Published in final edited form as:

Epilepsy Behav. 2010 August ; 18(4): 404–413. doi:10.1016/j.yebeh.2010.05.009.

Cortical and subcortical contributions to absence seizure onset examined with EEG/fMRI

Jerzy P. Szaflarski, MD, PhD^{1,2,3,4,*}, Mark DiFrancesco, PhD^{4,7}, Thomas Hirschauer⁴, Christi Banks, CCRC¹, Michael D. Privitera, MD¹, Jean Gotman, PhD⁶, and Scott K. Holland, PhD^{2,4,5,7}

¹ Department of Neurology, University of Cincinnati Medical Center, Cincinnati, OH, USA

² Department of Neuroscience, University of Cincinnati Medical Center, Cincinnati, OH, USA

³ Center for Imaging Research at the University of Cincinnati Medical Center, Cincinnati, OH, USA

⁴ Imaging Research Center at the Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

⁵ Department of Pediatrics, University of Cincinnati Medical Center, Cincinnati, OH, USA

⁶ Montreal Neurological Institute at the McGill University, Montreal, CA

⁷ Department of Radiology, University of Cincinnati Medical Center, Cincinnati, OH, USA

Abstract

In patients with idiopathic generalized epilepsies (IGE), bursts of generalized spike and wave discharges (GSWD) lasting ≥ 2 seconds are considered absence seizures. The location of the absence seizures generators in IGEs is thought to involve interplay between various components of thalamo-cortical circuits; we have recently postulated that medication resistance may, in part, be related to the location of the GSWD generators (1). In the present study we hypothesized that patients with medication-refractory IGE (R-IGE) and continued absence seizures may have location of the GSWD generators other than the thalamus, as typically seen in the IGE patients. Hence, the objective of this study was to determine the location of the GSWD generators in patients with R-IGE using EEG/fMRI. 83 patients with IGE received concurrent EEG/fMRI at 4T. Nine of them (ages 15–55) experienced absence seizures during EEG/fMRI and were included; all were diagnosed with R-IGE. Subjects participated in up to three 20-minute EEG/fMRI sessions (400 volumes; TR = 3 seconds) performed at 4T. After removing fMRI and ballistocardiographic artifacts, 36 absence seizures were identified. Statistical parametric maps were generated for each of these sessions correlating seizures to BOLD response. Timing differences between brain regions were tested using statistical parametric maps generated by modeling seizures with onset times shifted relative to the GSWD onsets. While thalamic BOLD responses peaked at approximately 6 seconds after the onset of absence seizures, other areas including the prefrontal and dorsolateral cortices showed brief and non-sustained peaks occurring ~ 2 seconds prior to the maximum of the thalamic peak. Temporal lobe peaks occurred at the same time as the thalamic peak with a cerebellar peak occurring ~ 1 second later. Confirmatory analysis averaging cross

*Address for Correspondence: Jerzy P. Szaflarski, MD, PhD, Department of Neurology, University of Cincinnati College of Medicine, 260 Stetson Street, Cincinnati, OH 45267-0525, Phone: 513.558.5440, Jerzy.Szaflarski@uc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

correlation between cortical and thalamic ROIs across seizures corroborated these findings. Finally, Granger causality analysis showed effective connectivity directed from frontal lobe to thalamus supporting the notion of an earlier frontal than thalamic involvement. The results of this study support our original hypothesis and suggest that in the studied patients with R-IGE, absence seizures may be initiated by widespread cortical (frontal and parietal) areas and sustained in subcortical (thalamic) regions suggesting that the examined patients have cortical onset epilepsy with propagation to thalamus.

Keywords

EEG/fMRI; absence seizures; epilepsy; seizure onset; medication resistance; Granger causality; thalamus; IGE

INTRODUCTION

Epilepsy is one of the most common neurological illnesses with 6.4 – 35.8% of patients carrying the diagnosis of idiopathic generalized epilepsy (IGE) (2–4). Overall, IGEs are clinically and genetically heterogeneous. Due to their presumed genetic etiologies and generalized seizure onset, IGEs are not amenable to surgical management and AEDs are thought to be the only remedy for these patients. In up to 30% of patients with IGEs polypharmacy with multiple AEDs and/or vagus nerve stimulator (VNS) does not control seizures (5,6). These patients with so-called atypical or medication-refractory IGEs (R-IGEs) are sentenced to life-long medication-resistant seizures and associated complications including low self-esteem, emotional and mood problems, and poor quality of life (7–9). Despite the fact that the resistance to AEDs in patients with IGEs is common, relatively little is known about the sources of the generalized spike and wave discharges (GSWD) in these patients. If available, such information could provide clues regarding the potential reasons for medication-resistance.

The typical EEG pattern in patients with IGEs consists of abrupt onset 2–5 Hz GSWD, frequently with bifrontal and paracentral predominance, superimposed on a normal alpha background. By definition (“generalized”), GSWD should be present in all brain areas and should be associated with the typical IGE seizure patterns – absences, myoclonic jerks or generalized tonic-clonic seizures (1,10). The fact that GSWD are symmetric suggests deep brain structures (e.g., thalamus) as their source. But, the results of studies of EEG patterns in patients with IGEs are divergent and suggest the possibility of either cortical or deep brain sources of GSWD. In one study, asymmetry of the epileptiform discharges on scalp EEG pointed towards potentially different seizure onset as the etiology of AED resistance in patients with juvenile myoclonic epilepsy (JME), an idiopathic generalized epilepsy syndrome (11); patients with asymmetric GSWD are much more likely to have R-IGE (1,11). Studies utilizing dipole modeling showed widespread cortical (predominantly frontal) GSWD onset in patients with IGEs (medication response not provided) (12,13) and corroborated the evidence from morphometric studies suggestive of frontal cortical anatomical abnormalities in patients with IGEs (14,15). Similarly, recent magnetoencephalographic (MEG) source analysis in patients with predominantly R-IGEs showed localization of the GSWD generators mainly in the central and premotor regions of the frontal lobes (16). In contrast to those studies, a recent EEG/fMRI study of patients with IGEs showed increases in BOLD signal responses in the thalami and decreases in the frontal and parietal cortical structures suggestive of the presence of GSWD generators in the deep brain structures (17) while another EEG/fMRI study of AED-naïve patients with absence seizures showed clear thalamic BOLD signal increases with only negative BOLD signal correlates to GSWDs in other brain regions (18). Therefore, the origins of GSWD in patients

with IGEs remain unclear and contributions from both, deep brain and cortical structures are suspected. Some of the differences seen in the studies performed thus far may be related to patient selection with studies including usually mixed groups of AED-responsive and AED-resistant patients. Further, technical difficulties with localization of sources deep within the brain using scalp EEG arrays or magnetoencephalography and algorithms for localization that rely on assumptions about the discrete, dipole character of the sources, may also lead to ambiguous localization of thalamic sources. Based on the above evidence from studies in patients with typical IGEs and R-IGEs we hypothesized that patients with R-IGEs have frontal/cortical location of GSWD generators and that thalamic either contribute to the generation of the GSWD or support their propagation.

