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Mini Review

EEG-fMRI in Epilepsy: An Overview

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Abstract

EEG-fMRI has undergone impressive technical improvements in recent years. The technique appears attractive to investigate patients with focal epilepsy to identify a surgical target. Yet, its role in identifying the epileptogenic focus is not yet established and abnormalities of BOLD signal have been revealed in scattered cortical regions, possibly reflecting not only the source but also the spreading of the epileptic activity. EEG-fMRI has also been applied to investigate the cortical networks underpinning generalized epilepsy showing a role central of thalamus and a frequent involvement of the Default Mode Network.

Keywords: *Neuroimaging; Seizures; Functional; Neurophysiology; Network*

Abbreviations

BOLD: Blood Oxygen Level Dependant; DMN: Default Mode Network; EPI: Echo-Planar Imaging; EEG: Electroencephalogram; fMRI: Functional Magnetic Resonance Imaging; GSW: Generalized Spike and Wave

Early development of the EEG-fMRI technique

In 1992 John Ives, Steve Warach and Franz Schmitt first performed an electroencephalogram (EEG) into a 1.5T MR magnet at the Beth Israel Hospital, Boston, to investigate a patient with epilepsy through correlation between EEG epileptiform abnormalities and BOLD signal (EEG-fMRI) [1]. The initial purpose was identifying the epileptogenic focus, defined as the brain region from which epileptic activity starts, overcoming the low spatial resolution and incomplete spatial sampling of surface EEG [2]. Thereafter, epilepsy was increasingly explored by the EEG-fMRI technique. First studies had to face technical challenges. Investigators initially employed a 'spike-triggered' empirical approach to couple EEG and BOLD signal, starting an Echo-Planar Imaging (EPI) sequence after direct on-line detection of an epileptiform abnormality on EEG. The 'spike-triggered' approach was necessary to avoid the perturbation of the EEG from the electric gradient artefacts arising into a static magnetic field [3]. However, the constant electro-cardio-balisto-graphic artefact originated by the electric heart activity hampered a continuous reading of the EEG track.

The EEG-fMRI technique flourished after the development of specific subtraction algorithms, synchronized with the EPI sequence, that were successfully applied to remove the gradient and electro-cardio-balisto-graphic artefact allowing a continuous reading of the EEG track [4].

EEG-fMRI in focal epilepsies

After the initial experiences, focal epilepsy appeared an ideal paradigm of study for EEG-fMRI. The technique appeared especially attractive to investigate both patients with lesional and non-lesional epilepsy with the aim of defining the epileptogenic focus to be surgically removed. Hence, EEG-fMRI could chaperon nuclear medicine investigations (PET, SPECT) as support to guide surgical planning.

However, earlier results suggested the increase of BOLD signal associated to the surface EEG interictal spikes did not constantly match the epileptogenic focus as defined by depth stereo-EEG but also spread to distant brain regions [5-8].

It has been hypothesized that the BOLD signal would be related to the spreading of epileptic discharges rather than to the initial epileptic activity. In fact, the low temporal resolution of fMRI identifies hemodynamic phenomena on a slower time frame compared to the underlying neurophysiological abnormalities (sec vs msec) [9,10]. Technical advancements have then allowed the co-registration between fMRI and depth stereo-EEG showing an increase of the BOLD signal both within the epileptogenic focus and in remote areas, including the default mode network, which occurred during both EEG interictal and ictal abnormalities [11,12]. The default mode network (DMN) is a network usually activated at rest and deactivated after a task, composed by interacting brain regions known to have activity highly correlated with each other and distinct from other networks in the brain [13].

Many evidences converge on the detrimental effect of interictal discharges on brain functional connectivity. It has recently been demonstrated that the epileptiform discharges can especially interfere with visual and attentional networks in focal epilepsy, irrespective from the location of the epileptogenic focus [14]. In benign rolandic epilepsy, epileptiform discharges would interfere with brain networks responsible for language, behaviour and cognition [15]. Such interferences with physiological brain networks might underpin the negative effect of epileptic activity on cognitive functioning.

In recent years specific syndromes and seizure types have also been explored. In 'vertiginous seizures', the ictal EEG/fMRI has revealed activation clusters in the temporo-parieto-occipital regions and deactivation in the ipsilateral cerebellar hemisphere, all regions involved in the vestibular integration network [16].

EEG-fMRI in focal epilepsies

The identification of brain networks in focal epilepsies prompted to investigate generalized epilepsies. In generalized epilepsies, it has long postulated a central role for the thalamus, which would be primarily activated ('centro-encephalic' or 'cortico-reticular' theories) or secondarily involved after trigger from a cortical focus ('cortical focus' theory) [17].

Each generalized epilepsy exhibits relatively homogeneous characteristics and is therefore particularly attractive for group analysis.

Early studies explored generalized spike-and-waves (GSW) discharges, irrespective from the specific syndrome, and demonstrated a constant increase of BOLD signal within the thalamus as well as variable BOLD modifications over distant cortical regions [18-21]. In particular, decrease of BOLD signal have been disclosed over the mesial frontal, insula, cingulate and parietal cortex, regions constituting the DMN. Therefore, GSW would perturb the normal resting state of the brain [22,23].

Such interference with the DMN has been specifically observed in childhood absence epilepsy (CAE) and in eyelid myoclonia with absences and has been hypothesized to underpin the altered state of consciousness typical of absence seizures [24-26]. Such widespread deactivations have been observed alternatively after thalamic activation or after an initial cortical activation (frontal or parietal) [27-29]. Such difference have been hypothesized to depend on drug responsiveness by Szaflarski., *et al.* A, who observed early thalamic activation in drug-responsive CAE, early cortical activation in drug-resistant CAE [30].

The time course of BOLD signal has also been investigated through innovative approaches, exploring the hemodynamic response which both precedes and follows the electroencephalographic abnormalities. According to this paradigm, Benuzzi., et al. found DMN activation to precede the GSW onset in absence seizures [31].

EEG-fMRI has also been applied to investigate photosensitivity in Juvenile Myoclonic Epilepsy, disclosing an increase of BOLD signal in putamen before the onset of the photoparoxysmal response, followed by thalamus activation and lately by widespread cortical, putamen and caudate deactivations [32]. Recent studies have also investigated genetic epilepsy such as GLUT1 Deficiency Syndrome, showing the an increased BOLD activity in the premotor-striatal network and a decrease in the thalamus [33-35].

Conclusion

The EEG-fMRI technique has undergone impressive technical improvements in recent years. Several studies have demonstrated the involvement of complex neuronal networks both in focal and generalized epilepsy. However, the relationship between EEG and BOLD signal has not been completely elucidated. Further studies exploring larger series, using ictal EEG abnormalities or studying the correlation between EEG and the BOLD signal at 7T ultra-high field could provide further advancements in non-invasively identifying the epileptic focus and in understanding the pathophysiological substrates of generalized epilepsies.

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