Simultaneous EEG and fMRI: towards the characterization of structure and dynamics of brain networks

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Progress in the understanding of normal and disturbed brain function is critically dependent on the methodological approach that is applied. Both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) are extremely efficient methods for the assessment of human brain function. The specific appeal of the combination is related to the fact that both methods are complementary in terms of basic aspects: EEG is a direct measurement of neural mass activity and provides high temporal resolution. FMRI is an indirect measurement of neural activity and based on hemodynamic changes, and offers high spatial resolution. Both methods are very sensitive to changes of synaptic activity, suggesting that with simultaneous EEG and fMRI the same neural events can be characterized with both high temporal and spatial resolution. Since neural oscillations that can be assessed with EEG are a key mechanism for multi-site communication in the brain, EEG-fMRI can offer new insights into the connectivity mechanisms of brain networks.

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Introduction

Since functional segregation and integration are key principles in the organization of brain function,[1] characterization of connectivity mechanisms in brain networks is a major goal in human neuroscience today.[2] At the same time, disturbances of connectivity are believed to be highly relevant in the pathophysiology of major neuropsychiatric disorders such as schizophrenia.[3] Functional magnetic resonance imaging (fMRI) is extremely helpful in characterizing the network structure, eg, brain regions involved in a specific cognitive task. Moreover, based on fMRI data different levels of insights concerning the interaction of brain regions can be reached starting from a more descriptive determination of a correlational relationship (functional connectivity) to more sophisticated specifications of the directed influence from one region to another.[4] However, fMRI-based analyses of connectivity do not directly measure neuronal activity. In fact, functional coupling in the brain is carried out by oscillation patterns in different frequency bands which can be directly assessed using methods such as electroencephalography (EEG) and magnetoencephalography (MEG).[5] For example, high-frequency oscillations in the gamma band frequency (>30 Hz) range play an important role for the coupling of neural ensem-

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Selected abbreviations and acronyms

BCG	*ballistocardiogram*
BOLD	*blood oxygenation level-dependent*
DAN	*dorsal attention network*
DMN	*default-mode network*
EEG	*electroencephalography*
fMRI	*functional magnetic resonance imaging*
LFP	*local field potential*
MEG	*magnetoencephalography*

bles during perceptual processing in the visual domain[6] or for cognitive processes.[7] Other frequency bands such as theta oscillations (4 to 8 Hz) have been identified to be critically relevant for the communication between the hippocampus and the prefrontal cortex.[8,9] Improved understanding of the mechanisms of disturbed connectivity in the brains of psychiatric patients could be linked to new therapeutic strategies: for example, disturbed gamma band oscillations are a common finding in schizophrenia.[10,11] Gamma-band oscillations are dependent on intact function of the N-methyl-D-aspartate (NMDA) receptor[12] and improvement of glutamatergic neurotransmission at the NMDA receptor has been suggested to be a promising new strategy for the treatment of patients with schizophrenia.[13] EEG-fMRI can be used to characterize network structure, eg, during cognitive processing and relevant coupling mechanisms such as gamma oscillations *(Figure 1)*.[14] Accordingly, the characterization of both the network structure and the neurophysiological mechanisms involved is highly desirable, and simultaneous EEG-fMRI provides the methodological basis for this goal.[15,16]

Physiology

In order to get an idea of the physiological background of simultaneous EEG-fMRI measurements, it is necessary to briefly sum up our present understanding about the origin of EEG and fMRI. EEG (like MEG) is well known to basically represent synaptic activity although there are some exceptions (eg, high-frequency bursts representing action potentials). On the cellular level, both excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) produce current sinks and sources in the extracellular medium next to the apical dendrite and the soma of a pyramidal cell, resulting in a dipolar source-sink configuration. Local field potentials (LFPs) are currents established by activity of a number of surrounding neurons and measured together in vivo. LFPs represent a summation of synaptic events, including afferent inputs and synaptic inputs originating from local neurons. Measured at the cortical surface, we can detect the electrocorticogram, or at an even longer distance from the scalp, the EEG.[15,17]

Given the strong representation of synaptic activity in the EEG, the question arises as to whether fMRI signals are related to similar or different aspects of neuronal activity, such as neuronal spiking. In fact, in many experimental situations, synaptic activity is highly correlated with the firing rate of the neuron to which the synapses under consideration belong. Accordingly, it is not surprising that in many cases the fMRI signal correlates equally well with LFPs and spiking activity. However, in a few studies, there has been successful differentiation between synaptic activity and spiking activity with regard to the related hemodynamic changes.[18] These studies have provided evidence for a much closer relationship between the blood oxygenation level-dependent (BOLD) contrast mechanism and presynaptic and postsynaptic processing of incoming afferents to a region and only to a lesser degree the activity of its output efferents.[19-22] In summary, although obviously very different in terms of the signal that is actually measured, both EEG and fMRI have a considerable overlap concerning the neuronal activity that they represent, which is mainly synaptic activity.