METHODS

Subjects

Subjects were identified based on chart review of all consecutive patients treated by epilepsy specialists. Charts were reviewed and, as previously, clinical data were collected using standardized case forms and data dictionary with explicit data definitions (1,19,20). All subjects identified in this manner with no contraindications to fMRI at 4T were offered participation. Concurrent EEG/fMRI at 4T was applied to 83 patients with IGEs after providing informed consent for protocol approved by the Institutional Review Boards of the University of Cincinnati and Cincinnati Children's Hospital Medical Center. This report focuses on 9 of these subjects (2 male), aged 15–55; these subjects were selected for this study because they experienced bursts of GSWD lasting 2 seconds or longer during their scanning sessions and carried the diagnosis of R-IGE based on chart review and the impression of the treating epileptologist (clinical and EEG data on all these patients are included in our recent publication (1)). For the purpose of this study, R-IGE was defined as a relative AED resistance defined as lack of seizure control when treated with maximally tolerated doses of AEDs typically used in patients diagnosed with IGEs (1). Six out of the nine patients became seizure free subsequent to the EEG/fMRI procedure after multiple AED adjustments were made. The clinical characteristics of these IGE patients are included in Table 1. Bursts of GSWD lasting ≥ 2 seconds are typically considered to be absence seizures regardless of the presence or absence of clinical correlates because they are usually associated with clinical signs when tested (21–24).

All subjects had a history of absence and generalized tonic-clonic seizures; patients with JME also experienced myoclonic jerks. We combined patients with different IGEs under the assumption that these patients are thought to have similar etiology of their epilepsy with different clinical presentation (age of onset, types of seizures) (25). All patients included in this study had normal MRI scans (1.5T or 3T). Subjects participated in up to three consecutive 20-minute EEG/fMRI sessions during which they were instructed to lie still, relax, and keep eyes closed. We excluded from inclusion in this study patients managed by physicians other than epilepsy specialists due to the fact that seizure control may be, in part, related to reception of specialized care (20).

fMRI Acquisition

This study was performed on a 61.5 cm bore 4T Varian Unity INOVA system (Varian, Inc., Palo Alto, CA) equipped with a standard head coil. fMRI data acquisition was comprised of T2*-weighted echo-planar images with TR/TA = 3000/1740 ms, FOV = 256×256 mm, matrix = 64×64 , and 5 mm thick slices. Thirty axial slices were collected for each volume in sequential descending order. Each 20-minute fMRI session included a continuous sequence of 400 volumes. Reconstruction of functional images included correction for ghosting and geometric distortion artifacts (26). A 3-dimensional high-resolution structural

image was acquired using a Modified Driven Equilibrium Fourier Transform (MDEFT) method (27,28) with TR/TE = 13.1/6.0 ms, inversion delay, $\tau = 1100$ ms, FOV = $256 \times 196 \times 196$ mm, and matrix = $256 \times 196 \times 196$. The structural image served as a T1-weighted anatomic reference onto which the functional results were overlaid after co-registration.

EEG Acquisition

Concurrent with the fMRI, 64-channels of EEG were recorded with electrodes arranged according to the international standard 10/20 system. Eye-movement and ECG data were also collected for subsequent ballistocardiographic artifact (BCA) removal. During EEG acquisition, time marks generated by the scanner were inserted automatically in the data stream corresponding to the beginning of each functional image acquisition. As previously, EEG data were collected continuously at 10 kHz using a MRI-compatible system (MagLink by Neuroscan, division of Compumedics Ltd, El Paso, TX) with software that included an algorithm to subtract gradient and ballistocardiographic artifacts (Scan 4.3.18) (29,30). After low-pass filtering with a cutoff frequency of 60 Hz, the EPI gradient artifacts induced by imaging were averaged over the first 9 TR periods and then subtracted from each epoch of the raw data following a method described previously (31). In the Scan software, this subtraction procedure was further improved by optimizing temporal alignment between the average gradient waveform and the raw data based on the position of the peak of their cross-correlation. BCA was removed in the same fashion using ECG events as time marks. The data were subsequently derived in a standard 16-channel bipolar montage for review. Fifteen fMRI runs (up to three, 20-minute runs per subject), undertaken by 9 subjects, were found to have at least one continuous burst of GSWD events ≥ 2 seconds in duration. The number of bursts occurring for each subject is detailed in Table 1. The timing of each event, including isolated GSWDs not associated with prolonged bursts, was marked relative to the initiation of fMRI image acquisition.

Data Analyses

Spatiotemporal preprocessing and statistical analysis under the general linear model (GLM) were performed for each individual subject using Statistical Parametric Mapping software (SPM5, <http://www.fil.ion.ucl.ac.uk/spm/>). Correction was first made for temporal differences in slice acquisition in each volume by shifting the Fourier phase of each slice relative to the central slice. Spatial preprocessing included rigid-body realignment of each image to the first image of each session, co-registration of session mean functional images to the corresponding anatomical images, normalization to the Montreal Neurological Institute (MNI) template, and smoothing using an 8 mm FWHM Gaussian kernel. Transformation parameters for the normalization into MNI space were obtained from the anatomical segmentation process in SPM5 based on gray matter, white matter, and cerebral spinal fluid templates. An event-related design model was created using the time course of GSWD events read on the EEG registered in time to the fMRI sequence. The GLM design matrix consisted of an absence seizure regressor as an event-of-interest. Non-seizure, isolated, GSWDs plus the 6 motion parameters from the realignment procedure served as covariates. The seizure and non-seizure event timecourses were convolved with the canonical hemodynamic response function under SPM5, which peaks at approximately 6 seconds after onset. A 128-second high-pass filter was applied to the timecourses. Data from those subjects who had seizure activity for multiple sessions were analyzed via a single multi-session design matrix to account for within-subject variation.

In order to investigate the potential that *brain activity associated with seizure events may precede or follow the detection of such events on scalp EEG*, the first-level GLM analysis outlined above was repeated for a series of models built by imposing shifts in the seizure event timecourse relative to the corresponding EEG event onset. Time shifts from -6

seconds to +6 seconds in 1-second intervals were employed resulting in a total of 13 activation maps for each imaging session (6 with positive time shift, 6 with negative time shift, and one with no time shift relative to EEG onset). Given that the canonical HRF peaks approximately 6 seconds after onset, these time shifts correspond to peak BOLD signal changes occurring at 0 to +12 seconds relative to EEG event onset. A second-level, random effects analysis was completed across sessions for each time shift using the corresponding contrast maps to determine where activity was present at the group level. A nonparametric, perturbation method was utilized for this level of analysis to threshold for significance (SnPM5 on SPM5: <http://www.sph.umich.edu/ni-stat/SnPM/>) (32,33). This resulted in a composite T-score map for each time shift which, after applying a family-wise error (FWE) corrected threshold for statistical significance, revealed activated voxels that could be localized by overlay on an anatomical reference image generated by averaging the individual normalized structural images of all subjects. These T-score maps were subsequently utilized to delineate seizure-relevant regions of interest (ROI) and to qualitatively assess the change in activation due to each time shift. Since quantitative voxel-wise comparisons between maps were not being made, no further correction of voxel p-values was done at this stage to account for multiple interdependent analyses.

