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Imaging Onset and Propagation of ECT-induced Seizures

*Miro Enev, *Kelly A. McNally, *George Varghese, †I. George Zubal, ‡Robert B. Ostroff, and *§¶Hal Blumenfeld

*Departments of Neurology, †Diagnostic Radiology, ‡Psychiatry, §Neurobiology, and ¶Neurosurgery, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

Summary: *Purpose*: Regions of seizure onset and propagation in human generalized tonic–clonic seizures are not well understood. Cerebral blood flow (CBF) measurements with single photon emission computed tomography (SPECT) during electroconvulsive therapy (ECT)-induced seizures provide a unique opportunity to investigate seizure onset and propagation under controlled conditions.

Methods: ECT stimulation induces a typical generalized tonic–clonic seizure, resembling spontaneous generalized seizures in both clinical and electroencephalogram (EEG) manifestations. Patients were divided into two groups based on timing of ictal (during seizure) SPECT tracer injections: 0 s after ECT stimulation (early group), and 30 s after ECT (late group). Statistical parametric mapping (SPM) was used to determine regions of significant CBF changes between ictal and interictal scans on a voxel-by-voxel basis.

Results: In the early injection group, we saw increases near the regions of the bitemporal stimulating electrodes as well as some thalamic and basal ganglia activation. With late injections, we observed increases mainly in the parietal and occipital lobes, regions that were quiescent 30 s prior. Significant decreases occurred only at the later injection time, and these were localized to the bilateral cingulate gyrus and left dorsolateral frontal cortex.

Conclusions: Activations in distinct regions at the two time points, as well as sparing of intermediary brain structures, suggest that ECT-induced seizures propagate from the site of initiation to other specific brain regions. Further work will be needed to determine if this propagation occurs through cortical–cortical or cortico-thalamo-cortical networks. A better understanding of seizure propagation mechanisms may lead to improved treatments aimed at preventing seizure generalization.
Key Words: Epilepsy—Generalized tonic–clonic seizures—Thalamus—Propagation—SPECT—SPM.

Generalized tonic–clonic seizures involve sudden dramatic changes in brain physiology and behavior. Widespread cortical and subcortical networks are engaged in this abnormal paroxysmal activity, which causes massive generalized convulsions. Generalized tonic–clonic seizures occur spontaneously in patients with epilepsy, often causing injuries or falls, but are also induced therapeutically in electroconvulsive therapy (ECT) for treating patients with refractory depression. Recent work suggests that so-called "generalized" seizures are not truly generalized (Blumenfeld et al., 2003b; Blumenfeld, 2005). Instead, "generalized" seizures appear to selectively involve certain focal cortical and subcortical networks most intensely, while other brain regions are relatively spared. One important unanswered question is whether separate focal areas are involved simultaneous during generalized seizures, or whether seizure activity begins in one location and then propagates to other regions.

Previous studies support the involvement of focal bilateral brain regions during generalized tonic–clonic seizures (Engel et al., 1978; Ackermann et al., 1986; Bajc et al., 1989; McIntyre et al., 1991; Handforth and Ackermann, 1995; Handforth and Treiman, 1995; McCown et al., 1995; Vollmer-Haase et al., 1998; Andre et al., 2002). Our recent work both in humans and animal models demonstrates that generalized tonic–clonic seizures cause local activation of the lateral frontal and parietal association cortex, along with subcortical structures such as the thalamus (Blumenfeld et al., 2003a,b; McNally and Blumenfeld, 2004; Nersesyan et al., 2004a). One useful approach for studying human generalized tonic–clonic seizures has been neuroimaging during ECT. In ECT a generalized tonic–clonic seizure is induced under controlled conditions and with predictable timing (American Psychiatric Association, 2001). ECT-induced seizures resemble spontaneous generalized tonic–clonic seizures both behaviorally and electrographically, and similar brain regions have been shown to be involved in ECT and in spontaneous

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Address correspondence and reprints requests to Dr. Hal Blumenfeld at Yale Departments of Neurology, Neurobiology, Neurosurgery, 333 Cedar Street, New Haven, CT 06520-8018, U.S.A. E-mail: hal.blumenfeld@yale.edu
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tonic–clonic seizures in patients with epilepsy (Blumenfeld et al., 2003b).

