Published in final edited form as:

Methods Mol Biol. 2009 ; 489: 189–209. doi:10.1007/978-1-59745-543-5_9.

Functional Neuroimaging of Spike-Wave Seizures

Joshua E. Motelow¹ and Hal Blumenfeld^{1,2,3,4}

¹Department of Neurology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520, USA

²Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520, USA

³Department of Neurosurgery, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520, USA

⁴QNMR, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520, USA

Abstract

Generalized spike-wave seizures are typically brief events associated with dynamic changes in brain physiology, metabolism, and behavior. Functional magnetic resonance imaging (fMRI) provides a relatively high spatio-temporal resolution method for imaging cortical-subcortical network activity during spike-wave seizures. Patients with spike-wave seizures often have episodes of staring and unresponsiveness which interfere with normal behavior. Results from human fMRI studies suggest that spike-wave seizures disrupt specific networks in the thalamus and fronto-parietal association cortex which are critical for normal attentive consciousness. However, the neuronal activity underlying imaging changes seen during fMRI is not well understood, particularly in abnormal conditions such as seizures. Animal models have begun to provide important fundamental insights into the neuronal basis for fMRI changes during spike-wave activity. Work from these models including both fMRI and direct neuronal recordings suggest that, like in humans, specific cortical-subcortical networks are involved in spike-wave, while other regions are spared. Regions showing fMRI increases demonstrate correlated increases in neuronal activity in animal models. The mechanisms of fMRI decreases in spike-wave will require further investigation. A better understanding of the specific brain regions involved in generating spike-wave seizures may help guide efforts to develop targeted therapies aimed at preventing or reversing abnormal excitability in these brain regions, ultimately leading to a cure for this disorder.

Introduction

The study of epilepsy can shed light on both normal and abnormal brain physiology. Generalized epileptic events such as absence seizures, with their characteristic spike-and-wave discharge (SWD), create transient and heterogeneous changes in neural activity throughout the brain. Dynamic functional imaging, with adequate temporal and spatial resolution, is an optimal technique with which to comprehend these complex changes as they occur throughout the brain. The discovery of the blood oxygenation level dependent (BOLD) signal and the advent of functional magnetic resonance imaging (fMRI) have opened a new window into the neurological correlates of normal and abnormal brain activity. Absence seizures, because they are not usually associated with movement in either

humans or animals, provide a rare opportunity to study ictal brain metabolism via a dynamic imaging modality such as fMRI, which is sensitive to patient movement. Animal models allow scientists to fully utilize the power of fMRI because researchers can simultaneously (1) control seizure onset and type, (2) map epileptic activity, and (3) invasively explore the neurological underpinnings and molecular mechanisms of fMRI and seizure genesis. The prevalence of fMRI in studying epilepsy reflects the excitement that this imaging modality has generated.

This chapter will begin with a discussion of generalized epilepsy and SWD. Next, we will review possible relationships between neuroenergetics and fMRI signals in human and animal BOLD experiments. We will then move on to human and animal studies of SWD, review possible mechanisms for fMRI decreases in epilepsy, and finally, discuss future directions and practical applications of these findings.

Generalized spike-wave seizures

Epileptic seizures are usually classified under two categories: generalized seizures, which involve widespread regions in both hemispheres of the brain, and partial seizures, which involve focal brain regions [1]. In fact, recent evidence suggests that so-called “generalized” seizures affect focal brain regions more intensely while sparing others [2–4], and “partial” seizures often involve widespread cortical-subcortical networks beyond the seizure focus [5, 6]. Nevertheless, the distinction between seizures that are predominantly unilateral (“focal”) vs. bilateral (“generalized”) in origin is helpful in establishing broad syndromes for clinical diagnosis. A variety of patterns of electrical activity can be seen in both partial and generalized seizures, including rhythmic spike-wave discharges (SWD). Typical large amplitude bilateral SWD are seen most commonly in absence epilepsy (Fig. 1), but are found in other forms of epilepsy as well [2]. Absence (*petit mal*) is considered a form of generalized epilepsy, and usually begins in childhood. Absence seizures consist of brief episodes of staring and unresponsiveness often accompanied by mild eyelid fluttering or myoclonic jerks. The duration of these seizures is usually less than 10 s, and post-ictal deficits are not common.

Electroencephalogram (EEG) recordings during typical absence seizures reveal large amplitude bilateral 3–4 Hz spike-wave discharges (Fig. 1). SWDs are usually bilaterally symmetric, however, left or right amplitude preponderance occurs occasionally [7]. Although absence seizures are considered generalized epileptic events, SWD amplitude in humans is seen maximally in the frontal cortices and greatest towards the midline (Fig. 1A) [8–11], and this distribution is also found in animal models of absence seizures [12–15] (Fig. 1B). Human and animal studies to date have implicated the cortex and thalamus in the generation of abnormal network oscillations involved in SWDs [16–23]. However, it has not been definitively determined whether it is an overall increase or decrease in neuronal activity in cortical and subcortical circuits that leads to spike-and-wave activity [14, 15, 24–26]. While the electrographic signature and distribution of SWDs have been characterized in previous studies, this review intends to discuss the question of metabolic activity and neuroenergetics during SWD. It is hoped that an extensive understanding of the neuronal activity changes during SWD might lead to improved treatment for absence seizures.

Neuroimaging in generalized epilepsy

Although EEG provides high temporal resolution, it is limited in its spatial sampling and cannot fully describe seizure activity throughout the brain. Neuroimaging techniques provide more comprehensive spatial sampling and can look into deep into subcortical structures in which EEG recordings are not generally feasible in humans. The first goal of neuroimaging studies of SWD is the localization of seizure activity in specific brain regions

as well as the identification of distributed networks during SWD. Because fMRI signals are only an indirect measure of neuronal activity, comparable animal models of SWD are necessary to (1) relate fMRI signal changes seen during SWD to underlying physiology and (2) aid the interpretation of fMRI changes seen in human SWD. Understanding the brain regions responsible for SWD generation yields numerous therapeutic implications including improved applications of deep brain stimulation, more effective medications, and the possibility of targeted gene therapy. A second goal of SWD fMRI research is to understand the brain's physiology during abnormal activity of spike-and-wave discharges. For example, the study of epileptogenesis might be furthered by identifying those areas which may be more susceptible to chronic activity-dependent changes [27]. Finally, a third goal is to relate fMRI changes throughout the brain to behavioral changes during seizures. Pairing behavioral analysis, including studies of impaired consciousness, with identification of the brain areas that demonstrate changes in fMRI signal will lead to a greater understanding of functional brain impairment during and between seizures [3, 17, 28].

