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'EEG-fMRI in Epilepsy'

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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 track from the electric gradient artefactsarising 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 algorhythms, synchronized with the EPI sequence, that were successfully applied to remove the gradient and electro-cardio-balisto-graphic artefactallowing a continuous reading of the EEG track [4].

EEG-FMRI IN FOCAL EPILEPSY

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 the surgical planning.

However, earlier results suggested the BOLD correlate of EEG abnormalities 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 low temporal resolution of fMRI allows recording more the BOLD correlate of the spread epileptic discharges than the initial epileptic activity [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 abnromalities [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.

EEG-FMRI IN GENERALIZED EPILEPSY

The identification of brain networks in focal epilepsy prompted to investigate the generalized epilepsies. In generalized epilepsy, 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) [16].

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Each generalized epilepsy exhibits relatively homogeneous characteristics and are therefore particularly attractive to group studies.

Early studies explored generalized spike-and-waves (GSW) discharges, irrespective from the specific syndrome, and demonstrated a constant BOLD signal increase in the thalamus as well as variable BOLD modifications in distant cortical regions [17-20].

Most deactivations involved bilaterally the mesial frontal, insula, cingulate and parietal cortex, regions constituting the DMN. Therefore, GSW would perturb the normal resting state of the brain [21,22].

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 in absence seizures [23-25].

Subsequent studies in patients with GSW have observed thalamic activation preceding DMN deactivation. On the contrary, other studies in CAE have demonstrated an initial cortical activation (frontal or parietal) [26-28]. Szaflarski et al. have observed early thalamic activation in drug-responsive CAE, and early cortical activation in drug-resistant CAE [29].

Different approaches have been subsequently developed to investigate the BOLD signal before GSW onset. In fact, the electric onset of epileptiform abnormalities expresses a neuronal hypersincronization that can only be measured by direct cell recording, while epileptiform discharges on surface EEG occur later. Following this study paradigm, DMN activation has been observed to precede GSW onset in absence seizures [30].

EEG-fMRI has also been applied to investigate photosensitivity in Juvenile Myoclonic Epilepsy highlighting a BOLD signal increase in putamen before the onset of the photoparoxysmal response, followed by thalamus activation and lately by widespread cortical, putamen and caudate deactivation [31].

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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