In a previous imaging study of cerebral blood flow (CBF) changes during generalized tonic–clonic seizures induced with bitemporal ECT, we found maximal increases in bilateral frontal and temporal cortex as well as in parietal association cortex and midline subcortical networks (Blumenfeld et al., 2003b). Interestingly, our results suggest a propagation mechanism since frontal and parietal regions were strongly activated but intervening regions were relatively spared. We hypothesized that our results reflected early CBF increases in the frontotemporal regions, together with late CBF increases in the parietal cortex. However, in this initial study we combined data from different time points at 0 and 30 s after seizure onset, which may have limited our ability to resolve sequential involvement of different brain regions. To further address the question of neural activity propagation, the present study analyzes CBF changes separately at 0 and 30 s after onset of ECT-induced generalized tonic–clonic seizures to understand how the focal activations we observe are temporally modulated. We use single photon emission computed tomography (SPECT) because this method of imaging allows us to scan the patient an hour or so after the seizure ends—thus eliminating potentially serious problems with movement artifact and the patient's clinical stability (Andersen, 1989; Devous et al., 1990). To analyze activation timing we used two configurations: (early) ictal injection 0 s after ECT stimulus and (late) ictal injection 30 s after ECT stimulus. Separating the data in this way enabled us to study the discrete CBF changes occurring at the two time steps. The 30 s interval between configurations was chosen to account for the temporal resolution of SPECT imaging which is dependent on cerebral uptake and distribution.

The novelty of our approach lies in the temporal nature of our analysis of CBF changes in induced generalized tonic–clonic seizures. We examine CBF changes at two distinct time points during the course of a seizure to understand the patterns of activation and propagation in the focal regions involved.

METHODS

Methods of patient recruitment, ECT treatment, and SPECT image acquisition and analysis were described previously (Blumenfeld et al., 2003b), and are summarized again briefly below. The new results for this study were produced by reanalysis of the data based on SPECT injection timing.

Patients

All experiments on human subjects were conducted in accordance with the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm) and Yale Human Investigations Committee guidelines. Informed consent was obtained from all subjects. Eight patients were studied who met DSM-IV criteria for major unipolar depressive disorder and were in maintenance ECT with bitemporal stimulation (American Psychiatric Association, 2001; Blumenfeld et al., 2003b). We divided the patients into two groups according to SPECT injection timing: an early group with ictal injection 0 s after ECT stimulus (N = 4 subjects), and a late group ictal injection 30 s after ECT stimulus (N = 7 subjects). Three of the patients in the late group were also imaged in the early group, for a total of eight unique patients.

Bitemporal ECT

ECT stimulation induces a typical generalized tonic–clonic seizure, resembling spontaneous generalized seizures in both clinical and electroencephalogram (EEG) manifestations (American Psychiatric Association, 2001). As described previously (Blumenfeld et al., 2003b), standard bitemporal electrode positions were used (Lawson et al., 1990), and treatments were given at 1.5 times threshold with a Mecta Spectrum Apparatus (Lake Oswego, OR, U.S.A.) and standard dose titration (Abrams, 1997; Kellner et al., 1997; American Psychiatric Association, 2001). Seizure threshold was determined at the initiation of treatment, and no further titration was done. Anesthesia consisted of methohexital (1–1.5 mg/kg) and neuromuscular blockade with succinylcholine (0.6 mg/kg). Motor and EEG seizure duration were monitored. Electrocardiogram, oxygen saturation, and blood pressure were also monitored throughout the procedure.

SPECT

We used SPECT to measure CBF during ECT-induced seizures (ictal) and compared the results to baseline (interictal) CBF between seizures for each patient. SPECT is particularly well suited to imaging seizures because it provides a snapshot of CBF changes at the time of injection, allowing the actual imaging to be done later when the patient is no longer moving. SPECT relies on injection of radioactive tracer, which is rapidly taken up by the brain but does not redistribute. Uptake of SPECT agent is nearly 100% complete within 30–60 s, reflecting CBF at the time of injection (Andersen, 1989; Devous et al., 1990).

