FUNCTIONAL IMAGING DEMONSTRATES SOURCE OF EPILEPTIFORM DISCHARGES IN GENERALIZED EPILEPSY

fMRI Activation during Spike-and-Wave Discharges in Idiopathic Generalized Epilepsy

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The objectives of this study were to evaluate the hemodynamic response of the cerebral cortex and thalamus during generalized spike-and-wave or polyspike-and-wave (GSW) bursts in patients with idiopathic generalized epilepsy (IGE). The hemodynamic response is measured by *f*MRI [blood oxygenation level–dependent (BOLD) effect]. We used combined EEG–functional MRI, a method that allows the unambiguous measurement of the BOLD effect during bursts, compared with measurements during the interburst interval. Fifteen patients with IGE had GSW bursts during scanning and technically acceptable studies. *f*MRI cortical changes as a result of GSW activity were present in 14 (93%) patients. Changes in the form of activation (increased BOLD) or deactivation (decreased BOLD) occurred symmetrically in the cortex of both hemispheres, involved anterior as much as posterior head regions, but were variable across patients. Bilateral thalamic changes also were found in 12 (80%) patients. Activation predominated over deactivation in the thalamus, whereas the opposite was seen in the cerebral cortex. These results bring a new light to the pathophysiolocal mechanisms generating GSW. The spatial distribution of BOLD responses to GSW was unexpected: it involved as many posterior as anterior head regions, contrary to the usual frontocentral predominance seen in EEG. The presence of a thalamic BOLD response in most patients provided, for the first time in a group of human patients, confirmation of the evidence of thalamic involvement seen in animal models. The possible mechanisms underlying these phenomena are discussed.

COMMENTARY

Idiopathic generalized epilepsy is a presumed genetic-related seizure disorder that is associated with multiple seizure types, including tonic–clonic seizures, clonic–tonic–clonic seizures, myoclonic seizures, and absence seizures. The scalp-recorded ictal EEG pattern may reveal a generalized, but anterior-predominant, discharge that is bisynchronous and symmetrical. The frequency of the epileptiform burst is variable, depending on the epileptic syndrome, and occurs at approximately 3- to 4-Hz spike-and-wave in individuals with childhood absence epilepsy and 4- to 6-Hz spike-and-wave in patients with juvenile myoclonic epilepsy.

The mechanism of epileptogenesis and site of seizure onset in patients with idiopathic generalized epilepsy is thought to involve an increase in diffuse cortical hyperexcitability related to an alteration in thalamocortical interaction. Individuals with these seizure types have previously been considered to have a corticoreticular epileptic disorder, based on the EEG pattern and animal models of epilepsy (1). Previous studies with positron emission tomography produced conflicting results in patients with idiopathic generalized epilepsy and variably revealed a change in cortical and thalamic cerebral blood flow and metabolism (2). In contrast, *f*MRI has been shown to permit accurate cortical localization of the sources of sensory, movement, and language stimulation (3,4). The blood oxygenation level–dependent (BOLD) response is analyzed to indicate the location of neuronal activity during the *f*MRI studies. Previous attempts at *f*MRI during ictal epileptiform activity revealed appropriate focal activation at the site of seizure onset. Spike-triggered *f*MRI previously was shown to be useful to localize anatomically the interictal epileptiform discharge in patients with partial seizure disorders (3,4).

Aghakhani et al. evaluated the results of *f*MRI at the Montreal Neurological Institute in 15 of 25 consecutive patients with idiopathic generalized epilepsy that had EEG-identified interictal generalized 2- to 4-Hz spike-and-wave discharges. A 1.5-Tesla MRI study was performed in all patients. The hemodynamic response was measured by using the BOLD effect. Nine patients were excluded because of the absence of epileptiform discharges during the *f*MRI study. One patient was not included because of "technical problems." Fifteen

patients had generalized spike-and-wave during the *f*MRI study. The patients predominantly had childhood or juvenile absence epilepsy, with or without myoclonic seizures ($n = 11$), generalized tonic–clonic seizures ($n = 3$), or juvenile myoclonic epilepsy ($n = 1$). Fourteen of the 15 patients were receiving antiepileptic drug therapy. In none of the patients did the structural MRI study show a substrate-directed lesion that was considered the etiology for the individual's seizure disorder. *f*MRI diffuse anterior or posterior cortical changes ("slightly" more prominent over the frontal and parietal head regions) were present in 14 (93%) of 15 patients. The activation or deactivation of BOLD responses was bisynchronous and symmetrical over the two cerebral hemispheres. No difference was noted in the BOLD responses between spike-and-wave and polyspike-and-wave discharges. Bilateral thalamic BOLD changes, predominantly activation, were present in 12 (80%) of 15 individuals.

The present study provides further compelling evidence that spike-triggered *f*MRI activation with off-line postprocessing of the EEG may indicate the anatomic source or generator of epileptiform discharges (1,2). The measured responses in the study of Aghakhani et al. were "directly linked" to the EEG pattern in these patients. Previous investigations confirmed the clinical application of this neuroimaging technique in patients with localization-related seizure disorders (3,4). The development of spike-triggered *f*MRI techniques permitted an important assessment of the mechanism of epileptogenesis in patients with idiopathic generalized epilepsy.

Aghakhani et al. demonstrated in a cohort of patients with generalized epileptic syndromes the pivotal interaction between the thalamus and cerebral cortex. This is the first demonstration in humans of the involvement of the thalamus in patients with generalized spike-and-wave discharges and seizure disorders. Activation or deactivation of the cortex was widely distributed and not limited to the anterior head regions. The authors of the study hypothesize that deafferentation of the cerebral cortex may be mediated by hyperpolarization of the thalamus. Finally, the results of the *f*MRI studies in these patients would appear to support the corticoreticular theory of idiopathic generalized epilepsy that was introduced by Gloor (1), based on a penicillin animal model of epileptogenesis.

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References

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