



## Editorial

## How focal is generalized epilepsy: A distinction with a difference?



The term “generalized epilepsy” was used by the first Commission on Classification and Terminology of the ILAE in 1970 to denote an epilepsy manifesting as “generalized seizures, bilateral seizures, or seizures without any local onset” [1]. Since then, experimental studies have challenged this entrenched opinion [2,3]. The lack of a justifiable therapeutic surgical opportunity in generalized epilepsy has limited the exploration of this condition with intracranial electrophysiology. Progress in understanding the anatomical substrate of generalized epilepsy has, therefore, been substantially slowed and has been based mainly on animal studies and a limited armamentarium of noninvasive investigations [4,5]. Among the latter, simultaneous recordings of fMRI and EEG (EEG/fMRI) appear to be a powerful and promising tool. By defining the electroclinical and hemodynamic correlates of EEG activity, fMRI has shed light on some neurophysiological mechanisms underlying epileptic phenomena. In this issue, Kay and Szaflarski have reviewed the role of EEG/fMRI in understanding genetic generalized epilepsies (GGEs). The authors have highlighted pertinent advances in the analysis of EEG/fMRI data, technical limitations of fMRI, and challenges facing EEG/fMRI studies at ultra-high strengths. They have organized their review around four key questions, paraphrased here, and we will organize our comments around the same four questions:

1. How has EEG/fMRI contributed to understanding the origins of generalized spike-and-wave discharges in GGEs?

An important part of the review is focused on the utility of EEG/fMRI to resolve the competing hypotheses regarding the fundamental pathophysiology of GGEs. The authors rely on advanced statistical analyses, including measurements of Granger causality, to conclude that cortical activity precedes, and presumably drives, thalamic responses, essentially an endorsement of the corticoreticular theory of Gloor [2]. A broader perspective and discussion on the significance of blood-oxygen-level dependent (BOLD) signal change and the ability to infer temporal relationships in physiological activity from it would help readers put this finding into perspective. Is it possible that the time constant of BOLD change in the thalamus is different from that in the cortex, thereby misrepresenting the actual direction of propagation or connectivity? After all, we are dealing with sequential events occurring over 1- to 5-second time scales. Similarly, is the BOLD response that is driven by inhibitory neuronal firing equivalent to that driven by excitatory firing? There are many other issues to be resolved before BOLD changes over a number of seconds can be accepted as a proxy for pathway connectivity and directionality.

2. Can EEG/fMRI assess the contribution of specific thalamic nuclei to generalized spike-and-wave discharges (GSWDs)?

An important goal of neurophysiologists is to unravel the details of thalamocortical circuits that mediate GSWDs. This will require a

detailed knowledge of the specific thalamic nuclei that participate in each aspect of the generation, synchronization, repetition, distribution, frequency, evolution, and termination of GSWDs. It is also likely that a better understanding of the roles of specific thalamic nuclei could illuminate the complex relationship between GGEs, GSWDs, and sleep. Nonetheless, the review indicates that current technology does not have the spatial resolution to distinguish specific nuclei in a reliable fashion. Whether higher field strength studies, with their attendant increased susceptibility to movement artifact, can improve the situation remains unclear.

3. What are the effects of GGEs and GSWDs on resting state connectivity in the human brain?

While there is no shortage of studies on the effects of GGE diagnosis, GSWD discharge, and cognitive performance on default mode network (DMN) activity cited in the review, in their present state, the findings are murky at best. Deactivation of the DMN may contribute to absence seizures, and reduction in DMN connectivity has been associated with time since diagnosis and pharmacoresistance, but patients with higher GSWD frequency appear to have increased connectivity. It remains difficult to fully reconcile these data.

4. Can fMRI constrain source analysis of simultaneous EEG data?

In this discussion, the authors point out that whereas EEG spikes represent high-frequency activity, fMRI signals appear to correspond to low-frequency energy driven by slow waves. It is, therefore, not surprising that intracranial studies in focal epilepsy suggest that EEG and fMRI are more concordant with intracranial EEG than they are with each other [6]. The authors conclude that because the time courses of EEG and fMRI sources may be discordant, source localization studies based on EEG/fMRI alone should be suspect.

Understanding the mechanism of ictogenesis is of paramount importance for designing new innovative therapy, especially in the 20–30% of patients whose seizures have failed to respond to multiple medications [7]. With the refinement of technologies, such as robot-assisted stereo-EEG implantation, laser-guided minimally invasive surgery, and neuromodulation, localizing the generalized epilepsies (a contradiction in terms perhaps) using EEG/fMRI tools may take on increased importance in planning novel treatment strategies. Additional potential applications for EEG/fMRI, including early identification/prediction of drug responsiveness, monitoring cognitive effects of interictal activity, and identifying mesial frontal lobe epilepsy masquerading as GGEs, each represent worthy goals for developers of this technology [8,9]. For the moment EEG/fMRI studies in GGEs are more than just pretty pictures and have reinvigorated the age-old debate, just how generalized is generalized epilepsy?

**References**

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