Patients were injected intravenously with 30 mCi of the SPECT agent Tc-99m hexamethylpropylene-amine-oxime (HMPAO). For each patient ictal and interictal SPECT images were acquired on different treatment days under the same anesthesia conditions. We used two ictal injection conditions: early and late. Early injections took place simultaneously with the ECT stimulus (0 s), while late injections were delivered 30 s after ECT stimulus. Interictal SPECT injections were administered under the same anesthesia conditions, but at least 2 min prior to the ECT stimulus as described previously (Blumenfeld et al., 2003b). Thus, for interictal scans uptake of the SPECT agent was complete well before the beginning of the seizure.

For all subjects, SPECT imaging took place within 90 min of radiopharmaceutical injection. Projection data were acquired on a Picker Prism 3000 (Philips Medical Systems, Best, The Netherlands) mounted with high-resolution fan beam collimators. Data were acquired into 128 × 128 matrices over 40 min during which each of the three heads makes a 120° orbit. Transverse slices were reconstructed using the routine clinical filtered back projection algorithm with a Chang attenuation correction (Zubal et al., 1995). For anatomical analysis of SPECT imaging changes, high resolution MRI images were acquired for each patient using 3D volume inversion recovery prepped fast spoiled gradient recalled echo (IR-FSPGR) imaging with 1.5 mm slices (or partitions), 22 cm field of view, minimum TR and TE, and 192 × 256 matrix, one excitation, on a 1.5-T GE Signa LX MRI system (Waukesha, WI, U.S.A.).

Imaging analysis

Analysis of SPECT data (for both early and late groups) was done using Statistical Parametric Mapping (SPM99) on a MATLAB platform as described previously (Chang et al., 2002; Blumenfeld et al., 2003b) (http://spect.yale.edu). Similar results were also found using SPM2. The preprocessing steps were realignment, spatial normalization, and smoothing. In the normalization step the bounding box parameter was set to the template; all other spatial normalization variables were kept at default values. The smoothing method employed a Gaussian kernel with a FWHM of 16 × 16 × 16 mm. Following preprocessing, paired *t*-test analysis was performed using SPM's statistical model: Population main effect, two conditions, one scan/condition. As in our prior studies (Blumenfeld et al., 2003a, 2004 McNally et al., 2005), the extent threshold (k) below which clusters were rejected was 125 voxels (equivalent to a volume of 1 cc with SPM voxel dimensions of 2 × 2 × 2 mm). Voxel level height threshold p was 0.01 corresponding to a Z score of 2.33. At the cluster level, we only considered those with cluster level significance $p < 0.05$, corrected for the entire analysis volume.

RESULTS

We observed different patterns of activation for early ictal injections (0 s after ECT stimulation) compared to late injections (30 s after ECT stimulation). In the early ictal group, regions of CBF hyperperfusion were anatomically related to the location of the stimulating bifrontotemporal ECT electrodes. The most significant clusters of CBF increases (Figs. 1a, 2a, and Table 1) occurred bilaterally in the inferior frontal gyri, and in the anterior insula. This is consistent with previous reports of bilateral frontal hyperperfusion with bitemporal ECT-induced generalized tonic–clonic seizures (Blumenfeld et al., 2003a,b), as well as postictal changes in these regions (Prohovnik et al., 1986; Rosenberg et al., 1988; Nobler et al., 2001).