Non-fMRI studies

Neuroimaging data of SWDs in the pre-fMRI era showed great variability. Global increases in cerebral metabolism or blood flow in human patients have been reported [24, 29–32] using single photon emission computed tomography (SPECT) studies or positron emission tomography (PET). At the same time, other PET, ^{133}Xe clearance, transcranial Doppler, and near-infrared spectroscopy (NIRS) studies of blood flow and metabolism have shown an absence of change, focal change, and generalized increased, decreased, and biphasic changes [29, 33–43]. One limitation of these studies is that the time resolution of Tc99m single photon emission computed tomography is approximately 30 s, the time resolution of fluoro-2-deoxy-D-glucose PET is approximately 30 min and the time resolution of ^{133}Xe clearance is a few minutes. These modalities may have trouble capturing the transient metabolic changes of absence seizures, which typically last less than 10 s. SPECT, PET, and ^{133}Xe are likely to integrate changes before, during, and after SWD episodes. Transcranial Doppler and NIRS have higher time resolution, but these methods lack sufficient spatial resolution. Animal studies have shown similarly confusing results (e.g. increased metabolism and decreased CBF during SWD in the same model) [37, 44].

EEG-fMRI

In order to capture adequately the dynamic neuroenergetic changes during brief absence seizures (less than 10 s) an imaging modality must have two characteristics. First, simultaneous EEG must be taken so that it is possible to distinguish interictal (non-seizure) and ictal (seizure) images. Second, the modality must have sufficient temporal resolution to capture individual seizure or SWD events while also having sufficient spatial resolution to distinguish brain regions. Using the above criteria, fMRI is the most effective imaging modality currently in use to capture the complex dynamic changes in energy metabolisms and blood flow of SWDs. Experiments utilizing fMRI and simultaneous EEG-fMRI [45–47] have begun to explore the relationship between electrophysiology and neuroimaging changes associated with SWDs in human and animal models.

Relation between fMRI and neuronal activity during spike-wave

Our interest in reviewing fMRI studies of SWD reflects (1) a belief that fMRI is the best modality to understand the neural activity underlying SWD and (2) a desire to understand the metabolic implications of the BOLD signal. “Neuronal activity” (ν), which includes presynaptic and postsynaptic membrane voltage changes associated with neural signaling, consumes energy (ATP). A large portion of this energy goes towards restoring equilibrium Na^+ and K^+ concentration gradients across the nerve membrane following the generation of

action potentials and postsynaptic potentials [48]. Net oxygen delivery to the brain reflects the balance between cerebral blood flow (CBF) and metabolic rate of oxygen consumption (CMRO₂) [49, 50]. Increased neural activity is linked to increased metabolism, which causes a CBF increase. Increased CBF causes an increase in oxygen delivery which normally exceeds metabolic demands, leading to an overall increase in blood and tissue oxygenation (pO₂). Since, as we will discuss shortly, deoxygenated hemoglobin reduces the BOLD fMRI signal intensity (S), increased oxygenation leads to an increase in S. Thus, increased neural activity and metabolism normally cause a paradoxical decrease in deoxygenated hemoglobin and an increase in the BOLD signal.

BOLD signal changes are related to baseline signal ($\Delta S/S$) and physiology by [51–53]:

$$\Delta S/S = A' [(\Delta CBF/CBF - \Delta CMRO_2/CMRO_2)/(1 + \Delta CBF/CBF) - \Delta CBV/CBV]$$

where A' is a measurable physiologic and magnetic field dependent constant, and CBV is cerebral blood volume. Measurement of S depends on the transverse relaxation time of tissue water (T_2 for spin-echo, or T_2^* for gradient echo image contrast), which, in turn, is related to red blood cell oxygenated hemoglobin [49]. This is because deoxyhemoglobin is an endogenous paramagnetic contrast agent and causes a decrease in T_2 (or T_2^*), leading to a decrease in the BOLD signal.

As a result of these complex interplays between CMRO₂, CBF, and CBV, neural energetics indirectly couple neuronal activity with fMRI signal intensity (S). CMRO₂ is currently the most direct neuroimaging measure of neuronal activity because oxidative metabolism supplies the vast majority of neuronal energy. Even in periods of transient dramatic increases in neuronal activity, the majority of pyruvate and lactate molecules in the brain are eventually metabolized aerobically [54]. CMRO₂ can be measured by neuroimaging methods, but the BOLD fMRI signal is a more convenient, although indirect, method of mapping neuronal activity, and BOLD fMRI benefits from a higher spatiotemporal resolution than spectroscopic CMRO₂ measurements.

In summary, BOLD fMRI increases and decreases are usually interpreted, respectively, as increases and decreases in neuronal activity. However, as we will discuss next, it cannot always be assumed that this simple relationship holds, particularly under abnormal conditions such as epilepsy.

Increases

fMRI signal changes, resulting from changes in neuronal activity, must be interpreted cautiously due to the complexity of the underlying mechanisms contributing to the BOLD signal. Positive changes in the BOLD signal can result from two different mechanisms (Figs. 2A, B): (i) increased neuronal activity (ν) and CMRO₂, accompanied by sufficiently increased CBF and oxygen delivery to exceed metabolic demands, which leads to increased pO₂ and S (Fig. 2A), or (ii) decreased ν and CMRO₂, with no change (or minimal decreases) in CBF, so that oxygen delivery again exceeds metabolic demands, leading to an increase in pO₂ and in S (Fig. 2B). Although increased BOLD signal is usually thought to reflect *increases* in neuronal activity [14, 55, 56], BOLD signal increase may also accompany *decreased* neuronal activity (if CBF does not change, or does not decrease sufficiently to reduce net oxygenation). Similarly, BOLD increases without changes in neuronal activity are possible if CBF is abnormally increased [57].

Decreases

Like BOLD increases, BOLD decreases can reflect either decreases or increases (or no change) in neuronal activity (Figs. 2C, D), depending on the direction and magnitude of CBF changes. Usually, fMRI decreases are interpreted as *decreased* neuronal activity accompanied by an excessive decrease in CBF. This causes reduced net oxygen levels and therefore a decrease in pO_2 and in S (Fig. 2C) [58, 59]. However, as has recently been shown in some brain regions during intense seizure activity, it is also possible to observe BOLD fMRI decreases in the presence of increased v and $CMRO_2$ if CBF does not change, or does not increase sufficiently to meet metabolic demands, leading to a decrease in pO_2 and in S (Fig. 2D) [60, 61]. Similarly, it is possible for fMRI signals to decrease with little or *no change* in neuronal activity if CBF is abnormally reduced (e.g., by vascular steal or vasospasm).