Technique: safety and quality issues

From the very early days of simultaneous EEG-fMRI, safety issues have been an important aspect. Radiofrequency-related heating of electrodes or brain tissue has to be considered, and there are several factors that are relevant such as the scanning sequence, the number of EEG electrodes, or the field strength of the MRI scanner.[23] Taking all aspects into account, simultaneous EEG-fMRI recordings have been safely performed at many different MRI centers, and simultaneous EEG-fMRI is considered as a standard imaging technique. Since simultaneous EEG-fMRI recordings today are typically performed with commercially available MR-compatible EEG equipment, specific safety instructions are provided by the companies. Another issue in simultaneous EEG-fMRI is the quality of the EEG recorded in the scanner. Here, two main artefacts have to be considered: the cardiac pulse-related artefact and the image acquisition artefact. For both types of artefacts, today there are

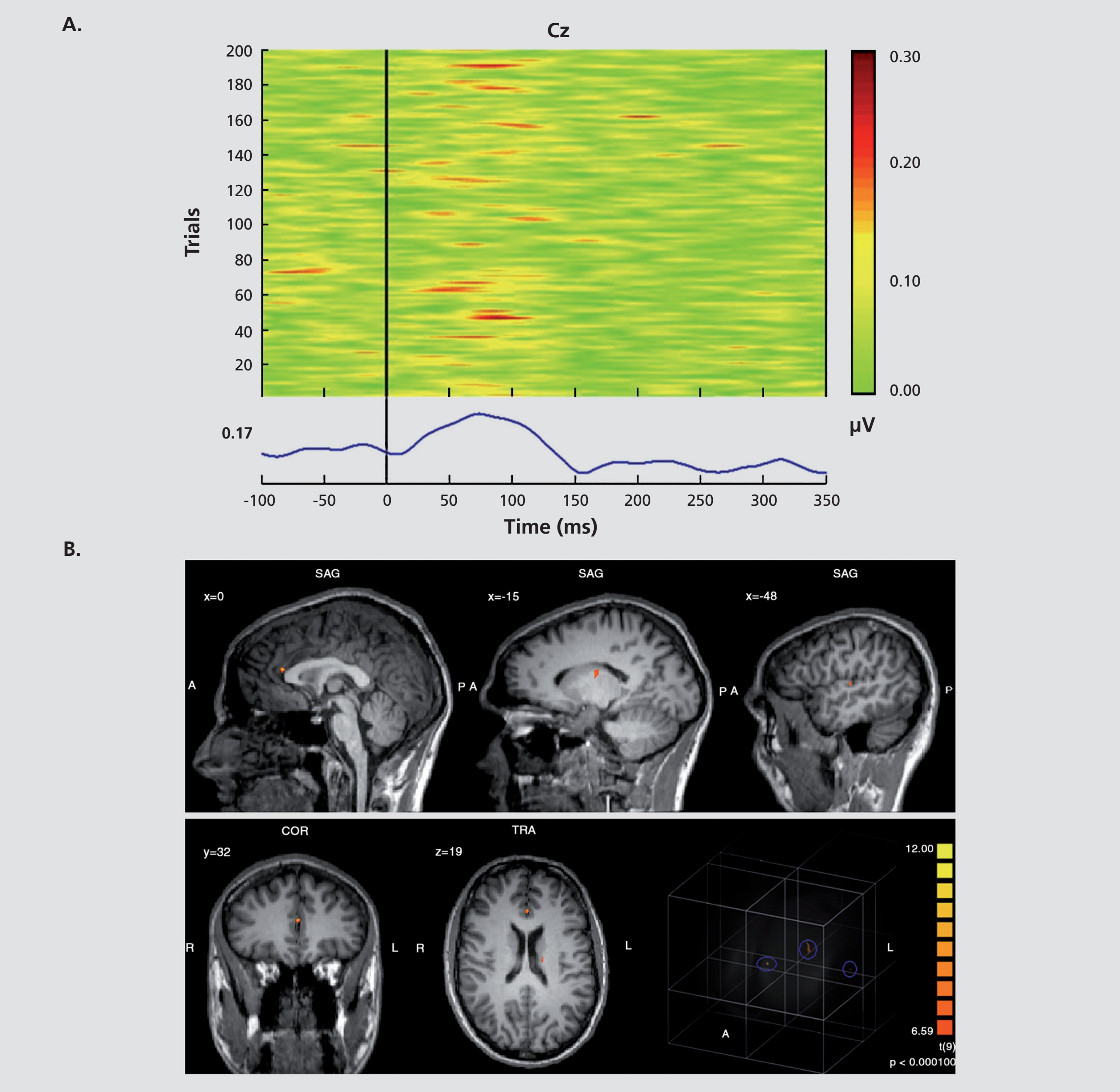

Figure 1. EEG-informed fMRI analysis in an auditory choice reaction task. A) EEG single-trial data of a typical data set at electrode Cz. In many trials, a GBR between 30 and 100 ms post-stimulus is present. However, the amplitudes of the GBR are variable over time. This variability can be used for specific predictions of the related BOLD signal. In the lower part of the figure, the corresponding averaged GBR is shown. B) GBR-specific BOLD activation based on the single-trial coupling of GBR amplitude variation and corresponding BOLD activation. Activations can be seen in the left auditory cortex (gyrus temporalis superior, Brodmann area 41/22, highest *t*-value 8.3), the thalamus (highest *t*-value 7.6) and the anterior cingulate cortex (Brodmann area 24, highest *t*-value 10.1). In the lower right corner, a glass brain view is provided, demonstrating a 3D view of the three abovementioned clusters. Activations are shown at *P*<0.0001 (random effects analysis, uncorrected for multiple testing). EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GBR, gamma-band response; BOLD, blood oxygenation level-dependent

Reproduced from ref 14: Mulert C, Leicht G, Hepp P, et al. Single-trial coupling of the gamma-band response and the corresponding BOLD signal. *Neuroimage*. 2010;49:2238-2247. Copyright © Elsevier 2010 post-processing artefact removal strategies available with sufficient efficacy. The pulse-related artefact, which is often also referred to as a ballistocardiogram, or BCG artefact, is complex in its origin with a role of pulsatile movements of scalp vessels on adjacent electrodes and head rotation. Post-processing strategies are based either on waveform removal approaches such as the average artefact subtraction algorithm[24] or on pattern removal approaches such as independent component analysis.