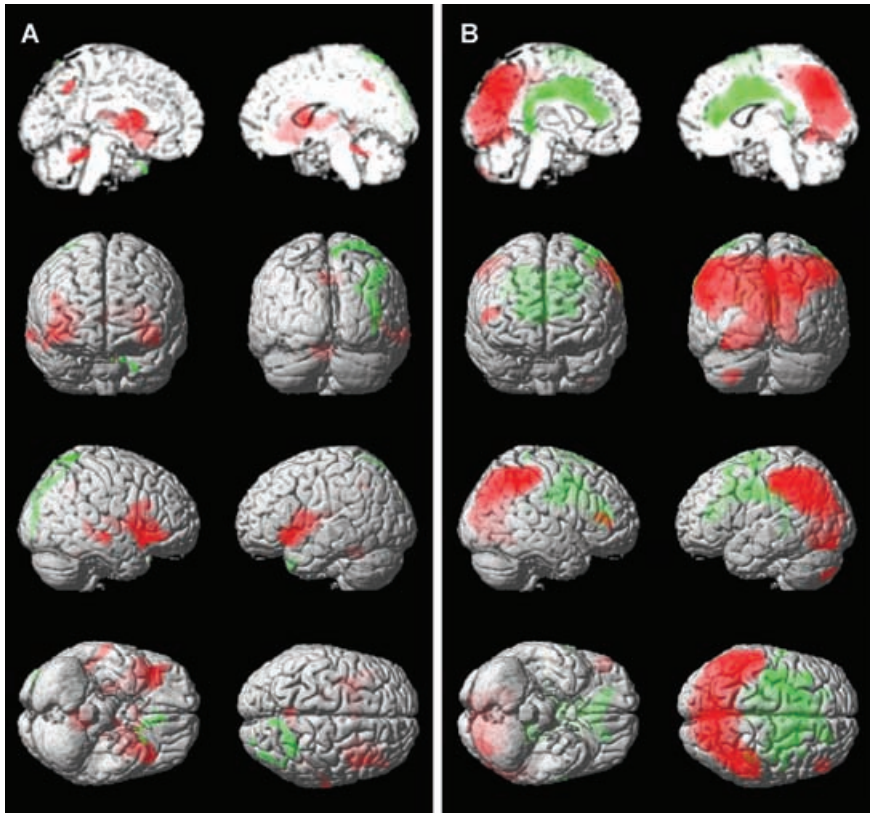

FIG. 1. Early CBF increases in frontal cortex and late CBF increases in parietal cortex with bitemporal ECT. SPECT images of significant CBF changes during bitemporal ECT-induced seizures. Statistical parametric maps depict CBF increases (hyperperfusion) in red and decreases (hypoperfusion) in green. **(A)** CBF changes in patients with ictal injections at onset (0 s after ECT stimulus). Increases occur in the bilateral inferior frontal gyrus, anterior insula, putamen and thalamus. No significant decreases were found (n = 4). **(B)** Changes in patients with ictal injections 30 s after ECT stimulus. Increases occur in bilateral parietal and occipital cortex, while decreases occur in the bilateral cingulate gyrus and left dorsolateral frontal cortex (n = 7). For **(A)** and **(B)**, extent threshold, k = 125 voxels (voxel size = 2 × 2 × 2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

