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Analysis of the BOLD responses on EEG-fMRI acquisition in patients with epilepsy

Análises da resposta BOLD em aquisições de EEG-fMRI (eletroencefalografia e imageam por ressonância magnética funcional) em paciente com epilepsia

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Abstract

The technique of magnetic resonance imaging (MRI), characterized by high spatial resolution, associated with electroencephalography (EEG), characterized by high temporal resolution, can be a powerful tool to study neurological disorders, including epilepsy. Electroencephalography is a mechanism to record electrical brain activity, using principles of Electronics, Physics and Physiology. Functional MRI (fMRI) relies on the different magnetic properties of blood depending on its oxygen content. The goal of functional imaging is to obtain images that are sensitive to brain function. To this end, we aimed to understand the mechanisms of neural activity and the processes related to it. This paper describes the methodology of the combined EEG-fMRI method in a tertiary hospital, and assesses the results of 16 exams regarding their concordance with the clinical history and clinical applicability of the technique. The results of the exams were statistically analyzed with the software SPM8. BOLD (Blood Oxygenation Level Dependent) responses were analyzed considering the clinical history of each volunteer. The studies that showed statistically significant activation areas consistent with clinical history were considered compatible (seven exams) while the studies with results not consistent were considered incompatible (one exam). Six compatible exams were considered clinically relevant, because they add information regarding the definition of the epileptogenic zone or epileptic syndrome. The studies with absence of epileptiform activity on EEG (three exams) or significant BOLD activations (three exams) were considered null. Two exams were excluded due to excessive head motion. EEG-fMRI is a promising technique that can be important to improve the understanding of neurological disorders, including epilepsy. The method may be used in the future as an important diagnostic tool for refractory epileptic patients as it may add information about the localization of epileptogenic zone or definition of epileptic syndrome.

Keywords: EEG-fMRI, neurology, fMRI, epilepsy.

Resumo

A técnica de imagem por ressonância magnética (MRI), caracterizada pela alta resolução espacial, associada com a eletroencefalografia (EEG), caracterizada pela alta resolução temporal, pode ser uma ferramenta poderosa para estudar distúrbios neurológicos, inclusive a epilepsia. A eletroencefalografia é um mecanismo feito para registrar a atividade elétrica cerebral, que utiliza princípios de Eletrônica, Física e Fisiologia. A imagem por ressonância magnética funcional (fMRI) conta com diferentes propriedades magnéticas do sangue, dependendo do seu conteúdo de oxigênio. A meta da visualização funcional é obter imagens que sejam sensitivas à função cerebral. Para esse fim, objetivamos entender os mecanismos da atividade neural e seus processos relacionados. Este trabalho descreve o método combinado de eletroencefalografia e imagem por ressonância magnética funcional (EEG-fMRI) em um hospital terciário, e avalia os resultados de 16 exames quanto à concordância deles com o histórico clínico e a aplicabilidade clínica da técnica. Os resultados dos exames foram analisados estatisticamente com o software SPM8. As respostas BOLD foram analisadas levando em consideração o histórico clínico de cada voluntário. Os estudos que mostraram áreas de ativação estatisticamente significantes consistentes com o histórico clínico foram considerados compatíveis (sete exames), enquanto os estudos com resultados não consistentes foram considerados incompatíveis (um exame). Seis exames compatíveis foram considerados clinicamente relevantes, pois adicionam informações a respeito da definição da zona epileptogênica ou síndrome epilética. Os estudos com ausência de atividade epileptiforme na eletroencefalografia (três exames) ou ativações BOLD significantes (três exames) foram considerados nulos. Dois exames foram excluídos devido ao excessivo movimento da cabeça. A eletroencefalografia e a imagem por ressonância magnética funcional é uma técnica promissora que pode ser importante para melhorar o entendimento dos distúrbios neurológicos, inclusive a epilepsia. O método pode ser usado futuramente como uma importante ferramenta de diagnóstico para pacientes com epilepsia refratária, já que pode acrescentar informações sobre a localização da zona epileptogênica ou sobre a definição da síndrome epilética.

Palavras-chave: eletroencefalografia e imagem por ressonância magnética funcional, neurologia, imagem por ressonância magnética funcional, epilepsia.

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Introduction

General introduction

The technique of magnetic resonance imaging (MRI), characterized by high spatial resolution, associated with electroencephalography (EEG), characterized by a high temporal resolution, can be a powerful tool to study neurological disorders, including epilepsy.