Group activation was quantified for specific anatomical ROIs in the 13 composite T-score maps. Positive and negative regional BOLD signal changes were calculated separately and only in those regions containing suprathreshold voxels ($p < 0.05$ corrected) at the group level for any time shift. Activation level as a function of modeled time shift described the group activation timecourse for each ROI. Timecourses were calculated for a variety of relevant bilateral ROIs separately covering the frontal, parietal, limbic, and temporal lobes as well as thalamus and cerebellum. In SPM5, masks for these regions, shown in Figure 1, were provided by the WFU_PickAtlas toolbox (34,35). Although analyzing the data based on lobar ROIs may appear overly simplistic, this was done under the assumption that if lobar (e.g. frontal) onset is the rule then it may occur over any area of the ROI, differing from one patient to the other. This is in parallel to a recent MEG study that observed asymmetric dipole distribution in IGE patients despite symmetric-appearing GSWD (13). Quantification of activation, precluding the need for a strict threshold and providing a measure of the distribution of T-scores, was achieved via a bootstrap technique. Mean positive and/or mean negative T-scores for each ROI were calculated for 1000 random resamplings of its voxel T-scores (with replacement). This resulted in a distribution of mean T values from which an overall mean and standard deviation were calculated. Group activation timecourses, based on the bootstrap distribution means for each time shift, were generated including error bars reflecting the extents of each mean T distribution.

Two secondary analyses (cross-correlation analysis and Granger causality analysis) were also performed *in order to confirm or disprove* the results of the primary analysis, to avoid the imposition of a fixed hemodynamic response function, and to evaluate for possible interactions between ROIs. These analyses were performed on voxel BOLD signal data on a seizure-by-seizure basis. First, a mask was generated within each of the anatomical ROIs described above that included all voxels that activated under group analysis at the FWE-corrected threshold of $p < 0.05$ at the peak of that region's group activation timecourse. The variance attributed to non-seizure GSWD and motion correction parameters was filtered out of the BOLD signal timecourse of each retained voxel. About each seizure event onset in each imaging session, a 36-second (12 TR) span of data was extracted from the signal timecourse including the preceding 12 seconds and the following 24 seconds. These data were applied directly to Granger causality analysis while, for cross-correlation analysis, the data were interpolated to 0.1-second intervals by zero-filling followed by application of a low pass filter that maintained the values of the original data points.

Cross correlation analysis used a bootstrapping approach whereby interpolated data for random pairs of suprathreshold voxels, one from a selected cortical ROI and one from the thalamus, were employed to calculate correlation coefficients for a systematic series of relative shifts, both positive and negative. The peak coefficient was found as well as the time shift that produced it. These were calculated for 1000 random pairings of voxels, with replacement, from which a mean peak shift and corresponding correlation coefficient were calculated. This process was repeated 100 times resulting in distributions of peak shifts and correlation coefficients from which corresponding overall mean values were calculated for each seizure. Results for all seizures were then compiled in a group mean.

The same pairs of ROIs analyzed by cross-correlation were examined for causal relationships. Granger causality, a measure of effective connectivity, was assessed between voxel pairs in the paired ROIs, comparing the error variances of linearly predicting a voxel timecourse in one region using a first-order autoregressive (AR(1)) model vs. an autoregressive exogenous (ARX(1)) model that also includes past data from the paired voxel in the other region (36,37). The Granger analysis, as applied here, results in three measures of interdependence for each pair of voxels, A and B: 1) the causal dependence of B on A (F_{AB}), 2) the causal dependence of A on B (F_{BA}), and 3) the instantaneous dependence between A and B for which causality cannot be discerned (F_i). The net strength and direction of effective connectivity between A and B is measured by the difference $F_{BA} - F_{AB}$ (37). Bootstrapping was employed for this analysis for random pairs of voxels pulled from paired ROIs just as it was for cross-correlation. A group mean for net causal relationship was calculated across all seizures for each ROI pair.

RESULTS

The nine subjects considered for this report experienced a total of 36 seizures detected in processed EEG from 15 imaging sessions. The number of seizures per fMRI run ranged from 1 to 10 (Table 1) with GSWD burst durations ranging from 2.0 seconds to 11.9 seconds (mean $\pm$ SD = 3.8 seconds $\pm$ 2.2 seconds). Individual functional imaging sessions during which seizures occurred resulted in widespread positive and negative BOLD signal changes, particularly if one considers results using any time shift of the modeled BOLD onsets relative to the beginning of the EEG events. Figure 2 shows representative activation patterns from subject, #2, at time shifts of 0 seconds and -2 seconds.

Second-level group activation maps calculated for each time shift in modeled BOLD effect onset (Figure 3) suggest a progression of peak positive activation, relative to the EEG seizure event timing, residing first in parietal and frontal regions followed by the thalamus and the temporal lobes. This progression is captured by the transverse slice images in Figure 3. Parietal activity appears at -3 and -2 seconds in the $z = 48$ mm slice while frontal activation peaks in the 34 mm slice at a -2 second time shift. Limbic activation appears strongest in the 34 mm slice at the time of the seizure onset together with the peak temporal and thalamic activity in the 9 mm slice. Cerebellar activity exceeded the threshold at 0 and +1 seconds in the -21 mm slice. Negative BOLD signal changes were not detected in any voxels at the group level at corrected $p < 0.05$.

The progression of positive activation in each anatomical ROI is quantified in plots of mean positive T-scores as a function of time shift shown in Figure 4. The error bars indicate the full range of the bootstrap distributions of mean T values. Differences between neighboring mean T scores were subjected to 2-sample t tests for significance based on their respective distributions. Mean T-scores whose distributions did not overlap were significantly different to a high degree ($p < 10^{-6}$), even considering that comparisons are being made between interdependent measures. For each ROI, one or two mean T-scores peaked significantly

above the rest. The relative peak timings among the ROIs reflect the qualitative observations described above for Figure 3. These measures suggest that the parietal lobe activated 2 to 3 seconds prior to EEG seizure events, overlapping frontal activation whose peak closely followed at the -2 second time shift. Thalamic, limbic, and temporal regions peaked later, coinciding closely in time with the onset of GSWD trains defining seizures. Interestingly, maximal cerebellar response appeared to lag these EEG event onsets by as much as one second. Peak response timings are summarized in Table 2, along with the corresponding number of group activating voxels and locations of activating clusters at the group level for each ROI (refer to Figure 3).

Seizure-by-seizure cross-correlations of BOLD signal between the thalamus and select cortical regions were calculated using ROIs defined by masking for suprathreshold voxels at the peak of the group response timecourse for each region (see Table 2). Correlation analysis between voxels in the thalamus and those in the parietal, frontal, limbic, temporal, and cerebellar regions, respectively, resulted in a mixture of positive and negative mean relative time shifts necessary to maximize the correlation coefficient (see Figure 5). Negative time shifts correspond to the need to shift thalamic signals to earlier times in order to maximize correlation, thus suggesting that the cortical region precedes the thalamus. The mean $\pm$ standard error time shift relative to the thalamus across all seizures, was $-0.5s \pm 0.2s$ for the parietal region, $-0.5s \pm 0.2s$ for the frontal region, $-0.1s \pm 0.2s$ for the limbic region, $-0.4s \pm 0.1s$ for the temporal region, and $-0.1s \pm 0.2s$ for the cerebellar region. The null hypothesis of zero time shift was rejected, by signed rank test, at the $p < 0.05$ level for the parietal, frontal and temporal regions only.

