Sir, We read with great interest the paper by Siniatchkin et al. (2010), in which they report the results of electroencephalogram (EEG) combined with functional MRI studies performed in children with epileptic encephalopathies with continuous spike-waves during sleep (CSWS). This paper undoubtedly brings novel and valuable data on the pathophysiology of epileptic encephalopathies with CSWS, pointing out the implication of subcortical structures such as the striatum and the thalamus in these disorders. This study actually supports the hypothesis that the neurological regression in CSWS is not only related to the neurophysiological impairment at the site of the epileptic focus but also to epilepsy-induced changes in distant and connected brain areas with a particular involvement of the default mode network (De Tie`ge et al., 2009). Nevertheless, we would like to address some limitations regarding the methodology used in this work.

The EEG-functional MRI methodology enhances the statistical model used for functional MRI data analysis thanks to various EEG features such as timing, duration, amplitude, morphology and topography of the epileptic activity. In preliminary analyses, Siniatchkin et al. (2010) found a poor correlation between functional MRI results and electrical source imaging results obtained after averaging all the spike-wave discharges. The authors attributed this poor correspondence to discordance between the brain areas generating the first and the subsequent spike-wave discharges in a sequence. Based on this assumption and preliminary electrical source imaging analysis, the authors used the averaged first spike of every spike-wave discharge sequence to characterize the chronology of neuronal recruitment within the identified functional MRI neuronal network. This approach raises an important pathophysiological issue that the authors did not explore—would a functional MRI statistical model integrating separately initial and subsequent spikes of spike-wave discharge sequences evidence different neuronal networks? Further, to support their assumption, the authors should have directly compared electrical source imaging based on averages of initial versus subsequent spikes of spike-wave discharge sequences. If present, differences in shape and topography between those spike-wave discharges would have supported the assumption made, and these differences should have been accessible from the semi-automatic method used for spike-wave discharge classification. These additional pieces of information are essential; they would not only justify the methodological approach but also improve our understanding of the disorder. In fact, experimental confirmation is required for the assumed difference between generators of first and subsequent spikes in spike-wave discharge sequences because the theoretical justification derived from observations made on seizure activity (Ebersole, 2000) might not be extended to CSWS in which bursts and sequences have no recognized significance in pathophysiological and electrophysiological terms. In our opinion, the unmatched functional MRI and electrical source imaging results obtained on spike-wave discharge averaged on whole spike-wave discharge sequences might actually reflect the existence of multiple independent spike-wave discharge generators or propagation pathways as frequently found in CSWS (Fig. 1). Under this alternative hypothesis, which precludes the averaging approach adopted by the authors, single spike-wave discharge source reconstruction would have been required. This latter methodology is actually preferred for magnetic source imaging investigations to characterize the neuronal networks involved in CSWS activity at the individual level (Paetau, 2009; De Tie`ge et al., 2010).
The EEG pattern of CSWS is typically characterized by a major sleep-related increase in spike-wave discharge frequency, amplitude and diffusion, usually occupying >85% of non-rapid eye movement sleep. As illustrated in Fig. 1 of the Siniatchkin et al. (2010) paper and in our Fig. 1, amplitude and diffusion pattern of spike-wave discharges associated with CSWS may vary from spike to spike. It is tempting to conceive that spike-wave discharges characterized by differing amplitude and diffusion to the rest of the brain would contribute differently to the blood oxygenation level-dependent signal. In this regard, several EEG-functional MRI studies have shown the advantage of considering spike-wave discharges with different amplitudes in separate regressors (Krakow et al., 2001a, b; Salek-Haddadi et al., 2006; De Tiège et al., 2007). Several clinical and neuroimaging studies suggest that in

Figure 1 Fifteen seconds of magnetoencephalographic signals obtained in a 4.5-year-old boy with a Landau–Kleffner syndrome. This figure illustrates the existence of various spike-wave discharge amplitudes and diffusion patterns, and bilateral independent temporal generator throughout continuous spike-wave during sleep.
CSWS, amplitude and diffusion might actually predominate over frequency as determinant factors for detrimental effects of sleep-related spike-wave discharge intensification on brain function (Aeby et al., 2005; De Tiege et al., 2008, 2009; Buzatu et al., 2009). Therefore, EEG-functional MRI demonstration of a differential functional impact of spike-wave discharges varying for amplitude and diffusion would represent a pathophysiopathological advance.

Finally, as stated by the authors, it is interesting to note that the spike-wave discharge frequency associated with CSWS (1163–2407 spike-wave discharges during the 20 min of EEG-functional MRI data acquisition) did not violate the assumptions of the general linear model. Nevertheless, to fully characterize the impact of spike-wave discharge frequency on haemodynamic responses, it is necessary to estimate the Volterra kernels, which search for non-linear effects in the blood oxygenation level-dependent response. This approach has indeed previously demonstrated significant and quantitatively important non-linear effects of events frequency on haemodynamic responses (Friston et al., 1998). Such non-linear effects have been previously demonstrated using EEG-functional MRI and the Volterra kernels in epileptic patients with high frequency of spike-wave discharges (Salek-Haddadi et al., 2006).

In conclusion, the paper by Siniatchkin et al. (2010) is an important contribution to the understanding of the pathophysiology of CSWS epileptic encephalopathies. We highlight the fact that more in-depth analysis of EEG-functional MRI data obtained in this population of patients might further improve our understanding of these disorders.

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