Thus, fMRI signal change alone is not adequate to determine the underlying changes in neuronal activity in the imaged system. While the relationship between the BOLD signal and the underlying hemodynamics is being studied and characterized, it is generally true, under *normal* physiological conditions, that fMRI increases reflect increased neuronal activity and that fMRI decreases reflect decreased neuronal activity [56, 59]. However, additional study of these relationships is necessary to fully understand these relationships under abnormal circumstances such as those seen in epilepsy [14, 15, 61, 62]. Possible relationships between fMRI decreases and neuronal activity during SWD will be more fully discussed towards the end of this chapter.

Human fMRI studies of spike-wave

Attempts to identify BOLD changes in humans associated with SWD have yielded fascinating, though confusing, and sometimes contradictory results. Human studies to date have investigated patients with a broad spectrum of epileptic disorders, ages, and treatments. These studies have attempted to localize those brain regions associated with SWD while teasing apart the significance and meaning of the BOLD signal increases and decreases observed in their analyses. There remain many important unanswered questions regarding both human SWD as well as the physiological and neurological underpinnings of the BOLD signal. More extensive experimentation, in both human and animal models, is required. We will now discuss BOLD fMRI changes in specific anatomical regions during human SWD.

Cortical BOLD changes

The importance of the cortex in SWD generation and maintenance has been widely shown in animal models [2, 18, 23]. Human fMRI experiments have reported cortical BOLD signal change to be predominately negative during SWD although positive changes have also been documented. Negative BOLD changes in the cortex during SWD have drawn the most intense scrutiny and speculation regarding their role in the clinical manifestations of absence seizures. Experiments have shown deactivations ranging from nearly the entire cortex [25] to smaller subsets of the cortex [28, 63–67] though the meaning of cortical BOLD decreases during SWD remains unknown. Experimenters have seen bilateral decreased BOLD signal change in the anterior and posterior interhemispheric regions, lateral frontal and parietal association cortices, and the posterior cingulate/retrosplenial/precuneus areas [25, 28, 63–65, 67, 68]. Several investigators [63, 66, 69] have noted the similarity between the BOLD deactivation pattern generated by SWD and those areas that characterize normal brain activity [70]. While much work has been done to pinpoint cortical decreases associated with SWD, variable results have been found and further study is necessary.

Reports of positive cortical changes in BOLD signal during SWD are less consistent and less pronounced than negative changes. Activations have been found in the bilateral

precentral sulci [64], mesial frontal cortex, bilateral insula [69], bilateral motor cortex [65], occipital cortex, and inferior parietal cortex [66]. Most of these studies have reported variable fMRI increases in the lateral frontal and parietal cortical regions [28, 68]. The variation and lack of consistency seen in labeling positive cortical BOLD changes suggests additional study is necessary.

Thalamic BOLD changes

Like the cortex, the thalamus has long been implicated in SWD generation and maintenance [2, 18, 23, 71]. Human BOLD studies, especially those implementing continuous EEG-fMRI, have consistently found bilateral thalamic increases [25, 26, 28, 63, 65, 66, 68] though some studies have also found thalamic decreases [26, 63]. Some investigators have attempted to differentiate the BOLD signal changes in different thalamic nuclei, but the currently available spatial resolution of fMRI as well as the image processing necessary for analysis does not necessarily allow it [26]. Thalamic activity is, at times, seen only at higher field strengths (3T) [66] and continued advances in fMRI technology may reveal more information regarding the thalamus' metabolic activity during SWD.

Basal ganglia, cerebellum, and brainstem

BOLD changes outside of the cortex and thalamus have been reported, though these changes have received much less attention, and some studies have chosen to focus solely on the corticothalamic network [67]. Increases in the cerebellum have been found [63, 69] as have increases (probably artifactual) in the lateral ventricles [69] and white matter tracts associated with the thalamus [65]. Cerebellar activity during SWD has been previously noted [72, 73], but the cerebellum's role has not yet been defined. Decreases have also been found in the basal ganglia [25, 28, 68]. The importance of the basal ganglia and the brainstem in absence epilepsy has been demonstrated in animal models [74–77] and human patients [78, 79]. Currently, little emphasis has been placed on BOLD signal changes outside the thalamocortical network, but this is an area worthy of further study.

Discussion of human fMRI studies of spike-wave

SWD is a rhythm that arises out of normal brain circuitry and physiology but is a distortion of normal mechanisms [2]. It affects specific circuits in the brain while sparing others. Structures that are affected by spike-and-wave discharge are the same networks that are important for normal oscillations, and the involvement of these structures interrupts normal brain activity. Much attention has been paid to the possible connection between the behavioral deficits seen in absence seizures and the cortical deactivations seen in human BOLD studies [69]. This should not lead investigators to ignore prominent BOLD changes in subcortical structures or BOLD increases in the cortex.

fMRI increases in the thalamus have been observed repeatedly, but the mechanism that drives the BOLD changes is as yet unknown. Are the BOLD increases in the thalamus due to increased activity of excitatory or inhibitory neurons? Are neurons firing more or *less* in the thalamus during SWD? Thalamic decreases remain unexplained (as do the mechanism that underlies all BOLD decreases in SWD). It has also been suggested that SWD may be generated by more than one mechanism, which might explain the varied cortical BOLD signal changes [25, 67]. Finally, the relatively consistent BOLD changes seen in the thalamus, fronto-parietal cortex, and posterior cingulate/retrosplenial/precuneus (Fig. 3) areas may represent an important functional network in SWD generation.

Cortical fMRI increases have not been given the same attention as cortical decreases in SWD. The possible role of these regions in SWD generation and behavioral deficits warrants further investigation. One author suggested the variability in cortical signal might

have less to do with SWD generation and more to do with the normal baseline activity of each individual [66]. If SWD leads to an interruption of normal activity, then baseline activity would dictate which cortical areas showed increases and decreases [69].

Limitations of human studies to date

Attempts to localize SWD using BOLD fMRI have produced inconsistent results. Studies have been limited by heterogeneous patient populations (e.g. age, medication, diagnosis, seizure activity) (reviewed in [66]). As has already been noted, stronger field strengths have allowed researchers to find signal changes that were not apparent at lower field strengths, and continued advances in fMRI research techniques may reveal a more consistent pattern of significant fMRI signal changes. Furthermore, while several researchers have connected their fMRI data with the behavioral deficits often associated with absence seizures, simultaneous behavioral testing may allow researchers to understand the relationship between fMRI changes and behavioral changes [28, 68]. Thus, it will be critical in further studies to directly link fMRI signal changes with behavioral deficits. Finally, techniques to date have not necessarily differentiated BOLD activity based on seizure duration. CBF and brain metabolism may differ in brief SWD as opposed to in prolonged seizures or absence status epilepticus. Furthermore, fMRI signal changes and the spatial heterogeneity of SWD amplitude in different brain regions based on EEG (or MEG) have not yet been correlated.