Finally, Granger causality outcomes were obtained between the same ROIs used for cross-correlation analysis. Again, all interdependence measures varied such that the mean net causality measure between the thalamus and each cortical region had a distribution of values, both positive and negative, among the seizures. These distributions for the parietal, frontal, limbic, temporal, and cerebellar ROIs are shown in Figure 6. Group mean $\pm$ standard error outcomes for net causal influence between these cortical ROIs and the thalamus were: 0.06 ± 0.04 for the parietal region, 0.10 ± 0.03 for the frontal region, 0.05 ± 0.03 for the limbic region, 0.02 ± 0.03 for the temporal region and 0.03 ± 0.04 for the cerebellar region. All cortical ROIs had net causality directed to the thalamus, but *only* the frontal ROI had a significant causal relationship to the thalamus ($p < 0.01$ by signed rank test).

DISCUSSION

The aim of this study was to evaluate the origins of absence seizures in patients with IGEs using combined EEG/fMRI and to test the hypothesis that in patients with R-IGEs the origin of absence seizures is frontal/cortical. The results of time-shifted GLM analyses, confirmed additionally and separately by cross-correlation and Granger causality analyses, appear to support our hypothesis and suggest that the examined R-IGE patients who experienced absence seizures during the EEG/fMRI procedure have broad cortical (e.g., frontal and parietal) rather than thalamic seizure onset. Although this finding may be surprising, the credence of our results is supported by congruent findings from confirmatory analyses including Granger causality that showed causal directionality from the cortical regions to thalami and findings from previously published animal and human studies.

There are two main and contradictory theories in support of the GSWD generators in human brain. Originally in 1947 Jasper and Droogleever-Fortuyn proposed the idea of a deep “pacemaker” as a source of *petit mal* seizures (38). An invasive study by Williams led Penfield and Jasper to propose the *centrencephalic* theory, which posits the thalamus and the upper brain stem as the origin of GSWD in generalized epilepsies (39,40). Other invasive

studies did not confirm these findings (41,42). In fact, the study by Niedermeyer et al. indicated that patients with similar phenotypes suggestive of generalized epilepsy might have had different sources of the GSWD leading to different responses to antiepileptic drugs; at least two of his patients with a typical IGE phenotype proved to have frontal lobe epilepsy; one of them became seizure-free after surgical intervention (41). Therefore, Niedermeyer proposed the more global, *cortical theory* of generalized absence seizure onset postulating that typical generalized seizures are triggered by localized, (e.g., frontal) cortical foci (43,44). Finally, Pierre Gloor based on feline experiments attempted to reconcile the above theories by proposing the *corticoreticular* theory whereby both, functional cortex and functional thalami are necessary for the development of GSWD (45–48). It is possible that all these theories are correct and the results of a study depend on patient/subject selection.

Rodent models of generalized epilepsies provide mixed and at times conflicting results regarding seizure and/or GSWD onset. Some studies suggested Na⁺- and/or Ca⁺⁺-channel mutations in thalamic neurons as the etiology of absence epilepsy (49,50). In contrast, studies of ethosuximide in the genetic rat model of absence epilepsy showed that this AED diminished the firing rate of nucleus reticularis thalami by 90% when administered systemically, but the response was much slower and of lower magnitude when it was administered directly into the thalamus suggesting that the thalamus might not be the only source of GSWD and that the participation of the cortical structures in the generation of GSWD remains likely (51). Another study in WAG/Rji rats potentially contradicted the thalamic theory of GSWD onset – lidocaine injected into the somatosensory cortex led to a decrease in GSWD supporting the notion that the somatosensory (i.e., fronto-parietal) cortex may play an important role for the occurrence of GSWD (52). Finally, a recent EEG/fMRI study of WAG/Rij rats showed BOLD signal changes in both, cortical and thalamic structures in response to absence seizures (53).

Although the animal studies indicate that the thalamus and its connections are essential for the production of GSWD and their characteristic morphology, the major differences between these models and human generalized epilepsy are that these models are “man-made” and that the discharges in these models are much faster than in human IGEs therefore making these models similar to but not exactly like human epilepsy (43,49). While the thalamus, with its connections to all areas of the cortex and its baseline rhythmic firing of bursts of action potentials appears to be an important, if not the most important part of the network underlying GSWD generation, evidence suggests that there may be cortical sources contributing to the etiology of IGEs (54). This notion is consistent with the early human epilepsy literature focusing on cortical onset as the main source of generalized epileptic seizures (41,55). Certainly, our findings in patients with R-IGEs are in agreement with the *cortical theory* of generalized absence seizure onset (43,44). While we observed BOLD signal changes in both thalami and symmetrically in widespread cortical areas, the cortical BOLD signal increases preceded thalamic changes suggesting that the cortical areas are initiating and the thalami sustaining the GSWD.

The frontal involvement in generalized epilepsies is further supported by abnormal neuroimaging and neurocognitive results in IGE patients that are similar to abnormalities identified in frontal lobe epilepsies. For example, the issue of frontal lobe dysfunction in patients with frontal lobe epilepsy and JME was previously examined using neuropsychological testing and PET (56–61). These studies found frontal lobe dysfunction in patients with JME to be similar to the abnormalities seen in patients with frontal lobe epilepsy. Furthermore, MRI studies at 1.5T confirmed that up to 40% of patients with JME have minor structural abnormalities (62–64), but neither these nor other studies have addressed the issue of whether the functional and structural abnormalities are more prevalent in patients with medication-resistant vs. medication-responsive IGEs. These structural/

anatomical studies confirmed though the previous autopsy findings of a few small series of patients with IGE and/or JME that have shown cortical and subcortical dystopic neurons and microdysgenesis in some of these patients (65,66). In contrast to the above studies, cross-sectional MRS evaluation of thalamic structures in patients with IGEs revealed reduction in NAA/Cr ratio in comparison to healthy controls, that was dependent on the duration of epilepsy (67). This is again suggestive of thalamic neuronal dysfunction and a possibility of thalamic participation in the etiology of generalized seizures but it does not exclude the possibility of seizure onset in frontal lobes with later thalamic involvement and possible damage (67). In search of an explanation for these discrepancies one study examined EEGs of patients with JME, and found that patients with VPA-resistant JME have SWD asymmetries in 40% vs. 5% with VPA-responsive JME (11). Another study showed that patients with AED-resistant (VPA $\pm$ other AEDs) JME have higher frequency of all types of seizures (myoclonic + generalized + absence) than patients with AED-responsive (VPA $\pm$ other AEDs) JME (62.5% vs. 23.3%) and that the presence of psychiatric problems pointing toward possible frontal lobe dysfunction is higher in AED-resistant JME patients (58.3% vs. 19%) suggesting again that some patients with otherwise typical IGEs may have frontal abnormalities that may be the cause of their epilepsy (61). The above issues, especially the possibility of focal cortical abnormalities causing an IGE-like syndrome associated with asymmetric SWD remain controversial (1,61,68). The availability of high-field/high-resolution MRI, EEG/fMRI and modern data analysis methods makes addressing some of these questions possible.

