

## ARE GENERALIZED TONIC–CLONIC SEIZURES REALLY “GENERALIZED”?

**Cortical and Subcortical Networks in Human Secondly Generalized Tonic–Clonic Seizures.** Blumenfeld H, Varghese GI, Purcaro MJ, Motelow JE, Enev M, McNally KA, Levin AR, Hirsch LJ, Tikofsky R, Zupal IG, Paige AL, Spencer SS. *Brain* 2009;132(Pt 4):999–1012. Generalized tonic–clonic seizures are among the most dramatic physiological events in the nervous system. The brain regions involved during partial seizures with secondary generalization have not been thoroughly investigated in humans. We used single-photon emission computed tomography (SPECT) to image cerebral blood flow (CBF) changes in 59 secondarily generalized seizures from 53 patients. Images were analyzed using statistical parametric mapping to detect cortical and subcortical regions most commonly affected in three different time periods: 1) during the partial seizure phase prior to generalization; 2) during the generalization period; and 3) postictally. We found that in the pregeneralization period, there were focal CBF increases in the temporal lobe on group analysis, reflecting the most common region of partial seizure onset. During generalization, individual patients had focal CBF increases in variable regions of the cerebral cortex. Group analysis during generalization revealed that the most consistent increase occurred in the superior medial cerebellum, thalamus, and basal ganglia. Postictally, there was a marked progressive CBF increase in the cerebellum that spread to involve the bilateral lateral cerebellar hemispheres, as well as CBF increases in the midbrain and basal ganglia. CBF decreases were seen in the fronto-parietal association cortex, precuneus, and cingulate gyrus during and following seizures, similar to the “default mode” regions reported previously to show decreased activity in seizures and in normal behavioral tasks. Analysis of patient behavior during and following seizures showed impaired consciousness at the time of SPECT tracer injections. Correlation analysis across patients demonstrated that cerebellar CBF increases were related to increases in the upper brainstem and thalamus, and to decreases in the fronto-parietal association cortex. These results reveal a network of cortical and subcortical structures that are most consistently involved in secondarily generalized tonic–clonic seizures. Abnormal increased activity in subcortical structures (cerebellum, basal ganglia, brainstem, and thalamus), along with decreased activity in the association cortex may be crucial for motor manifestations and for impaired consciousness in tonic–clonic seizures. Understanding the networks involved in generalized tonic–clonic seizures can provide insights into mechanisms of behavioral changes, and may elucidate targets for improved therapies.

## COMMENTARY

Although the division of epileptic seizures into generalized and focal types began with Hughlings Jackson in 1870 (1), generalized seizures were originally defined by the 1969 Commission on Classification as: “referable to an anatomical and/or motor changes which are generalized or at least bilateral” (2). This concept, particularly the word “generalized,” might lead to the false assumption that generalized tonic–clonic seizures (GTCS), including those that are secondarily generalized, involve global excitation of the entire brain. On thoughtful reflection, this is implausible. Propagation of seizures must follow defined pathways, and excitation in some neural systems will lead to inhibition of others. The stereotyped behavioral manifestations of GTCS must also be mediated by specific motor systems. However, the scalp electroencephalogram (EEG), which is the traditional method of studying seizure spread, has limited spatial resolution and cannot detect seizure propaga-

tion in subcortical structures. For this reason, the functional anatomy of human GTCS has been difficult to characterize.

Evidence that GTCS may not involve the entire cerebral cortex comes from invasive monitoring that showed that even with limited sampling, it is not uncommon to find electrodes that are quiescent throughout the course of the seizure (3). Neuroimaging is the best way to visualize subcortical systems, but the intense motor activity of GTCS precludes use of functional magnetic resonance imaging (fMRI). Therefore, the most useful tools are ictal positron emission tomography (PET) and single-photon emission computed tomography (SPECT), which have previously been utilized to study the convulsions induced by electroconvulsive therapy for depression (4,5). [<sup>15</sup>O] PET and HMPAO (Tc-99m hexamethylpropylene-amine-oxime) SPECT have demonstrated ictal increases in cerebral blood flow (CBF) in some basal ganglia and thalamic regions, but PET also showed increases in frontal, parietal, and temporal neocortex, whereas SPECT showed parietal and occipital increases (4,5). With injections later during the seizure, both methods showed decreased blood flow in cingulate and medial frontal cortices (4,5). Therefore, these induced GTCS are associated with a

widespread, but circumscribed pattern of regional activation and inactivation.

The study by Blumenfeld and colleagues builds upon this prior work, by using ictal (before and after the appearance of the GTCS) and postictal SPECT to provide a more detailed map of CBF during spontaneous secondarily GTCS. Adequate resolution to delineate subcortical regions was obtained by use of ictal–interictal difference analysis, using statistical parametric mapping (6,7). In the current study, the most common site of seizure origin was the temporal lobes, with approximately equal right- and left-sided onset when seizures could be lateralized. Analyses were performed for right- and left-sided onset cases, as well as for all cases combined, to identify patterns common to all situations.

Although there was variability in the pattern of increased CBF in the cerebral cortex during generalization, a common finding was decreased blood flow in frontoparietal and cingulate cortices. Subcortical regions of increased blood flow included the thalamus, basal ganglia, and superior medial cerebellum. In particular, a marked and progressive increase in cerebellar blood flow during generalization, persisting into the postictal phase, led the authors to suggest a role for the cerebellum in seizure termination. They also proposed an anatomical mechanism for impairment of consciousness during GTCS and other seizures: abnormal activation of the thalamus and upper brainstem disrupts ascending arousal mechanisms, leading to abnormally reduced function in the frontoparietal association cortex, resulting in impairment of attention and consciousness.

A limitation in the approach in the current study is that SPECT resolution is not adequate to distinguish among adjacent small thalamic and brainstem structures, which may have quite different connections and functions. In addition, the speculated roles for different brain regions in seizure termination and alteration of consciousness are difficult to directly test and confirm in humans. Therefore, the implications of the findings of Blumenfeld and his coworkers are best understood in the context of extensive prior investigations of functional seizure anatomy in experimental animals (8,9). These studies conclusively demonstrated the importance of subcortical systems in GTCS, since tonic convulsions can be readily elicited in rats with electroshock even after precollicular transection of the brainstem (10). Although the nucleus reticularis pontis oralis has been shown to be critical for tonic convulsions, most likely several bulbospinal pathways participate in the motor expression of GTCS (8,9). In addition to regions of seizure origination, spread, and expression, there is experimental evidence for nuclei that regulate (gate) seizures by controlling the threshold for their occurrence, without necessarily participating in the seizure itself. These seizure regulating structures include the substantia nigra pars reticularis and connected structures,

the central medial intralaminar nucleus and associated components of thalamic and mesencephalic arousal systems, ascending noradrenergic systems, the fastigial cerebellar nucleus, and the medial septal nucleus in the forebrain (8,9). Therefore, these animal studies of functional seizure anatomy not only allow a better understanding of the process of secondary generalization, but also provide a theoretical foundation for clinical trials of deep brain stimulation for treatment of intractable epilepsy.

Although the vast majority of seizures begin in the cerebral cortex or limbic system, they propagate through many subcortical pathways. A focal seizure generalizes and becomes a GTCS when it spreads to specific brainstem regions. GTCS are not the result of diffuse brain activation, but rather, have a characteristic pattern of activation and inactivation at many levels of the central nervous system. Therefore, traditional seizure nomenclature does not adequately represent the current state of knowledge of the anatomy and physiology of generalized seizures.

by John W. Miller, MD, PhD

## References

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