Animal fMRI studies of spike-wave

Animal studies are vital companions to human studies and provide advantages for studying epilepsy and conducting fMRI experiments. Animal models of epilepsy often allow investigators to control seizure type, frequency and onset, which enable the collection of the most consistent and reproducible data possible. Animals may be restrained and/or anesthetized to reduce movement artifact, and animal models make possible the study of fMRI and its neural correlates by allowing direct study of neural activity using combined imaging, electrophysiological measurements with microelectrodes and other techniques [14, 15, 55, 56, 80]. Tissue collected from specific brain regions identified by animal fMRI studies may uncover the molecular mechanisms giving rise to seizure susceptibility in those regions.

Of course, animal models of epilepsy are limited in that they are models. Results from animal models must be analyzed with the understanding that human and animal physiologies are crucially different. For example, SWD have a faster frequency in rodent models (7–8 Hz) than in humans (3–4 Hz), and SWD persist in adulthood in rodents, while they usually disappear in adolescence in humans. Other difficulties and technical challenges arise from the high magnetic field strength used to image small animals, including difficulty in obtaining simultaneous EEG during fMRI recordings [15, 81], the sensitivity of imaging signals to movement artifact, and magnetic susceptibility artifact often found at air-tissue interfaces.

Anesthesia, if used, must be chosen with care. Anesthetic agents may suppress seizure activity or alter cerebral hemodynamics, introducing a confounding factor in fMRI analysis. While under anesthesia or otherwise, systemic physiology should be monitored in ventilated animals during fMRI studies. Changes in blood pressure and pCO₂ may confound imaging results. Ideally, SWD seizures should be imaged in animals without anesthesia [81, 82]. However, this is a technical challenge due to the extensive animal training required to habituate them to the recording procedures [83, 84].

Human experiments have left many unanswered questions about the meaning of SWD-induced fMRI signal increases and decreases. It is hoped that accurate animal models may

answer these questions by elucidating the relationships between the fMRI signal changes, underlying neuronal activity, and molecular mechanisms (Blumenfeld 2005b). The main animal models of SWD studied with fMRI to date include spontaneous seizures in rat SWD models, and chemically induced seizures using gamma-butyrolactone (GBL).

WAG/Rij

Prominent animal models of SWD include spontaneous seizures seen in Wistar Albino Glaxo rats of Rijswijk (WAG/Rij). WAG/Rij rats have spontaneous SWD and are an established model of human absence epilepsy [85]. As in human data, there has been some inconsistency in reported BOLD signal changes during SWD. Some experimental data of fMRI recordings during spontaneous SWD activity in WAG/Rij rats have revealed no significantly negative BOLD changes associated with SWDs [86]. The same experiment showed widespread increases in the thalamus and in the cortex. No significant changes were found in the hippocampus [86]. A second group utilizing continuous EEG-fMRI found increased BOLD signal change in several regions of the cortex and subcortical structures, without major fMRI decreases (Fig. 4) [15]. Increases were seen in the somatosensory cortex, motor cortex, thalamus, basal ganglia, hippocampus, and brainstem (tectum and tegmental nuclei) and were mostly bilaterally and symmetrically distributed [15]. More recent studies with a higher field (9.4T) system detected both fMRI increases as well as decreases in specific brain regions in the same rodent model [87]. fMRI decreases were seen mainly in the basal ganglia and hippocampus, but were also occasionally present in small regions of the neocortex [87].

Although absence epilepsy is considered a generalized seizure disorder, fMRI and electrical recordings of SWD have found that focal anterior regions of the brain were most intensively involved, while other brain regions remained relatively quiet (Figs. 2, 4) [13–15]. Studies in rodent models have revealed focal abnormalities in voltage gated channel expression which may be related to epileptogenesis in this form of epilepsy [27, 88]. The ability to non-invasively image focal network involvement may ultimately lead to a better understanding of mechanisms in specific brain regions crucial for generation of SWD in both animal models and human patients.

GBL rat model

GBL is a precursor of γ -hydroxybutyrate and produces robust SWDs in rats, resembling petit mal status epilepticus [82, 89]. There is evidence that anesthesia limits the BOLD signal change in GBL-induced SWD [82] but awake animals have yielded interesting BOLD fMRI data. GBL-induced SWDs showed widespread negative changes in the cortex while also showing positive changes in the somatosensory and parietal cortices. The thalamus showed only significant positive BOLD changes. While these findings in some ways resemble reported changes during human SWD, important differences include the frequency of the discharges (6–7 Hz in GBL rat model vs. 3–4 Hz in human) and their duration (continuous status epilepticus in rat GBL model vs. brief episodes in human). The GBL has some advantages compared to spontaneous rodent seizure models, since GBL-induced seizures are robust and long lasting, however, the spontaneous seizure models have the advantage of producing brief seizure episodes more similar to typical seizure durations in humans.

GBL monkey model

GBL seizures have also been studied in non-human primates. Advantages of primate models of SWD include SWD activity more closely resembling human SWD. Marmoset monkeys demonstrate 3 Hz SWD activity, which is more comparable to human SWD activity. Widespread increases were seen throughout cortical and subcortical structures including the

thalamus and hippocampus. Unlike in GBL-induced seizures in rats, no significant negative BOLD changes were seen although changes in the hippocampus and the anterior cingulate were only seen during shorter time points. As in the rat model, GBL-induced seizures in monkeys most closely resembles status epilepticus [90].

Discussion of animal studies of spike-wave

It is not yet clear why human fMRI studies of SWD show a mix of cortical increases and prominent decreases while animal models with brief episodes of SWD show mainly cortical increases. Similarly, it is unclear why prolonged SWD causes mainly BOLD increases in the monkey GBL model, but both increases and decreases in the rat GBL model. Some of this may reflect a lack of understanding of the fundamental mechanisms of fMRI increases and decreases during seizures. Direct recordings of neuronal activity, which can be performed in animal models (Figure 5), may provide a way to unravel the complex relationships between neuronal activity patterns and BOLD fMRI. Studies performed so far in WAG/Rij rats have demonstrated that regions with fMRI increases during SWD (e.g. barrel somatosensory cortex, S1BF, Figure 4) exhibit increases in neuronal firing and CBF during SWD (Figure 5). Meanwhile, regions with no fMRI signal changes during SWD (e.g. primary visual cortex, V1M, Figure 4) show no changes in neuronal firing or CBF (Figure 5). Further studies will be needed, particularly in regions showing fMRI decreases, to more fully understand these phenomena.