Although EEG/fMRI is a fairly new neuroimaging technique, it has been already extensively used in the studies of generalized epilepsies (17,69–72). In one of the early EEG/fMRI studies of patients with various types of IGEs (childhood and juvenile absence, JME, and generalized seizures only), 15/25 patients showed GSWD and BOLD signal response (69). BOLD signal changes related to GSWD were localized to the thalamus (in 80%), but increased BOLD signal was also noted in other, widespread cortical areas including all head regions in 5/15, anterior head regions in 6/15, and predominantly posterior activation in 3/15 (69). Subsequently, several other studies confirmed these results and showed thalamic and cortical BOLD signal increases but the temporal trajectory of BOLD signal changes has not been examined in detail thus far. Of note is that one of the more recent studies focusing on absence seizures during EEG/fMRI found mainly thalamic BOLD signal increases with only minimal and either coinciding or delayed signal decreases in other cortical areas (18). While our results in adults with prolonged bursts of GSWD suggestive of absence seizures during the EEG/fMRI procedure appear to contradict these results, the discrepancy appears to be only superficial. The main difference between these studies is that children studied by Moeller et al. were drug-naïve and once started on valproic acid all became seizure-free. This is in contrast to the patients enrolled in this study, none of whom had their epilepsy controlled at the time of scanning despite many medication trials. While several of these patients became subsequently seizure-free (Table 1) they require ≥ 2 AEDs (or VNS) for seizure control. Hence, all these patients have R-IGE that may be a result of an atypical (not thalamic) seizure generation.

Some weaknesses of this study warrant discussion. EEG/fMRI data associated with seizure activity were subjected to three analytical approaches attempting to discern relationships between pertinent cortical regions and the thalamus. The primary analysis used mean T-scores from time-shifted GLMs to assess the progression of brain activity from cortical to thalamic regions. Cross-correlation of the BOLD signal between various pairs of ROIs over a window of time straddling each seizure served as another measure of relative timing that provided a measure of seizure-to-seizure variation. Finally, the presence or absence of causal relationships between relevant cortical ROIs and the thalamus was determined. All three approaches are deeply influenced by the nature of the HRF. Implicit in the primary

analysis is the assumption that the HRF is fixed: it is the same between subjects, between regions, and between sessions. It is well understood, however, that this may not be the case (73). Evidence exists for variation of as much as a few seconds in the timing of the HRF peak between subjects and from region to region in the brain (74–76). In fact, variation on the order of seconds in BOLD response timing has been observed between sessions of the same subject in voxels that do not activate consistently. There appears to be no clear evidence from these studies, however, that HRF timing differences are systematic between brain regions, particularly between cortical and subcortical domains. Another consideration here is the reference of the relative HRF peak to the EEG GSWD onset at time $t = 0$ sec. This reference point assumes that the HRF corresponding to GSWD activity has the same morphology as the canonical HRF. However, this assumption has not been validated and could lead to systematic shifts or increased variance in the shift of the measured peak responses in the brain regions considered relative to the EEG reference point defined by the SWD onset. Given the sources of variance in the HRF timing, it is not, therefore, surprising that this study finds considerable seizure to seizure variation for cross-correlation and Granger causality measures (Figures 5 and 6). This multi-level variance limited the ability to find significant relative timing and causal relationships between brain regions, given 36 events over which to average. Despite this, a small but significant mean causal link directed from the frontal to the thalamic regions was discerned as well as a significant mean precedence of cortical vs. thalamic response. Still, although unlikely, it cannot be ruled out that these outcomes are indeed the result of subtle consistent regional differences in the HRF time-to-peak.

The relatively large number of EEG/fMRI sessions with absence seizure available for analyses was extracted from an ongoing, large study of epilepsy patients. In the parent EEG/fMRI study the fMRI parameters are designed to obtain functional scans of the entire brain with a TR of 3 seconds. This long TR is not optimal when the aim is to determine timing differences and causal links between brain regions. The effectiveness of Granger analysis, in particular, is well understood to be diminished by a low sampling rate, leading to reduction in the ability to discern causal links, i.e. more of the interdependence is rendered as instantaneous (37). Acquisition of the functional imaging component of an EEG/fMRI study like this one at a higher sampling rate should allow for improvement in effective connectivity outcomes.

The lack of negative activation in the group composite for any time shift in this study disagrees with some earlier results (17,18,69). Individual activation trends included negative response in parietal and frontal regions as shown in Figure 2. It is apparent, however, that negative activation was not consistent per voxel at any particular time shift among the individuals included in this study. It is conceivable that heterogeneity of this subject group regarding diagnosis, history, or AEDs, as detailed in Table 1, contributes to this variability in negative activation. This suggests future studies designed with subgroups of adequate sample size to allow discernment of potential differences in activation patterns. Another potential source of variability of activation or timing is differences in seizure characteristics. GSWD burst durations varied from 2.0 to 11.9 seconds, but no significant correlative relationships were found between burst duration and either the cross-correlation or the Granger connectivity outcomes.

Acknowledgments

This study was supported by NIH K23 NS052468 to JPS; TH was supported by a Summer Undergraduate Research Program in Neuroscience from UC and funds from Cincinnati Epilepsy Center. This study was presented in part at the 2nd Annual Meeting of the American Epilepsy Society/2nd Biennial North American Regional Epilepsy Congress, Seattle, WA 12/2008 and 61st Annual Meeting of the American Academy of Neurology, Seattle, WA, 4/2009.