Epilepsy is the most common neurological disorder, with prevalence of 2% of world population. It can cause serious consequences, including injuries, psychological problems, mental disorders and even sudden death. Since it is such a common disease and has a great impact on the lives of the affected ones, the establishment and development of techniques that can better guide the assessment of each case is of great value, increasing the chances of curing or improving the quality of patient's life.

The simultaneous acquisition of functional magnetic resonance imaging (fMRI) and EEG can be in a near future a valuable technique to the analysis and localization of neural activity and a complementary diagnostic method in clinical routine of patients with epilepsy.

This paper describes the methodology of the combined EEG-fMRI method in a tertiary hospital and assesses the results of 16 exams regarding their concordance with the clinical history and clinical applicability of the technique.

Functional magnetic resonance imaging

The goal of functional imaging is to obtain images that are sensitive to brain function. To this end, we aim to understand the mechanisms of neural activity and the processes related to it. There are electrophysiological methods that directly measure neural activity, but they are very invasive. FMRI is noninvasive and reveals the neural activity by the assessment of hemodynamic changes associated with it[1].

The study of brain functions requires acquisition methods with similar speeds to the physiological changes of interest. The technique of EPI (Echo Planar Imaging) scans the whole brain with strong gradients, covering the k-space in a rectangular manner on the order of seconds, which is the same order of magnitude of the hemodynamic response.

Since brain does not store energy, the ATP (adenosine triphosphate) must be formed mainly by oxidation of blood glucose. Experiments show that this consumption is concentrated in regions with increased neural activity.

Increased blood flow causes an increased transport of glucose and oxygen to the site of activation to meet the energy needs of nerve cells. The increase in local perfusion rate leads to dilution of venous deoxyhemoglobin (deoxygenated hemoglobin) and thus increase the concentration of oxyhemoglobin (oxygenated hemoglobin)[1].

Since oxyhemoglobin is diamagnetic (displays weak repulsion in a magnetic field) and deoxyhemoglobin is paramagnetic (displays attraction to a magnetic field), the presence of deoxyhemoglobin creates a higher local magnetic field. It is known that the magnetic susceptibility of deoxygenated blood is around 20% higher than that of oxygenated blood. This introduces local inhomogeneities and, therefore, variation in proton precession frequencies, which reduces T2* (transverse relaxation time including field inhomogeneity)[2].

In other words, the area of activation has a decreased concentration of deoxyhemoglobin and consequently an increase in the magnetic signal. Hence, this is called BOLD (Blood Oxygenation Level Dependent) signal and is the basis of fMRI.

Electroencephalography

Neurons have the ability to communicate quickly and accurately via action potentials (rapid membrane depolarization that propagates through the axon until its terminal). On average, a neuron can form one thousand synapses and receives more than ten thousand connections. When the action potential reaches the axon terminal, the presynaptic neuron releases neurotransmitters that will affect the membrane potential of the postsynaptic cell. This postsynaptic potential can be either excitatory or inhibitory. The neuronal information integration of the signals received from other cells occurs at the axon hillock (structure between the cell body and the axon), in which another action potential will be fired only if the threshold potential is crossed.

Electroencephalography is a mechanism to record electrical brain activity, using principles of Electronics, Physics and Physiology. The electrical activity recorded in EEG derives mainly from synchronized pyramidal cell postsynaptic potentials. Action potentials do not contribute to EEG signals because the fields generated by them decay faster with distance and they have a short duration (1-2 msec), overlapping much less in time – postsynaptic potentials last about 10-250 msec. Moreover, the EEG signal can be measured at a considerable distance from the source if the responsible neurons are regularly arranged and activated in a fairly synchronous way. These properties hold for pyramidal cells[3].

The potential difference between the electrodes and a reference electrode is measured, and a conductive gel is used to decrease the electrical resistance between electrode and scalp. After signal measurement, the signal is amplified and recorded.

Method and equipment

Clinical procedures

The procedures involved in preparing the experiment can be divided into three steps: 1) selection of a patient or volunteer, who meets the requirements and has all the physical and legal conditions for submission to the procedure; 2) preparation, assembly and obtainment of reference results of the EEG out of the scanning room; 3) positioning of the patient inside the MRI scanner (Philips Achieva 3T) and simultaneous fMRI and EEG (Brain Products, München, Germany) acquisition.