Possible mechanisms of fMRI decreases during seizures

From the above discussion, it follows that BOLD fMRI increases during SWD most likely reflect focal increases in neuronal activity. However, the mechanisms of BOLD decreases during SWD and other forms of seizure activity are not well understood. Possible mechanisms of BOLD fMRI decreases include: **(1) A primarily vascular mechanism**, where blood supply decreases in specific brain regions during seizures. Primary causes of decreased blood flow could include **(1A) vasospasm** or **(1B) vascular steal**. Excessive decreases in local blood flow will decrease net oxygenation, leading to a decrease in BOLD. Significant decreases in oxygenation (hypoxia) could also secondarily cause some reduction in neuronal activity (Figure 2C). **(2) A primarily neural mechanism** where cortical neuronal activity decreases in specific brain regions during seizures. If neurovascular coupling is normal, reduced neuronal activity usually leads to an excessive reduction in blood flow (Figure 2C), again causing a net decrease in oxygenation, and a decrease in the BOLD signal. A primary decrease in neuronal activity could occur in several ways: **(2A) Decreased neuronal activity in regions spared by seizures**. While seizures cause neuronal activity to increase in regions intensely involved in epileptic activity, network effect may cause neuronal activity to decrease in other regions of the brain which are *not* directly involved in the seizure. This could occur either through **(2Ai) active inhibition**, or **(2Aii) reduced excitation** in these regions. Examples of decreased neuronal activity and CBF have been observed while studying cortical brain regions spared by partial seizures in both animal models (Englot and Blumenfeld 2007; unpublished data), and in humans [5, 6]; **(2B) Decreased neuronal activity in regions involved by seizures**. A second primarily neural mechanism may occur in which some cortical regions which are *involved* in seizures could, nevertheless, show *reduced* neuronal activity. While seizure activity is generally thought to increase neuronal activity, SWD is associated with an alternating pattern, between increases in neuronal activity during the spike component, and decreases in neuronal activity during the wave [91]. It is possible that some brain regions may have subtle changes in intensity of firing during the spike or changes in duration of neuronal silence during the wave, which could lead to a mean *decrease* in neuronal activity during SWD, as discussed previously [2, 92]. **(3) Altered neuro-vascular coupling**. In this mechanism, unlike those above, the

primary event is an *increase* in neuronal activity during seizures. However, this increase in neuronal activity is met by an inadequate increase in blood flow to match metabolic demands, leading to a BOLD fMRI decrease (Figure 2D). Note that in this mechanism blood flow can increase (unlike Figure 2D); the main point is that the blood flow increase is inadequate. An example of this mechanism has recently been observed in a rodent model, where BOLD decreases in the hippocampus accompany intense seizure activity in the same region [61]. There are two main possibilities to explain abnormal neurovascular coupling during seizures: **(3A) Intense neuronal activity could overwhelm neurovascular coupling.** In this mechanism, sudden extreme increases in neuronal energy consumption could exceed the capacity of neurovascular coupling mechanisms to deliver adequate oxygen. **(3B) Dysregulation of the neurovascular coupling cascade.** In this mechanism, the inherent signaling cascade underlying neurovascular coupling could be altered acutely or chronically by seizures (or other causes), leading to an abnormal blunted response to neuronal activity changes.

Which of the above mechanisms are involved in BOLD fMRI decreases during SWD in both humans and animal models remains to be determined by further investigations.

Discussion and future directions

We have seen that fMRI during SWD in both humans and animal models can provide important information about abnormal network behavior during generalized seizures. Studies so far, have revealed focal bilateral increases in the fronto-parietal cortex and thalamus, decreases in other specific cortical regions, and decreases in the basal ganglia. These investigations support the concept that “generalized” spike-wave seizures, in fact, arise from focal network dysfunction in specific regions of cortical-subcortical networks.

Many important questions remain, which should be addressed by future studies. For example, do seizure in which consciousness is impaired differ from those in which consciousness is spared? Is the difference based on the brain regions involved? Are there different molecular mechanisms causing specific regions but not others to be involved during seizures? How do the circuit mechanisms differ for regions involved or spared by seizures? Is the impaired brain function and behavior during seizures caused by abnormally increased activity, abnormally decreased activity, or both? There remains much to learn about spike-and-wave discharges through the use of fMRI. Behavioral tests in both humans and animals must be added to simultaneous EEG-fMRI in order to fully correlate behavioral deficits with the anatomy of fMRI signal changes [68]. More sophisticated analytic techniques must be developed in order to explore the fMRI time-course, as well as to better correlate the electrophysiology data with the hemodynamic response measured by fMRI data. Long-range network changes can be further investigated using resting functional connectivity studies or the fMRI signals, and using technology such as diffusion tensor imaging (DTI). Numerous measurements, including CBF, CBV, and CMRO₂ have yet to be undertaken in human patients or animal models to more fully understand the fundamental neuroenergetics of SWD. fMRI investigation of additional rat, mouse, and feline models of SWD [23, 93, 94] can also provide a more general understanding of SWD mechanisms. Finally, these techniques should be applied to understand developmental changes that occur during the development of epilepsy. Neuroimaging has the potential to provide a safe, non-invasive biomarker for epileptogenesis and its prevention, and could ultimately be used as a way to monitor the success of treatments aimed at suppressing spike-wave development [27]. Much exciting research remains to be done using fMRI to investigate the unknowns of spike-and-wave discharges and epilepsy in the future.

Acknowledgments

We thank Mi Hae Chung for assistance with the figures. This work was supported by NIH R01 NS055829, R01 NS049307, the Donaghue Foundation, and by the Betsy and Jonathan Blattmachr family.