References

1. Szaflarski JP, Lindsell CJ, Zakaria T, Banks C, Privitera MD. Seizure control in patients with idiopathic generalized epilepsies: EEG determinants of medication response. *Epilepsy Behav* 2010 Apr;17(4):525–30. [PubMed: 20227351]
2. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;34(3):453–68. [PubMed: 8504780]
3. Loiseau P, Duche B, Loiseau J. Classification of epilepsies and epileptic syndromes in two different samples of patients. *Epilepsia* 1991 May–Jun;32(3):303–9. [PubMed: 2044494]
4. Murthy JM, Yangala R, Srinivas M. The syndromic classification of the International League Against Epilepsy: a hospital-based study from South India. *Epilepsia* 1998 Jan;39(1):48–54. [PubMed: 9578012]
5. Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. *Seizure* 2004 Apr;13(3):176–8. [PubMed: 15010055]
6. Prasad A, Kuzniecky RI, Knowlton RC, Welty TE, Martin RC, Mendez M, et al. Evolving antiepileptic drug treatment in juvenile myoclonic epilepsy. *Arch Neurol* 2003 Aug;60(8):1100–5. [PubMed: 12925366]
7. Gilliam F, Kuzniecky R, Faught E, Black L, Carpenter G, Schrodt R. Patient-validated content of epilepsy-specific quality-of-life measurement. *Epilepsia* 1997;38(2):233–6. [PubMed: 9048677]
8. Devinsky O, Vickrey BG, Cramer J, Perrine K, Hermann B, Meador K, et al. Development of the quality of life in epilepsy inventory. *Epilepsia* 1995;36(11):1089–104. [PubMed: 7588453]
9. Szaflarski JP, Szaflarski M. Seizure disorders, depression, and health-related quality of life. *Epilepsy Behav* 2004 Feb;5(1):50–7. [PubMed: 14751207]
10. Blume, W.; Kaibara, M. *Atlas of Adult Electroencephalography*. New York: Raven Press; 1995.
11. Fernando-Dongas MC, Radtke RA, VanLandingham KE, Husain AM. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. *Seizure* 2000 Sep;9(6):385–8. [PubMed: 10985993]
12. Santiago-Rodriguez E, Harmony T, Fernandez-Bouzas A, Hernandez-Balderas A, Martinez-Lopez M, Graef A, et al. Source analysis of polyspike and wave complexes in juvenile myoclonic epilepsy. *Seizure* 2002 Jul;11(5):320–4. [PubMed: 12076104]
13. Westmijse I, Ossenblok P, Gunning B, van Luijckelaar G. Onset and propagation of spike and slow wave discharges in human absence epilepsy: A MEG study. *Epilepsia*. 2009 Jun 10;
14. Kim JH, Lee JK, Koh SB, Lee SA, Lee JM, Kim SI, et al. Regional grey matter abnormalities in juvenile myoclonic epilepsy: a voxel-based morphometry study. *Neuroimage* 2007 Oct 1;37(4):1132–7. [PubMed: 17689105]
15. Woermann FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. *Brain* 1999 Nov; 122(Pt 11):2101–8. [PubMed: 10545395]
16. Stefan H, Paulini-Ruf A, Hopfengartner R, Rampp S. Network characteristics of idiopathic generalized epilepsies in combined MEG/EEG. *Epilepsy Res*. 2009 Apr 24;
17. Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci U S A* 2005 Oct 18;102(42):15236–40. [PubMed: 16217042]
18. Moeller F, Siebner HR, Wolff S, Muhle H, Granert O, Jansen O, et al. Simultaneous EEG-fMRI in drug-naive children with newly diagnosed absence epilepsy. *Epilepsia* 2008 Sep;49(9):1510–9. [PubMed: 18435752]
19. Black LC, Schefft BK, Howe SR, Szaflarski JP, Yeh HS, Privitera MD. The effect of seizures on working memory and executive functioning performance. *Epilepsy Behav* 2010 Mar;17(3):412–9. [PubMed: 20153981]
20. Szaflarski JP, Rackley AY, Lindsell CJ, Szaflarski M, Yates SL. Seizure control in patients with epilepsy: the physician vs. medication factors. *BMC Health Serv Res* 2008;8:264. [PubMed: 19094222]
21. Panayiotopoulos CP, Chroni E, Daskalopoulos C, Baker A, Rowlinson S, Walsh P. Typical absence seizures in adults: clinical, EEG, video-EEG findings and diagnostic/syndromic considerations. *J Neurol Neurosurg Psychiatry* 1992 Nov;55(11):1002–8. [PubMed: 1469393]

22. Porter RJ, Penry JK. Responsiveness at the onset of spike-wave bursts. *Electroencephalogr Clin Neurophysiol* 1973 Mar;34(3):239–45. [PubMed: 4129611]
23. Sadleir, L. Doctorate Thesis. Wellington, New Zealand: University of Otago; 2005. The Electro-Clinical Features of Typical Absence Seizures in Untreated Children.
24. Sadleir LG, Scheffer IE, Smith S, Carstensen B, Farrell K, Connolly MB. EEG features of absence seizures in idiopathic generalized epilepsy: impact of syndrome, age, and state. *Epilepsia* 2009 Jun;50(6):1572–8. [PubMed: 19243419]
25. Andermann F, Berkovic SF. Idiopathic generalized epilepsy with generalized and other seizures in adolescence. *Epilepsia* 2001 Mar;42(3):317–20. [PubMed: 11442147]
26. Schmithorst VJ, Dardzinski BJ, Holland SK. Simultaneous correction of ghost and geometric distortion artifacts in EPI using a multiecho reference scan. *IEEE Trans Med Imaging* 2001 Jun; 20(6):535–9. [PubMed: 11437113]
27. Duewell S, Wolff SD, Wen H, Balaban RS, Jezzard P. MR imaging contrast in human brain tissue: assessment and optimization at 4 T. *Radiology* 1996 Jun;199(3):780–6. [PubMed: 8638005]
28. Ugurbil K, Garwood M, Ellermann J, Hendrich K, Hinke R, Hu X, et al. Imaging at high magnetic fields: initial experiences at 4 T. *Magn Reson Q* 1993 Dec;9(4):259–77. [PubMed: 8274375]
29. Difrancesco MW, Holland SK, Szaflarski JP. Simultaneous EEG/functional magnetic resonance imaging at 4 Tesla: correlates of brain activity to spontaneous alpha rhythm during relaxation. *J Clin Neurophysiol* 2008 Oct;25(5):255–64. [PubMed: 18791470]
30. Espay AJ, Schmithorst VJ, Szaflarski JP. Chronic isolated hemifacial spasm as a manifestation of epilepsy partialis continua. *Epilepsy Behav* 2008 Feb;12(2):332–6. [PubMed: 17951112]
31. Allen PJ, Josephs O, Turner R. A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage* 2000 Aug;12(2):230–9. [PubMed: 10913328]
32. Holmes AP, Blair RC, Watson JD, Ford I. Nonparametric analysis of statistic images from functional mapping experiments. *J Cereb Blood Flow Metab* 1996 Jan;16(1):7–22. [PubMed: 8530558]
33. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002 Jan;15(1):1–25. [PubMed: 11747097]
34. Maldjian JA, Laurienti PJ, Burdette JH. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage* 2004 Jan;21(1):450–5. [PubMed: 14741682]
35. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003 Jul;19(3):1233–9. [PubMed: 12880848]
36. Goebel R, Roebroeck A, Kim DS, Formisano E. Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magn Reson Imaging* 2003 Dec;21(10):1251–61. [PubMed: 14725933]
37. Roebroeck A, Formisano E, Goebel R. Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage* 2005 Mar;25(1):230–42. [PubMed: 15734358]
38. Jasper H, Droogleever-Fortuyn J. Experimental studies on the functional anatomy of petit mal epilepsy. *Res Publ Assoc Nerv Ment Dis* 1947;26:272–98.
39. Penfield, W.; Jasper, H. *Epilepsy and the functional anatomy of the human brain*. Boston: Little Brown; 1954.
40. Williams D. A study of thalamic and cortical rhythms in petit mal. *Brain* 1953 Mar;76(1):50–69. [PubMed: 13041922]
41. Niedermeyer E, Laws ER Jr, Walker EA. Depth EEG findings in epileptics with generalized spike-wave complexes. *Arch Neurol* 1969 Jul;21(1):51–8. [PubMed: 4977267]
42. Hayne R, Belinson L, Gibbs F. Electrical activity of subcortical areas in epilepsy. *Electroencephalogr Clin Neurophysiol* 1949;1:437–45.
43. Niedermeyer E. Primary (idiopathic) generalized epilepsy and underlying mechanisms. *Clin Electroencephalogr* 1996 Jan;27(1):1–21. [PubMed: 8719497]
44. Pavone A, Niedermeyer E. Absence seizures and the frontal lobe. *Clin Electroencephalogr* 2000 Jul;31(3):153–6. [PubMed: 10923203]

