortical arousal systems including the brainstem, intralaminar thalamus and basal forebrain which causes the cortex to enter a state resembling deep sleep. These subcortical and cortical decreases in activity are not part of the seizure *per se* since they differ drastically from the increases typically associated with seizures. However, they are an important effect of the seizure network on other parts of the brain, and have a major clinical impact including impaired consciousness.

Important unanswered questions remain about these seizure networks. For example, although the presence of GABAergic neurons in structures involved in seizures (such as the lateral septum or anterior hypothalamus) suggests these may inhibit subcortical arousal systems, direct demonstration of subcortical inhibition has not yet been confirmed. Additional experiments including local infusion of GABAergic agonists and antagonists will be crucial. In addition, while cholinergic arousal was found to be depressed during limbic seizures, the possible involvement of other neurotransmitter systems should be investigated further. Another important direction for future investigation is the development of treatments to prevent long-range network impairment. Although ideally the seizures themselves should be stopped, in some patients this is not possible. In these medically and surgically refractory cases, treatments aimed at preventing the impaired consciousness which accompanies depressed cortical function would be highly beneficial. Possible treatments based on the findings above would include deep brain stimulation targeted at arousal regions such as the thalamic intralaminar region [33, 34] or pharmacological treatments such as modafinil [35] aimed at increasing alertness in the ictal and post-ictal periods. Hopefully, further investigation of the interactions between local seizures and long-range network interactions will make such treatments possible, improving the lives of people with epilepsy.

Acknowledgements I would like to especially thank Phil Schwartzkroin for his many leadership roles in the field of epilepsy including original scientific research, organizational leadership, publishing and education. He serves as an exemplary role model for colleagues in the field.

Other Acknowledgements This work was supported by NIH R01NS055829, R01NS066974, R01MH67528, P30NS052519, U01NS045911, and the Betsy and Jonathan Blattmachr Family.

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