References

1. ILAE. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1981; 22(4):489–501. [PubMed: 6790275]
2. Blumenfeld H. Cellular and network mechanisms of spike-wave seizures. *Epilepsia*. 2005; 46(Suppl 9):21–33. [PubMed: 16302873]
3. Blumenfeld H. Consciousness and epilepsy: why are patients with absence seizures absent? *Prog Brain Res*. 2005; 150:271–86. [PubMed: 16186030]
4. Blumenfeld H, et al. Selective frontal, parietal and temporal networks in generalized seizures. *Neuroimage*. 2003; 19:1556–1566. [PubMed: 12948711]
5. Blumenfeld H, et al. Positive and negative network correlations in temporal lobe epilepsy. *Cerebral Cortex*. 2004; 14(8):892–902. [PubMed: 15084494]
6. Blumenfeld H, et al. Ictal neocortical slowing in temporal lobe epilepsy. *Neurology*. 2004; 63:1015–1021. [PubMed: 15452292]
7. Ebersole, JS.; Pedley, TA. *Current Practice of Clinical Electroencephalography*. 3. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
8. Weir B. The morphology of the spike-wave complex. *Electroencephalography & Clinical Neurophysiology*. 1965; 19(3):284–90. [PubMed: 4157831]
9. Rodin E, Ancheta O. Cerebral electrical fields during petit mal absences. *Electroencephalography & Clinical Neurophysiology*. 1987; 66(6):457–66. [PubMed: 2438111]
10. Coppola, R. Topographic display of spike-and-wave discharges. In: Mysobodsky, MS.; Mirsky, AF., editors. *Elements of Petit Mal Epilepsy*. Peter Lang; New York: 1988. p. 105-130.
11. Holmes MD, Brown M, Tucker DM. Are “generalized” seizures truly generalized? Evidence of localized mesial frontal and frontopolar discharges in absence. *Epilepsia*. 2004; 45(12):1568–79. [PubMed: 15571515]
12. Vergnes M, Marescaux C, Depaulis A. Mapping of spontaneous spike and wave discharges in Wistar rats with genetic generalized non-convulsive epilepsy. *Brain Research*. 1990; 523(1):87–91. [PubMed: 2207693]
13. Meeren HK, et al. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *Journal of Neuroscience*. 2002; 22(4):1480–95. [PubMed: 11850474]
14. Nersesyan H, et al. Relative changes in cerebral blood flow and neuronal activity in local microdomains during generalized seizures. *J Cereb Blood Flow Metab*. 2004; 24(9):1057–1068. [PubMed: 15356426]
15. Nersesyan H, et al. Dynamic fMRI and EEG recordings during spike-wave seizures and generalized tonic-clonic seizures in WAG/Rij rats. *J Cereb Blood Flow Metab*. 2004; 24(6):589–599. [PubMed: 15181366]
16. Williams D. A study of thalamic and cortical rhythms in petit mal. *Brain*. 1953; 76:50–69. [PubMed: 13041922]
17. Blumenfeld H, Taylor J. Why do seizures cause loss of consciousness? *The Neuroscientist*. 2003; 9(5):301–310. [PubMed: 14580115]
18. Avoli, M., et al., editors. *Generalized Epilepsy*. Birkhauser; Boston: 1990.
19. Blumenfeld H, McCormick DA. Corticothalamic inputs control the pattern of activity generated in thalamocortical networks. *Journal of Neuroscience*. 2000; 20(13):5153–62. [PubMed: 10864972]
20. Kostopoulos G. Involvement of the thalamocortical system in epileptic loss of consciousness. *Epilepsia*. 2001; 42(3):13–19. [PubMed: 11520316]
21. McCormick DA, Contreras D. On the cellular and network bases of epileptic seizures. *Annual Review of Physiology*. 2001; 63:815–46.

22. Blumenfeld H. The thalamus and seizures. *Arch Neurol*. 2002; 59(1):135–137. [PubMed: 11790241]
23. Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. *Nature Reviews Neuroscience*. 2002; 3(5):371–82.
24. Engel J Jr, et al. Local cerebral metabolic rate for glucose during petit mal absences. *Annals of Neurology*. 1985; 17(2):121–8. [PubMed: 3919636]
25. Salek-Haddadi A, et al. Functional magnetic resonance imaging of human absence seizures. *Annals of Neurology*. 2003; 53(5):663–7. [PubMed: 12731002]
26. Aghakhani Y, et al. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain*. 2004; 127(Pt 5):1127–44. [PubMed: 15033899]
27. Blumenfeld H, et al. Early treatment suppresses the development of spike-wave epilepsy in a rat model. *Epilepsia*. 2007 In press.
28. Berman, R., et al. Simultaneous EEG and fMRI recordings of childhood absence seizures. *Soc Neurosci Abs*. 2005. Online at <http://web.sfn.org/>
29. Theodore WH, et al. Positron emission tomography in generalized seizures. *Neurology*. 1985; 35(5):684–90. [PubMed: 3921871]
30. Prevett MC, et al. Demonstration of thalamic activation during typical absence seizures using H₂(15)O and PET. *Neurology*. 1995; 45(7):1396–402. [PubMed: 7617203]
31. Engel J Jr, Kuhl DE, Phelps ME. Patterns of Human Local Cerebral Glucose Metabolism During Epileptic Seizures. *Science*. 1982; 218:64–66. [PubMed: 6981843]
32. Yeni SN, et al. Ictal and interictal SPECT findings in childhood absence epilepsy. *Seizure*. 2000; 9(4):265–9. [PubMed: 10880286]
33. Buchheim K, et al. Decrease in haemoglobin oxygenation during absence seizures in adult humans. *Neurosci Lett*. 2004; 354(2):119–22. [PubMed: 14698453]
34. Bode H. Intracranial blood flow velocities during seizures and generalized epileptic discharges. *European Journal of Pediatrics*. 1992; 151(9):706–9. [PubMed: 1396936]
35. De Simone R, et al. Changes in cerebral blood flow velocities during childhood absence seizures. *Pediatric Neurology*. 1998; 18(2):132–5. [PubMed: 9535298]
36. Klingelhofer J, et al. Do brief bursts of spike and wave activity cause a cerebral hyper- or hypoperfusion in man? *Neuroscience Letters*. 1991; 127(1):77–81. [PubMed: 1881621]
37. Nehlig A, et al. Absence seizures induce a decrease in cerebral blood flow: human and animal data. *Journal of Cerebral Blood Flow & Metabolism*. 1996; 16(1):147–55. [PubMed: 8530547]
38. Sanada S, Murakami N, Ohtahara S. Changes in blood flow of the middle cerebral artery during absence seizures. *Pediatric Neurology*. 1988; 4(3):158–61. [PubMed: 3149478]
39. Sperling MR, Skolnick BE. Cerebral blood flow during spike-wave discharges. *Epilepsia*. 1995; 36(2):156–63. [PubMed: 7821273]
40. Diehl B, et al. Cerebral hemodynamic response to generalized spike-wave discharges. *Epilepsia*. 1998; 39(12):1284–9. [PubMed: 9860063]
41. Ochs RF, et al. Effect of generalized spike-and-wave discharge on glucose metabolism measured by positron emission tomography. *Annals of Neurology*. 1987; 21(5):458–64. [PubMed: 3109317]
42. Park YD, et al. Focal cerebral metabolic abnormality in a patient with continuous spike waves during slow-wave sleep. *Journal of Child Neurology*. 1994; 9(2):139–43. [PubMed: 8006363]
43. Ferrie CD, et al. Focal abnormalities detected by 18FDG PET in epileptic encephalopathies. [comment]. *Archives of Disease in Childhood*. 1996; 75(2):102–7. [PubMed: 8869188]
44. Nehlig A, et al. Local cerebral glucose utilization in rats with petit mal-like seizures. *Annals of Neurology*. 1991; 29(1):72–7. [PubMed: 1899987]
45. Ives JR, et al. Monitoring the patient's EEG during echo planar MRI. *Clin Neurol*. 1993; 87:417–420.
46. Goldman RI, et al. Acquiring simultaneous EEG and functional MRI. *Clinical Neurophysiology*. 2000; 111(11):1974–80. [PubMed: 11068232]
47. Gotman J, et al. Combining EEG and fMRI: a multimodal tool for epilepsy research. *Journal of Magnetic Resonance Imaging*. 2006; 23(6):906–20. [PubMed: 16649203]

48. Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow & Metabolism*. 2001; 21:1133–1145. [PubMed: 11598490]
49. Ogawa S, et al. On the characteristics of functional magnetic resonance imaging of the brain. *Annu Rev Biophys Biomol Struct*. 1998; 27:447–74. [PubMed: 9646874]
50. Hyder F, et al. Quantitative functional imaging of the brain: towards mapping neuronal activity by BOLD fMRI. *NMR in Biomedicine*. 2001; 14(7–8):413–31. [PubMed: 11746934]
51. Ogawa S, et al. Functional Brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. *Biophys J*. 1993; 64:803–812. [PubMed: 8386018]
52. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissue. *Magn Reson Med*. 1994; 31:9–21. [PubMed: 8121277]
53. Weisskoff RM, et al. Microscopic susceptibility variation and transverse relaxation: theory and experiment. *Magn Reson Med*. 1994; 31:601–610. [PubMed: 8057812]
54. Shulman RG, Hyder F, Rothman DL. Biophysical basis of brain activity: implications for neuroimaging. *Quarterly Reviews of Biophysics*. 2002; 35(3):287–325. [PubMed: 12599751]
55. Logothetis NK, et al. Neurophysiological investigation of the basis of the fMRI signal. *Nature*. 2001; 412(6843):150–7. [PubMed: 11449264]
56. Smith AJ, et al. Cerebral energetics and spiking frequency: the neurophysiological basis of fMRI. [see comment]. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99(16):10765–70. [PubMed: 12134056]
57. Martin C, et al. Haemodynamic and neural responses to hypercapnia in the awake rat. *European Journal of Neuroscience*. 2006; 24(9):2601–10. [PubMed: 17100848]
58. Stefanovic B, Warnking JM, Pike GB. Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage*. 2004; 22(2):771–8. [PubMed: 15193606]
59. Shmuel A, et al. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nature Neuroscience*. 2006; 9(4):569–77.
60. Suh M, et al. Neurovascular coupling and oximetry during epileptic events. *Molecular Neurobiology*. 2006; 33(3):181–97. [PubMed: 16954595]
61. Schridde, U., et al. Negative BOLD with large increases in neuronal activity. 2007. In press
62. Stefanovic B, et al. Hemodynamic and metabolic responses to activation, deactivation and epileptic discharges. *Neuroimage*. 2005; 28(1):205–15. [PubMed: 16000253]
63. Hamandi K, et al. EEG-fMRI of idiopathic and secondarily generalized epilepsies. *Neuroimage*. 2006; 31(4):1700–10. [PubMed: 16624589]
64. Archer JS, et al. fMRI “deactivation” of the posterior cingulate during generalized spike and wave. *Neuroimage*. 2003; 20(4):1915–22. [PubMed: 14683697]
65. Labate A, et al. Typical childhood absence seizures are associated with thalamic activation. *Epileptic Disorders*. 2005; 7(4):373–7. [PubMed: 16338682]
66. Laufs H, et al. Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia*. 2006; 47(2):444–8. [PubMed: 16499775]
67. Aghakhani Y, et al. Cortical and thalamic fMRI responses in partial epilepsy with focal and bilateral synchronous spikes. *Clin Neurophysiol*. 2006; 117(1):177–91. [PubMed: 16314143]
68. Berman R, et al. Combined EEG and fMRI during typical childhood absence seizures at 3T. *Epilepsia*. 2005:AES abstracts.
69. Gotman J, et al. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102(42):15236–40. [PubMed: 16217042]
70. Raichle ME, et al. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98(2):676–82. [PubMed: 11209064]
71. Pinault D, et al. Intracellular recordings in thalamic neurones during spontaneous spike and wave discharges in rats with absence epilepsy. *Journal of Physiology*. 1998; 509(Pt 2):449–56. [PubMed: 9575294]
72. Kandel A, Buzsaki G. Cerebellar neuronal activity correlates with spike and wave EEG patterns in the rat. *Epilepsy Reseach*. 1993; 16:1–9.