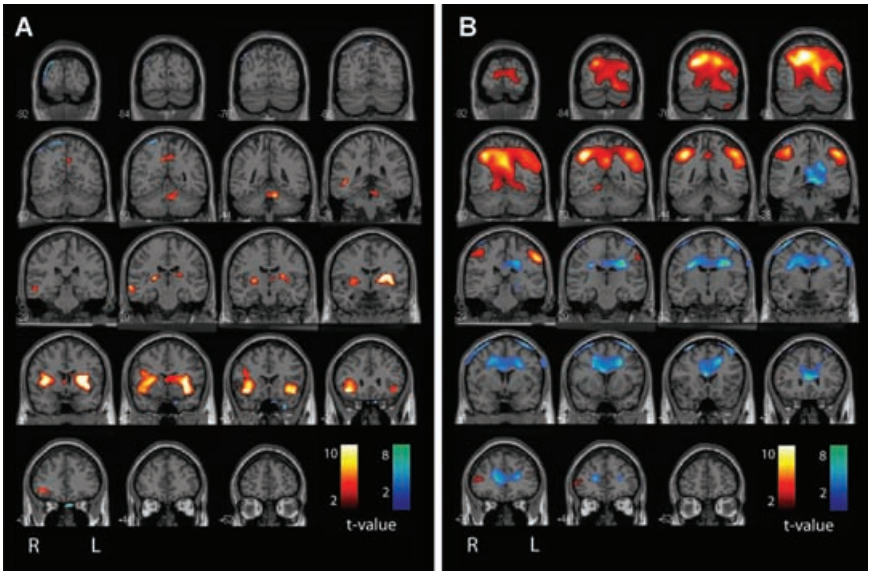

FIG. 2. CBF increases and decreases in early and late group overlaid on a structural MRI in the coronal plane. Same patients and data are shown as in Fig. 1. CBF increases are (hyperperfusion) shown in red and decreases (hypoperfusion) in blue. **(A)** CBF changes in patients with early ictal injections (0 s after ECT stimulus), showing increases in bilateral inferior frontal gyrus, anterior insula, putamen, and thalamus (n = 4). **(B)** Changes in patients with ictal injections 30 s after ECT stimulus (late group). Increases occur in bilateral parietal and occipital cortex, while decreases occur in the bilateral cingulate gyrus and left dorsolateral frontal cortex (n = 7). For **(A)** and **(B)**, extent threshold, k = 125 voxels (voxel size = 2 × 2 × 2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

Additional regions of activation in the early ictal group occurred in the putamen and thalamus – regions whose role in seizure initiation and propagation has long been recognized in the epilepsy literature (Avoli et al., 1990; Norden and Blumenfeld, 2002). No significant regions of CBF decreases (hypoperfusion) were observed in the early ictal injection group.

With delayed ictal injections (30 s after onset), CBF increases were no longer present in the frontal cortex. Instead regions of CBF hyperperfusion were localized to bilateral parietal and occipital cortex (Figs. 1b, 2b, and Table 1). Decreases were observed in the bilateral cingulate gyrus and left dorsolateral frontal cortex (decreases in right frontal cortex were not significant at the cluster level). Notably, intervening regions between the early and late hyperperfused regions were spared. This finding supports our hypothesis of propagation of activation.

Table 1 provides additional information regarding the regions of hyperperfusion and hypoperfusion in the early and late ictal injection groups. Aside from SPECT injection timing the early (0 s) and late (30 s) groups were comparable in other ways. Thus, the mean seizure duration for both groups together was 41.91 s without significant differences between early and late groups (early 36.25 s; late 47.57 s; two-tailed *t*-test = 0.27). The average patient age at the time of study was 50 yr (47 early group; 53 late group; two-tailed *t*-test = 0.39). Mean ECT stimulation energy was 46J (early 45; late 47; two-tailed *t*-test = 0.89). There were slight variations above and below the 30mCi dose of the HMPAO radioactive tracer injected for

TABLE 1. *Brain regions with significant changes during generalized seizures induced by bitemporal ECT*

Brain regions (voxel clusters)	Cluster Significance (P)	Cluster Volume (k)	Maximum voxel location	x, y, z	Maximum voxel z-score
Generalized seizure (0 s)					
Hyperperfusion					
Bilateral inferior frontal gyrus, anterior insula, putamen, and thalamus	<0.001	6,674	Left anterior insula	–30, 6, 0	4.42
Hypoperfusion					
No significant clusters	–	–	–	–	–
Generalized seizure (30 s)					
Hyperperfusion					
Bilateral parietal and occipital cortex	<0.001	26,600	Right parietal	24, –74, 32	4.92
Hypoperfusion					
Bilateral cingulate gyrus	<0.001	11,466	Left cingulate	–30, –14, 34	4.58
Left dorsolateral frontal cortex	0.038	1,668	Left middle frontal gyrus	–30 12 72	3.73

Same data as in Figs. 1 and 2. P: cluster-level significance corrected for multiple comparisons for the entire brain. Only clusters with cluster-level significance $p < 0.05$ are listed. k: cluster size in voxels (voxel size = 2 × 2 × 2 mm). x, y, z are coordinates in MNI space of the voxel with maximum z-score for the cluster.

SPECT imaging with an average of 29.5 mCi (early 29.5; late 29.5; two-tailed t-test = 0.44).

