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ScienceDirect
Magnetic Resonance Imaging 27 (2009) 1120–1130
MAGNETIC RESONANCE IMAGING

Distributed analysis of simultaneous EEG-fMRI time-series: modeling and interpretation issues

Fabrizio Esposito[a,b,*], Adriana Aragri[b,c], Tommaso Piccoli[b], Gioacchino Tedeschi[c,d], Rainer Goebel[b], Francesco Di Salle[b,e]

[a]Department of Neuroscience, University of Naples "Federico II", 80131 Naples, Italy
[b]Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands
[c]Department of Neurological Sciences, Second University of Naples, Naples, Italy
[d]Neurological Institute for Diagnosis and Care "Hermitage Capodimonte", Naples, Italy
[e]Department of Neurosciences, University of Pisa, Pisa, Italy

Received 25 October 2008; revised 28 November 2008; accepted 9 January 2009

Abstract

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) represent brain activity in terms of a reliable anatomical localization and a detailed temporal evolution of neural signals. Simultaneous EEG-fMRI recordings offer the possibility to greatly enrich the significance and the interpretation of the single modality results because the same neural processes are observed from the same brain at the same time. Nonetheless, the different physical nature of the measured signals by the two techniques renders the coupling not always straightforward, especially in cognitive experiments where spatially localized and distributed effects coexist and evolve temporally at different temporal scales.

The purpose of this article is to illustrate the combination of simultaneously recorded EEG and fMRI signals exploiting the principles of EEG distributed source modeling. We define a common source space for fMRI and EEG signal projection and gather a conceptually unique framework for the spatial and temporal comparative analysis. We illustrate this framework in a graded-load working-memory simultaneous EEG-fMRI experiment based on the *n*-back task where sustained load-dependent changes in the blood-oxygenation-level-dependent (BOLD) signals during continuous item memorization co-occur with parametric changes in the EEG theta power induced at each single item. In line with previous studies, we demonstrate on two single-subject cases how the presented approach is capable of colocalizing in midline frontal regions two phenomena simultaneously observed at different temporal scales, such as the sustained negative changes in BOLD activity and the parametric EEG theta synchronization. We discuss the presented approach in relation to modeling and interpretation issues typically arising in simultaneous EEG-fMRI studies.

Keywords: EEG; fMRI; Distributed source modeling; Working memory; Default-mode

1. Introduction

Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a noninvasive technique for mapping human brain functions "in vivo" with high reliability and a spatial resolution of a few millimeters [1]. However, BOLD-fMRI signals provide only an indirect measure of brain activity via the haemodynamic response transfer function, and the precise mechanism behind the vascular coupling with electrical activity is currently poorly understood and not easily modeled in fMRI. Electroencephalography (EEG) measures the scalp electrical potentials generated by neuronal activity and, therefore, offers a more direct measure of neuronal activity. However, the ill-posed nature of the EEG inverse problem and the inhomogeneous conductivity profile in the head seriously limits its spatial resolution. For these reasons, the simultaneous application of fMRI and EEG represents a very attractive opportunity for the combined measurement of

* Corresponding author. Department of Neuroscience, University of Naples Federico II, Unita' di Audiologia e Vestibologia, 80131 Naples, Italy. Tel.: +39 081 746 2883; fax: +39 081 746 3581.
E-mail address: fabrizio.esposito@unina.it (F. Esposito).

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doi:10.1016/j.mri.2009.01.007

electrical and haemodynamic activity at excellent spatial and temporal resolution.

Simultaneous EEG-fMRI is difficult for both technical and conceptual reasons. Technically, the major problem consists in the cleaning of EEG data sets from two serious fMRI-related artifacts, the gradient artifact [2,3] and the ballistocardiogram artifact [2–4]. Conceptually, a major difficulty is given by the need of modeling and interpreting not only EEG and fMRI effects but also their spatial and temporal correlations, resulting in a new effect often referred to as "EEG-fMRI coupling." A successful and exhaustive modeling of the EEG-fMRI coupling is especially difficult in cognitive experiments, where anatomically localized and distributed effects are expected to coexist and dynamically evolve at multiple spatial and temporal scales.