73. Norden AD, Blumenfeld H. The Role of Subcortical Structures in Human Epilepsy. *Epilepsy & Behavior*. 2002; 3(3):219–231. [PubMed: 12662601]
74. Paz JT, et al. Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway. *J Neurosci*. 2007; 27(4):929–41. [PubMed: 17251435]
75. Tolmacheva EA, et al. Cortical and limbic excitability in rats with absence epilepsy. *Epilepsy Res*. 2004; 62(2–3):189–98. [PubMed: 15579307]
76. Slaght SJ, et al. On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. *J Neurosci*. 2004; 24(30):6816–25. [PubMed: 15282287]
77. Deransart C, et al. Inhibition of the substantia nigra suppresses absences and clonic seizures in audiogenic rats, but not tonic seizures: evidence for seizure specificity of the nigral control. *Neuroscience*. 2001; 105(1):203–211. [PubMed: 11483312]
78. Kohsaka S, et al. Brainstem activates paroxysmal discharge in human generalized epilepsy. *Brain Res*. 2001; 903:53–61. [PubMed: 11382387]
79. Kohsaka S, et al. Brainstem triggers absence seizures in human generalized epilepsy. *Brain Res*. 1999; 837:277–288. [PubMed: 10434013]
80. Schwartz TH, Bonhoeffer T. In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex. *Nature Medicine*. 2001; 7(9):1063–7.
81. Van Camp N, et al. Simultaneous electroencephalographic recording and functional magnetic resonance imaging during pentylenetetrazol-induced seizures in rat. *Neuroimage*. 2003; 19:627–636. [PubMed: 12880793]
82. Tenney JR, et al. Corticothalamic modulation during absence seizures in rats: a functional MRI assessment. *Epilepsia*. 2003; 44(9):1133–40. [PubMed: 12919383]
83. Khubchandani M, et al. Stereotaxic assembly and procedures for simultaneous electrophysiological and MRI study of conscious rat. *Magnetic Resonance in Medicine*. 2003; 49:962–967. [PubMed: 12704780]
84. Sachdev RN, et al. Experimental model for functional magnetic resonance imaging of somatic sensory cortex in the unanesthetized rat. *Neuroimage*. 2003; 19(3):742–50. [PubMed: 12880803]
85. Coenen AM, Van Luijckelaar EL. Genetic Animal Models for Absence Epilepsy: A Review of the WAG/Rij Strain of Rats. *Behav Genet*. 2003; 33:635–655. [PubMed: 14574120]
86. Tenney JR, et al. fMRI of brain activation in a genetic rat model of absence seizures. *Epilepsia*. 2004; 45(6):576–82. [PubMed: 15144421]
87. Mishra, AM., et al. Physiology and imaging of increases and decreases in BOLD signals during spike-wave seizures in WAG/Rij rats. 2007. Online at <http://web.sfn.org/>
88. Klein JP, et al. Dysregulation of sodium channel expression in cortical neurons in a rodent model of absence epilepsy. *Brain Research*. 2004; 1000:102–109. [PubMed: 15053958]
89. Snead OC 3rd, et al. Absence epilepsy: advances in experimental animal models. *Advances in Neurology*. 1999; 79:253–78. [PubMed: 10514819]
90. Tenney JR, et al. fMRI of generalized absence status epilepticus in conscious marmoset monkeys reveals corticothalamic activation. *Epilepsia*. 2004; 45(10):1240–7. [PubMed: 15461678]
91. Kostopoulos G, et al. A study of the transition from spindles to spike and wave discharge in feline generalized penicillin epilepsy: microphysiological features. *Experimental Neurology*. 1981; 73(1):55–77. [PubMed: 7250289]
92. Blumenfeld H. Functional MRI studies of animal models in epilepsy. *Epilepsia*. 2007; 48(Suppl 4): 18–26. [PubMed: 17767572]
93. Marescaux C, Vergnes M, Depaulis A. Genetic absence epilepsy in rats from Strasbourg--a review. *Journal of Neural Transmission Supplementum*. 1992; 35:37–69. [PubMed: 1512594]
94. Prince DA, Farrell D. "Centrencephalic" spike and wave discharges following parenteral penicillin injection in the cat. *Neurology*. 1969; 19:309–310.

Figure 1.

Typical spike-wave EEG discharges during absence seizures, show some regions intensely involved, and others relatively spared by seizures. **A.** EEG recordings of a typical absence seizure from a 7-year old girl, reveals bilateral synchronous 3–4 Hz spike-wave discharges, with an anterior to posterior amplitude gradient. (Inset of electrode positions modified with permission from Fisch, B.J. (1991) *Spehlmann's EEG Primer*. Elsevier, Amsterdam. EEG recording modified with permission from Daly, D.D. and Pedley, T.A. (1990) *Current Practice of Clinical Electroencephalography*. Raven Press, New York.). **B.**

Electrocorticography from the surface of the WAG/Rij rat cortex during spike-and-wave seizures exhibits intense involvement of the anterior cortex and relative sparing of the occipital lobes. (Reprinted with permission from Meeren et al., 2002. Copyright 2002, Society for Neuroscience.)

Figure 2.

Schematic representation of increases and decreases in the BOLD signal (S) as a result of possible changes in neuronal activity (v), CMRO_2 , cerebral blood flow (CBF), and tissue oxygenation (pO_2). **A, B.** Examples of changes leading to increases in the BOLD signal. **C, D.** Examples of changes leading to decreases in the BOLD signal. Note: relative changes among v , CMRO_2 , CBF, and pO_2, S are not drawn to scale but are exaggerated for illustrative purposes. (Reprinted with Permission from Blumenfeld, 2007, *Epilepsia* [92]).

Figure 3. FMRI changes in group analysis of generalized spike-wave seizures (15 patients with idiopathic generalized epilepsy). **A.** Significant increases are shown in the bilateral thalami and in several cortical areas. **B,C.** Decreases are shown in bilateral interhemispheric regions, lateral frontal cortex, and parietal association cortex. Modified with permission from Gotman et al, 2005 *PNAS* [69].

Figure 4.

Map of cortical and thalamic fMRI changes during spike-wave seizures in WAG/Rij rat. **A.** Example of BOLD fMRI activations during SWD in a WAG/Rij rat under fentanyl-haloperidol anesthesia. t-maps were calculated from 23 pairs of images in which a pair constituted one image acquired at baseline and one image acquired during SWD. Results were overlaid onto corresponding high-resolution anatomic images. The eight coronal slices displayed were acquired from back to front (numbered 1–8) at 1-mm intervals. The first was slice at approximately -7.04 and the last slice was at $+0.40$ mm relative to bregma (Paxinos and Watson, 1998). The frontoparietal (somatosensory and motor) cortex, thalamus, and brainstem nuclei showed bilateral and relatively symmetrical BOLD signal increases, whereas no significant changes were seen in the temporal and occipital regions. t-map display threshold = 2. **B.** Time course of BOLD fMRI signal changes shown with simultaneous EEG during spontaneous SWD. The onset of most SWD episodes, particularly those lasting more than 3 s, precedes increases in the BOLD fMRI signal ($\Delta S/S$) in barrel cortex (red line, S1BF) and thalamus (blue line, Thal). The primary visual cortex (green line, V1M) demonstrated no significant changes related to seizure activity. Same experimental run, and same animal as in A. Reproduced with permission from Nersesyan et al 2004B, *J Cerebral Blood Flow Metab* [15].

Figure 5.

CBF and neuronal activity recorded dynamically during SWD. **(A)** Combined laser Doppler flowmetry and extracellular multiunit data recorded changes in CBF and neuronal activity simultaneously during multiple episodes of SWD, along with EEG and arterial blood pressure (BP) monitoring in a WAG/Rij rat under fentanyl-haloperidol anesthesia. **(B)** Parallel increases in CBF and neuronal firing rate (ν) in barrel cortex (S1BF), and no or very small increases in primary visual cortex (V1M) induced by spontaneous SWD. Panel **(B)** shows the data from the boxed region of panel **A** on an expanded time scale. Reproduced with permission from Nersesyan et al 2004A, *J Cerebral Blood Flow Metab* [14].