DISCUSSION

Generalized tonic–clonic seizures are often thought of as maximal events in which there is paroxysmal and ubiquitous activation of the entire nervous system. However, even these most extreme seizure events seem to involve specific regions of the brain while sparing others. Our previous work with controllably induced generalized tonic–clonic seizures supports this notion of nonhomogeneous involvement of brain regions. Specifically, in a study of ECT-induced seizures, we found CBF increases in focal cortical areas and subcortical structures with relatively little activation in intervening regions (Blumenfeld et al., 2003a,b McNally and Blumenfeld, 2004). This led us to hypothesize that the region of seizure onset determines the initial pattern of relative signal increases (e.g., in the frontotemporal regions) and that subsequent activations (e.g. in the parietooccipital cortex) were produced by propagation mechanisms. If such a mechanism of propagation is validated, new approaches for reducing seizure propagation could become feasible for treatment of epilepsy.

In the present study, we were interested in understanding the time courses of focal activations in ECT-induced generalized tonic–clonic seizures. We hypothesize that focal regions are either simultaneously engaged, or that epileptiform activity begins in one set of regions and dynamically spreads to additional areas. To bring out the differences between these possible modes of seizure genesis, we measured CBF changes using early and late SPECT injections. In our early group, patients were injected with SPECT radiotracer 0 s after ECT stimulation (injection simultaneous with seizure onset). In the late group, a SPECT radiotracer injection was administered 30 s after ECT stimulation (half minute after seizure onset).

Findings

In the early injection group, we see increases near the regions of the stimulating electrodes as well as some thalamic and basal ganglia activation. This observation is consistent with previous studies of ictal and postictal CBF changes with ECT (Rosenberg et al., 1988; Scott et al., 1994; Nobler et al., 2001). Later increases occur mainly in the parietal and occipital lobes, regions that were quiescent 30 s prior. Significant decreases occur only in the later stage of activity, and these are localized to the bilateral cingulate gyrus and left dorsolateral frontal cortex. Our results seem to support the hypothesis that CBF increases occur early in the regions of seizure onset, and later in the parietal cortex, possibly reflecting seizure propagation.

Possible mechanisms

What drives this pattern of activation? More work remains to be done before we understand generalized tonic–clonic seizures, their focal onset, and their mechanisms of spread. We propose that the streams of propagation are driven by (1) corticocortical networks, or by (2) cortico-thalamo-cortical networks. Corticocortical seizure propagation between frontal and parietal association cortex with relative sparing of intervening cortical regions may occur through long association fiber pathways such as the superior longitudinal fasciculus (Schwartz et al., 1991; Makris et al., 2005). This could occur either through orthodromic conduction, or perhaps via antidromic backpropagation of epileptiform activity along white matter pathways (Gutnick and Prince, 1972). Another possible theory is that seizure activity in a focal cortical region can trigger recruitment of subcortical projection sites that in turn produce the spreading phenomenon via their other cortical projections. In this line of reasoning, the thalamus plays an active role as a relay between cortical propagation from early to late phases of the seizures episode. In support of this view is the marked early thalamic hyperperfusion that we observe in our results. One potential pathway for the spread of activations would involve descending connections from frontal cortex to the thalamus including the pulvinar, and lastly signal relays to large regions of the parietal and occipital association cortex (Guillery and Sherman, 2002; Sherman, 2005).

Limitations

The present study was most significantly hindered by its small sample size. In future experiments, our observations need to be validated on a larger scale and confirmed in patient populations large enough to be protected against statistical chance. Currently we only have two time points separated by a half-minute interval, a lengthy time span in the context of electric signaling. On the other hand, despite the potential for fast propagation, secondarily generalized tonic–clonic seizures are known to progress through a series of electrical and behavioral stages that evolve over tens of seconds (Theodore, 1994; Jobst, 2001). We can speculate that these sequential changes may depend on slow, regional movement of the most intense seizure activity through long-range network connections. It is theoretically possible that the methohexital anesthesia used in this study produced slower propagation of seizures than would be observed without anesthesia. In subsequent work we would like to increase the ictal conditions to include additional injection times–both before and after ECT stimulation. Increasing the number of time points would provide us with a richer data set of propagation patterns and potentially allow us to discriminate between the corticocortical and cortico-thalamo-cortical pathways. Placement of stimulating electrodes in bitemporal, bifrontal, or right unilateral configurations has been shown previously to produce different patterns of CBF increases (Blumenfeld et al., 2003a,b McNally and Blumenfeld, 2004). It would, therefore, be of interest in future studies, to investigate effects of stimulating electrode placement on the progression of CBF changes at different time points. An