45. Gloor P, Quesney LF, Zumstein H. Pathophysiology of generalized penicillin epilepsy in the cat: the role of cortical and subcortical structures. II. Topical application of penicillin to the cerebral cortex and to subcortical structures. *Electroencephalogr Clin Neurophysiol* 1977 Jul;43(1):79–94. [PubMed: 68876]
46. Quesney LF, Gloor P, Kratzenberg E, Zumstein H. Pathophysiology of generalized penicillin epilepsy in the cat: the role of cortical and subcortical structures. I. Systemic application of penicillin. *Electroencephalogr Clin Neurophysiol* 1977 May;42(5):640–55. [PubMed: 67024]
47. Avoli M, Gloor P. The effects of transient functional depression of the thalamus on spindles and on bilateral synchronous epileptic discharges of feline generalized penicillin epilepsy. *Epilepsia* 1981 Aug;22(4):443–52. [PubMed: 7262050]
48. Avoli M, Siatitsas I, Kostopoulos G, Gloor P. Effects of post-ictal depression on experimental spike and wave discharges. *Electroencephalogr Clin Neurophysiol* 1981 Oct;52(4):372–4. [PubMed: 6169514]
49. Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. *Nat Rev Neurosci* 2002 May;3(5):371–82. [PubMed: 11988776]
50. Tsakiridou E, Bertolini L, de Curtis M, Avanzini G, Pape HC. Selective increase in T-type calcium conductance of reticular thalamic neurons in a rat model of absence epilepsy. *J Neurosci* 1995 Apr;15(4):3110–7. [PubMed: 7722649]
51. Richards DA, Manning JP, Barnes D, Rombola L, Bowery NG, Caccia S, et al. Targeting thalamic nuclei is not sufficient for the full anti-absence action of ethosuximide in a rat model of absence epilepsy. *Epilepsy Res* 2003 May;54(2–3):97–107. [PubMed: 12837561]
52. Sitnikova E, van Luijckelaar G. Cortical control of generalized absence seizures: effect of lidocaine applied to the somatosensory cortex in WAG/Rij rats. *Brain Res* 2004 Jun 25;1012(1–2):127–37. [PubMed: 15158169]
53. Tenney J, Duong T, King J, Ferris C. fMRI of brain activation in a genetic rat model of absence seizures. *Epilepsia* 2004;45:576–82. [PubMed: 15144421]
54. Blumenfeld H. The thalamus and seizures. *Arch Neurol* 2002 Jan;59(1):135–7. [PubMed: 11790241]
55. Hayne RA, Belinson L, Gibbs FA. Electrical activity of subcortical areas in epilepsy. *Electroencephalogr Clin Neurophysiol* 1949 Nov;1(4):437–45. [PubMed: 18421833]
56. Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. *Neuropsychiatry Neuropsychol Behav Neurol* 1997;10(4):243–6. [PubMed: 9359121]
57. Swartz BE, Delgado-Escueta AV, Walsh GO, Rich JR, Dwan PS, DeSalles AA, et al. Surgical outcomes in pure frontal lobe epilepsy and foci that mimic them. *Epilepsy Res* 1998;29(2):97–108. [PubMed: 9477141]
58. Swartz BE, Halgren E, Simpkins F, Fuster J, Mandelkern M, Krisdakumtorn T, et al. Primary or working memory in frontal lobe epilepsy: An 18FDG-PET study of dysfunctional zones. *Neurology* 1996;46(3):737–47. [PubMed: 8618675]
59. Swartz BE, Halgren E, Simpkins F, Mandelkern M. Studies of working memory using 18FDG-positron emission tomography in normal controls and subjects with epilepsy. *Life Sci* 1996;58(22):2057–64. [PubMed: 8637437]
60. Swartz BW, Khonsari A, Vrown C, Mandelkern M, Simpkins F, Krisdakumtorn T. Improved sensitivity of 18FDG-positron emission tomography scans in frontal and “frontal plus” epilepsy. *Epilepsia* 1995;36(4):388–95. [PubMed: 7607118]
61. Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry* 2001 Feb;70(2):240–3. [PubMed: 11160477]
62. Woermann FG, Sisodiya S, Free S, Duncan JS. Quantitative MRI in patients with idiopathic generalized epilepsy. Evidence of widespread cerebral structural changes. *Brain* 1998;121:1661–7. [PubMed: 9762955]
63. Woermann FG, Free S, Koepp M, Sisodiya S, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. *Brain* 1999;122:2101–7. [PubMed: 10545395]

64. Woermann FG, Free S, Koepp M, Ashburner J, Duncan JS. Voxel-by-voxel comparison of automatically segmented cerebral gray matter - A rater-independent comparison of structural MRI in patients with epilepsy. *Neuroimage* 1999;10:373–84. [PubMed: 10493896]
65. Meencke HJ, Janz D. Neuropathological findings in primary generalized epilepsy: a study of eight cases. *Epilepsia* 1984 Feb;25(1):8–21. [PubMed: 6692795]
66. Meencke HJ, Janz D. The significance of microdysgenesis in primary generalized epilepsy: an answer to the considerations of Lyon and Gastaut. *Epilepsia* 1985 Jul–Aug;26(4):368–71. [PubMed: 4006898]
67. Bernasconi A, Bernasconi J, Natsume J, Antel S, Andermann F, Arnold D. Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. *Brain* 2003;126:1–8.
68. Lyon G, Gastaut H. Considerations on the significance attributed to unusual cerebral histological findings recently described in eight patients with primary generalized epilepsy. *Epilepsia* 1985 Jul–Aug;26(4):365–7. [PubMed: 4006897]
69. Aghakhani Y, Bagshaw AP, Benar CG, Hawco C, Andermann F, Dubeau F, et al. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 2004 May;127(Pt 5):1127–44. [PubMed: 15033899]
70. Aghakhani Y, Kobayashi E, Bagshaw AP, Hawco C, Benar CG, Dubeau F, et al. Cortical and thalamic fMRI responses in partial epilepsy with focal and bilateral synchronous spikes. *Clin Neurophysiol* 2006 Jan;117(1):177–91. [PubMed: 16314143]
71. Gotman J. Epileptic networks studied with EEG-fMRI. *Epilepsia* 2008;49(Suppl 3):42–51. [PubMed: 18304255]
72. Moeller F, Siebner HR, Ahlgrimm N, Wolff S, Muhle H, Granert O, et al. fMRI activation during spike and wave discharges evoked by photic stimulation. *Neuroimage*. 2009 Jul 18;
73. Tyvaert L, Chassagnon S, Sadikot A, Levan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: An EEG-fMRI study. *Neurology* 2009 Dec 8;73(23):2018–22. [PubMed: 19996076]
74. Aguirre GK, Zarahn E, D’Esposito M. The variability of human, BOLD hemodynamic responses. *Neuroimage* 1998 Nov;8(4):360–9. [PubMed: 9811554]
75. Handwerker DA, Ollinger JM, D’Esposito M. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *Neuroimage* 2004 Apr;21(4):1639–51. [PubMed: 15050587]
76. Neumann J, Lohmann G, Zysset S, von Cramon DY. Within-subject variability of BOLD response dynamics. *Neuroimage* 2003 Jul;19(3):784–96. [PubMed: 12880807]

Figure 1.
Anatomical ROIs for which group activation timecourses were calculated.