A typical approach used in EEG-fMRI analysis consists in first analyzing the EEG data in the time or time-frequency domain and, then, producing a model time-course to be used as a temporal reference for fMRI responses. When building up such a model for fMRI, the trial-by-trial variation (modulation) or the continuous (time point by time point) spectrotemporal evolution of one or more EEG channels or sources is used. The effective integration of EEG data into the fMRI temporal model requires correcting for fMRI hemodynamics via linear convolution with a model haemodynamic response function [5] and, with the sole exception of resting-state fMRI studies [6,7], the orthogonalization of the EEG measures to the standard fMRI response [8–10]. The EEG-fMRI results will thus reveal those brain regions where the EEG-derived signal is temporally correlated with the BOLD-fMRI time courses. The implicit assumption before any interpretation of these patterns is that a local (voxelwise) temporal coupling exists on a scan-by-scan basis between the two modalities. In this model, however, the spatial coupling of the two measures is not taken explicitly into account. In the presence of highly distributed effects in both EEG and fMRI measurements, the approach of a voxel-by-voxel temporal modeling can be not sufficient to shed light about the possible common spatial origin of the detected EEG-fMRI effects, especially when the EEG topography does not easily match the location of the significant fMRI effect or significant activity spreads throughout a distributed network. This can be especially the case in cognitive experiments. Scheeringa et al. [11] have recently shown how the isolation of a given EEG source (e.g., a theta or alpha source) is able to produce significant EEG-fMRI correlations in multiple brain regions which are close or far from the EEG source. For instance, the typical frontal theta source has been show to be coupled to multiple regions within the default-mode network [12], suggesting a single-trial coupling effect between working-memory related BOLD deactivation and theta synchronization. Mizuhara and Yamagouchi [13] have shown a temporal EEG-fMRI coupling using the time course of theta phase synchronization between specific electrode pairs and were able to correlate this measure with the simultaneously evoked BOLD positive activation in executive regions. Such a possible coupling, while being extremely important and interesting in highlighting cognitively relevant dynamic coupling effects, cannot be used to show or infer directly about the spatial origins of the two simultaneously occurring BOLD and EEG effects. In fact, the temporal coupling between a specific EEG source and an fMRI network or vice versa is accompanied by the difficulty of interpreting the spatial correspondence of the coupled effects in relation to their physical origin. In the absence of a spatial coincidence between a given EEG and fMRI effect, any possible EEG-fMRI coupling can only be interpreted in terms of indirect mechanisms.

A complementary perspective for the study of the EEG-fMRI coupling problem is linking EEG and fMRI patterns on a purely spatial basis and then exploring the anatomical correspondence between the EEG and the fMRI time courses at their own temporal scale. Within the limit of EEG inverse modeling, this approach ultimately aims at identifying a relatively small set of virtual intracranial electrodes in regions of high spatial concordance between EEG and fMRI effects. Such an approach has been recently explored by Brookes et al. [14] who investigated the use of beamformers as inverse spatial filters for the projection of EEG signals from the channel to the fMRI space in a simultaneous EEG-fMRI visual experiment conducted on two subjects. In this framework, the EEG-fMRI coupling is addressed from a spatial and not from a temporal viewpoint, and the main purpose is explore the spatial coincidence of simultaneously evoked effects even if these are measured at the very different temporal scales.

The purpose of this article is to illustrate this framework in a working-memory simultaneous EEG-fMRI experiment based on the "*n*-back" task [15]. We use a cortically distributed source space for fMRI and EEG projection ending up with a conceptually unique framework for investigating the coupling of EEG and fMRI on a purely spatial basis [16]. The *n*-back paradigm is typically used in fMRI to elicit sustained positive and negative BOLD responses in executive and default-mode regions (see, e.g., Ref. [15,17]) during a blockwise presentation of series of items while the subject is holding in memory one, two or three (or no) items. In the present experiment, the trials inside each block corresponding to the single-item presentations have been suitably jittered in order to allow measuring possible induced changes in electrical activity with minimal confound from possible stationary activity. Thereby, we intended to investigate in a fully distributed comparative analysis the spatial correlations of haemodynamic and electrical effects at such two different temporal scales. More specifically, we intended to explore the amount of spatial coincidence between positive and negative sustained BOLD effects and EEG synchronization in the theta range of frequency.

Previous working-memory studies have reported EEG-fMRI coupling effects involving load-dependent theta