The positioning of the cap with 64 electrodes follows the international standard 10-20 system. This process requires a strong electrical coupling between electrodes and scalp (impedance below 5 kilo-ohms). On average eight, EPI sequences of six minutes are performed, depending on the patient conditions and possible emergencies. The technical characteristics of EPI were TE=30 ms, TR=2s, 240x240x117 mm^3 FOV, 39 slices, 3x3x3 mm^3 voxel and 180 volumes.

Computational procedures

The EEG is corrected for gradient and ballistocardiogram artifacts using the software *Brain Vision Analyzer2* (Brain Products, München, Germany). The gradient artifact is the sum of the interference generated by the magnetic gradients and the radiofrequency pulses. They generate electric current in the electrodes due to electromagnetic induction, masking the patient's signal. The correction method is the AAS (Average Artifact Subtraction), which subtracts out the sliding average (21 intervals window) from every TR interval, since the pulse sequence is exactly the same in each of these intervals. The heartbeat artifact is basically generated by small oscillations due to the patient's blood flow and heart rate, and is corrected in the same way.

The EEG is then examined by a specialist in order to locate epileptiform activity, whose timing and duration are recorded.

The preprocessing and statistical analysis of fMRI data are performed in SPM8 software (Wellcome Trust Centre for Neuroimaging, London, England). The fMRI images are preprocessed (realigned, slice timing corrected, normalized and smoothed) and the timings of the epileptiform activity are used as task in an fMRI paradigm to look for BOLD changes in the signal.

Results and discussion

The results of 16 exams were statistically analyzed with the program SPM8. BOLD responses were analyzed considering the clinical history of each volunteer. The results were then divided in compatible, incompatible or null (Table 1). The studies that showed statistically significant activation areas consistent with the clinical history were considered compatible (seven exams). The studies with BOLD activations with no apparent relation to the clinical history were considered incompatible (one exam). The studies were considered null for two different reasons: i) absence of epileptiform activity on EEG recorded inside the MRI (three exams) or ii) absence of significant BOLD activations (three exams). Since excessive head movement during the acquisition can result in false positive or negative results, we limited the accepted movement to 3 mm (voxel size in the EPI sequence) in the three coordinate axes. Two exams were excluded due to excessive head motion.

The null results related to the absence of epileptiform activity were expected and compatible with previous studies. It is known that the probability of an individual with epilepsy to have a normal EEG is close to 50%. This problem can be attenuated by the adequate choice of patient who may have previous routine EEG with frequent epileptiform abnormalities, and by appropriate number of EPI sequences, increasing as much as possible the time of the EEG-fMRI acquisition. The null results related to absence of BOLD activation were also expected and described in the literature[4]. It may be related to individual responses or to the necessity of different hemodynamic response function for different individuals. However, in our specific cases, we believe it occurred because of the small number of epileptic markers in these exams (two to six markers)[4].

The exam with incompatible result is also eventually expected[4]. But, in this case, it may be related to problems in the acquisition or data processing, or it may also be secondary to clinical data controversy of this specific patient.

A second classification of the studies was based on the clinical usefulness of EEG-fMRI results. The tests with incompatible or null findings and the tests discarded by head movement were considered not clinically useful (total of nine exams). One study with compatible result was considered with no clinical utility, once it did not add or reinforce any information that could have improved patient diagnosis or treatment. All the other compatible exams were considered clinically relevant.

The clinically relevant studies add two types of information: location of the epileptogenic zone and definition of epileptic syndrome. The epileptogenic zone was well defined in three patients with ictal recordings (seizures registered during the exam acquisition). In these patients, the BOLD maps revealed significant activation in areas already

Table 1. Results classification.