Figure 2. Representative activation pattern for subject #2 (Table 1) for time shifts of 0 and -2 seconds relative to EEG seizure onset. BOLD signal increases are shown in red and decreases are shown in blue with a T-score threshold of 2 and -2 respectively. Slice locations are provided in the sagittal brain view in the upper left.

Figure 3.

Group activation timecourse, shown from -4 sec. to +1 sec. in 1 second increments, for 6 axial brain slices. Timings indicate the shift of the BOLD HRF onset relative to the onset of seizure activity according to EEG. There is a progression of activation patterns, from -3 sec. to the time of the EEG onset, peaking in succession in parietal/frontal regions followed by temporal/limbic regions and the thalami. Activations shown are at $p < 0.05$, family-wise error corrected. Slice z coordinates, indicated on the sagittal view, are in MNI space.

Figure 4.

Group activation timecourses, represented as the bootstrapped mean of positive T scores in select anatomic regions of interest (ROI) vs. the time shift of the modeled BOLD response relative to the seizure onset on EEG. Error bars represent the extents of mean T bootstrap distributions. The ROI is indicated for each subplot. The shaded bar highlights zero time shift, where the BOLD onset is considered to coincide with seizure onset. Note that frontal/parietal activity peaks the earliest; 2–3 seconds prior to seizure onset. The limbic lobe peaks between 0 and –1 seconds while the temporal lobe and thalamus peak at the time of seizure onset. The cerebellar response tends to lag the beginning of seizure activity by 0 to 1 seconds.

Figure 5.

Distributions of time shifts maximizing cross-correlation between five cortical regions and the thalamus among all observed seizures. Frontal, parietal, and temporal regions were found to have significant mean time shifts. Negative shifts reflect the cortical region preceding the thalamus. Means are indicated in the figure along with the standard error of the mean. P values are for a test of the null hypothesis of zero mean.

Figure 6.

Distributions of net Granger causal link between each of five cortical regions and the thalamus among all observed seizures. Only the frontal region was found to have significant mean effective connectivity directed to the thalamus. Positive values reflect net connectivity directed from the cortical region to the thalamus. Means are indicated in the figure along with the standard error of the mean. P values are for a test of the null hypothesis of zero mean.

Table 1

Clinical characteristics of subjects who experienced absence seizures during EEG/fMRI scanning sessions (M – male; F – female; JAE –juvenile absence epilepsy; IGE – idiopathic generalized epilepsy; JME – juvenile myoclonic epilepsy; PHT – phenytoin, TPM – topiramate; LTG –lamotrigine; VPA – valproic acid/valproate; OXC – oxcarbazepine; ZNS – zonisamide; VNS – vagus nerve stimulator; LZP – lorazepam; LEV –levetiracetam; CBZ – carbamazepine; KLO – clonopin; PGB – pregabalin; FBM – felbamate; AVM – arterio-venous malformation). In all subjects the diagnosis of epilepsy syndrome is based on clinical and EEG characteristics and was determined by board-certified epilepsy specialists. The final column on the right lists the number of absence seizures experienced by each subject during the specified fMRI session. The total number of seizures observed was 36.

Subject	Sex	Age/Duration	Diagnosis	Family history	Current AEDs	Failed AEDs	Current status	EEG characteristics	Seizure types*	Absence seizure count during fMRI
1	F	27/3	IGE (onset >20 years of age)	none	TPM, LTG, VPA	PHT	Seizure-free	3–4 Hz GSWD	GTC	Session 1: 4 Session 2: 3 Session 3: 1
2	M	23/7	JAE	none	OXC, ZNS, VNS	PHT, LEV, TPM, LTG, PGB, VPA, KLO	Cont. absence seizures, GTC controlled	1–3 Hz GSWD; intermittent focal slowing	GTC	Session 1: 10
3	F	55/40	IGE (few seizures at 1 month; seizure-free till 15 not on meds)	Grandfather w/ epilepsy (possibly IGE)	PHT, VPA, LZP	ZNS, LTG, LEV, TPM	Seizure-free	3–4 Hz GSWD	GTC	Session 1: 1
4	M	15/2	JME	Maternal great aunt with seizure onset at 12 years (IGE)	VPA, ZNS	TPM, LEV, LTG	Seizure-free	3 Hz GSWD	Myoclonus and GTC	Session 1: 1 Session 2: 1 Session 3: 2
5	F	28/18	IGE	Febrile seizures – several family members	LEV, intermittent LZP	CBZ, PHT, LTG, TPM	Seizure-free	3–3.5 Hz GSWD	GTC	Session 1: 1
6	F	23/10	JME	Febrile seizures maternal aunt	VPA, LTG	LEV	Seizure-free	3 Hz GSWD	Myoclonus and GTC	Session 1: 2 Session 2: 1
7	F	25/9	JME	Focal onset epilepsy - mother	LEV, TPM	PHT, OXC, LTG, VPA, CBZ	Cont. absence seizures and GTC; no myoclonus	3–4 Hz GSWD	Myoclonus and GTC	Session 1: 2 Session 2: 3
8	F	22/9	JME	JME – mother and uncle	TPM, KLO	LTG, CBZ, VPA, PB, ETX, PHT	Cont. absence seizures and myoclonus; GTC controlled	3–5 Hz GSWD; photoparoxysmal response	Myoclonus and GTC	Session 1: 2

Subject	Sex	Age/Duration	Diagnosis	Family history	Current AEDs	Failed AEDs	Current status	EEG characteristics	Seizure types*	Absence seizure count during fMRI
9	F	43/17	JME	Brother with seizures (AVM)	CBZ, ZNS	FBM, PHT, VPA, TPM	Seizure-free	5Hz GSWD	Myoclonus and GTC	Session 1: 2

* All patients experienced absence seizures

Table 2

Time of peak group activation, defined as a mean positive T-score, for the anatomical regions of interest indicated. Timings are the shift in modeled HRF onset relative to seizure onset marked on the EEG. The two right-hand columns list respectively the total number of voxels activating at the group level above threshold ($p < 0.05$ corrected) at these timings and the locations of activating clusters. L=left, R=right, BA=Brodmann's Area, DLPFC=dorsolateral prefrontal cortex, FEF=frontal eye fields.

Anatomical Region of Interest	Peak time of group response (mean positive T-score) relative to EEG onset	Total number of voxels activating at $p < 0.05$ corrected	Locations of group activation
Parietal lobe	-3 sec. to -2 sec.	53	R, somatosensory, primary and medial associative, BA 2, 7
Frontal lobe	-2 sec.	1090	L and R, DLPFC, BA 9, 46 L and R, medial premotor, BA 6 L and R, FEF, BA 8 L, somatosensory, BA 3 L and R primary motor, BA 4 L and R operculum, BA 44
Limbic lobe	-1 sec. to 0 sec.	124	dorsal and ventral anterior cingulate, BA 32, 24
Thalamus	0 sec.	308	bilateral
Temporal lobe	0 sec.	925	L and R, auditory, primary and associative, BA 41, 42 L, fusiform gyrus, BA 37 L and R, superior temporal, BA 22 L and R, middle temporal, BA 21 L and R, inferior temporal, BA 20
Cerebellum	0 sec. to +1 sec.	45	L and R, anterior cerebellum