additional limitation is the lack of information relating the observed changes in CBF to underlying brain electrical activity. EEG recordings in the present study were limited to two contact pairs (left and right hemisphere). Although scalp EEG has relatively poor spatial resolution, further studies with more extensive EEG coverage may shed additional light on the timing of seizure propagation. In addition, invasive electrical recordings from animal models have the potential to explain the basic pathophysiology and networks involved in propagation of generalized tonic–clonic seizures (Nersesyan et al., 2004b,a).

Some additional sources of error arise from the nature of CBF changes measured with SPECT imaging. There is a delay of 20–30 seconds between SPECT tracer injection and brain uptake (Andersen, 1989). However, this may at least in part be offset by the delay between changes in neuronal activity and CBF changes (Nersesyan et al., 2004b). The relationship between CBF and neuronal firing is indirect, and in later studies it would be important to validate that focal CBF changes are indicators of focal neural network activity. Furthermore, SPECT is a method which relies on relative perfusion signal changes. SPECT data can be misinterpreted and has weaker spatial (1 cm) and temporal resolution (30 s) in comparison to fMRI and ^{15}O-PET, although SPECT has significant advantages for avoiding movement artifact during seizures. The time resolution could be improved using near-infrared spectroscopy (Watanabe et al., 2002; Franceschini and Boas, 2004), although this may sacrifice spatial resolution. In short, our results suggest a temporal evolution of activity changes from frontal to parietal cortex, but will need to be verified through additional multi-modal studies.

Anatomical correlates

The robust involvement of higher-order association cortex in the frontal and parietal lobes strongly resembles regions involved in perceptual discrimination and attention tasks (Lumer et al., 1998; Leonards et al., 2000; Rees and Lavie, 2001; Rees et al., 2002). Similarly, the upper brainstem and thalamus are known to play an important role in normal attention (Kinomura et al., 1996). The CBF decreases we observed in the cingulate cortex also include regions important for attention and response selection (Bunge et al., 2002). The intense involvement of thalamus, anterior cingulate, and frontoparietal association cortex in our imaging results suggests that disrupted function in these regions may contribute to the profound loss of consciousness that accompanies and follows generalized tonic–clonic seizures. Thus, despite the apparently generalized nature of tonic–clonic seizures, focal brain regions are preferentially involved while others are relatively spared, which has functional consequences for the cognitive impairment associated with seizures, including impaired consciousness (Blumenfeld and Taylor, 2003; McNally and Blumenfeld, 2004).

These results with ECT-induced seizures must be interpreted cautiously, since induced seizures in depressed patients may differ significantly from spontaneous seizures in epilepsy patients. Electrical stimulation likely causes both acute and chronic changes in neuronal excitability, synaptic connections, and propagation physiology, which may differ from changes seen in chronic epilepsy. Epilepsy patients are more difficult to study, because of the heterogeneity of seizure types in this population. However, early results suggest that similar patterns of activation occur in spontaneous secondarily generalized tonic–clonic seizures in patients with epilepsy. With secondarily generalized partial seizures in epilepsy patients, we also observe focal cortical regions of activation, subcortical activations in the thalamus, and significant decreases in the cingulate (Blumenfeld et al., 2003b; Varghese et al., 2005a,b). This would suggest that our present findings are applicable in other types of seizures, and increase the relevance of understanding the propagation mechanisms and their potential association to impaired consciousness. Thus, propagation of secondarily generalized seizures in patients with epilepsy warrants further investigation.

IMPLICATIONS

There are several important implications of understanding the mechanisms of propagation during generalized tonic–clonic seizures. Elucidating the methods of seizure spread can have a major impact on developing stabilizing mechanisms to prevent abnormal firing, and block seizure generalization. This is especially important if we can limit the profound impairments of consciousness produced by the intense focal involvement of higher order circuits. Understanding the onset and recruitment of focal network activations may provide new targets for more selective therapies for generalized seizures.

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