Patient	Ictal markers	Interictal markers	EEG-fMRI results	Clinical utility
1	0	0	Null	No
2	1CPS	3	Compat.	Yes
3	0	4	Null	No
4	0	10	Compat.	No
5	0	3	Incompat.	No
6	1CPS 4EleSz	10	EDEHM	No
7	1CPS 22EleSz	49	Compat.	Yes
8	0	30	Compat.	Yes
9	0	6	Null	No
10	0	116	Compat.	Yes
11	0	0	Null	No
12	0	189	Compat.	Yes
13	0	0	Null	No
14	1CPS 7EleSz	89	Compat.	Yes
15	0	2	Null	No
16	1 CPS	3	EDEHM	No

CPS: Complex Partial Seizure; EleSz: Electrical Seizure; EDEHM - Excluded Due to Excessive Head Motion; Compat: Compatible; Incompat: Incompatible.

suspected to be the epileptogenic zone in each case. The areas were consistent with structural MRI in all cases and were also concordant with ictal SPECT (single photon emission computed tomography) in two cases. Two of these patients were submitted to surgical resection including the BOLD activation area with significant improvement of seizure control. It is important to emphasize that all patients were closely observed during the EEG-fMRI acquisition and the seizures were registered safely, with no injury of none of these individuals.

The other three patients with clinically relevant studies had difficult clinical and electroencephalographic definition of the epileptic syndrome: primary generalized epilepsy *versus* frontal lobe epilepsy. These two epileptic syndromes have different treatments, so the precise diagnosis is very important. The EEG-fMRI acquisition revealed focal BOLD activation in two of them and it reinforced the possibility of frontal lobe epilepsy. The third patient had a BOLD activation map compatible with primary generalized epilepsy, as previously defined by the literature[5].

The BOLD maps (Figure 1 and Figure 2) were based on the time and duration of each interictal or ictal epileptiform event seen on EEG of each patient. As an example, Figures 1 and 2 show BOLD activation and deactivation maps of patients 2 (Figure 1) and 7 (Figure 2). These specific exams were based on one complex partial seizure (ictal event) occurred during EEG-fMRI acquisition of each individual.

For patient 2, the activation (Figure 1-A) was observed in right parietal region (precuneus) and was compatible with the area of MRI structural abnormality (focal cortical dysplasia) and the region of epileptic abnormality observed on EEG. Another activation area was observed in the right frontal region (precentral gyrus) and was consistent with seizure propagation as seen in this patient semiology. Sparse areas of deactivation (Figure 1-B) were observed mainly in right and left frontal regions.

For patient 7, the activation in Figure 2-A was observed in right frontal region and was compatible with the area of MRI structural abnormality (focal cortical dysplasia) and the region of epileptic abnormality observed on EEG. This activation was also compatible with the significant area observed on an ictal SPECT. Deactivation in Figure 2-B was observed on extensive areas including both frontal, temporal and caudate nuclei regions.

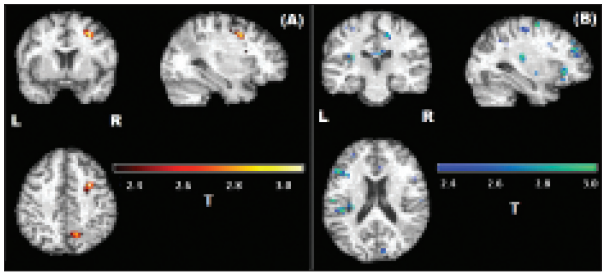

Figure 1. Statistical parametric map of patient 2. (A) Positive BOLD or activation. (B) Negative BOLD or deactivation. (L) is Left and (R) is Right. (T) is a T score of the T test.

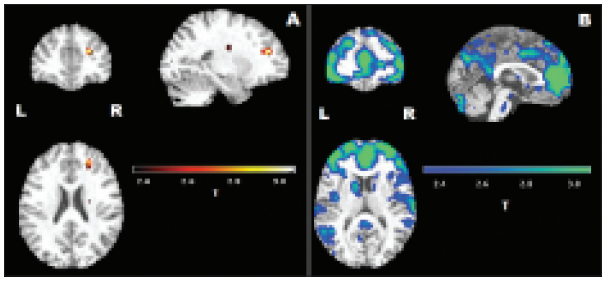

Figure 2. Statistical parametric map of patient 7. (A) Positive BOLD or activation. (B) Negative BOLD or deactivation. (L) is Left and (R) is Right. (T) is a T score of the T test.

Conclusion

The EEG-fMRI study is a safe and promising technique that can be important to improve the understanding of neurological disorders, including epilepsy. Its utility can be improved by appropriate selection of patients, adequate preparation of each individual, including head fixation, and increasing acquisition time. Also, EEG-fMRI may be used in the future as an important diagnostic tool for refractory epileptic patients as it may add information about the localization of epileptogenic zone or definition of epileptic syndrome.

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