[25] In addition to a priori avoiding of BCG artefacts,[26] new strategies include the application of optical motion tracking systems.[27] Concerning the image acquisition artefact, which is related to the application of rapidly varying magnetic field gradients for spatial encoding and which causes a complete obscuration of the physiological EEG,[28] artefact template subtraction strategies combined with synchronization of EEG and fMRI data acquisitions are very efficient and used today even as online artifact removal that allows immediate inspection of the ongoing EEG.[29]

Characterization of brain networks

Based on the spatial patterns of correlated time series that are quite reliably identified in resting state BOLD signals, several intrinsic brain networks have been identified such as the default-mode network (DMN), the dorsal attention network (DAN) or the salience network (SN). Within these networks, brain regions show increased functional connectivity on time-scales of seconds to minutes. Alterations in resting state networks are found in several neuropsychiatric conditions such as Alzheimer s disease.[30] Early studies with simultaneous EEG-fMRI for the resting state have tried to identifiy BOLD correlates of specific frequency patterns such as alpha oscillations.[31-33] However, in order to characterize network dynamics the idea emerged of relating the EEG signal to the functional connectivity within and between networks. For example, Hlinka et al showed that 70% of the DMN variance of functional connectivity is explained by delta and beta oscillations.[34] Scheeringa et al demonstrated that when alpha power increases, BOLD connectivity between the primary visual cortex and occipital regions decreases as well as the negative coupling between visual areas and regions of the DMN.[35] Chang et al investigated the functional connectivity between the DMN, DAN, and SN. They found an inverse relationship between alpha power and the strength of connectivity between DMN and DAN. Moreover, alpha power correlated with the spatial extent of anticorrelation between DMN and DAN.[36] While these studies were performed form the perspective of linking established fMRI resting state networks and to investigate the relationship to EEG power of distinct frequency bands, another approach is to relate fMRI patterns with more complex patterns of EEG organization. For example, the topographic representation of the EEG remains stable over periods of around 100 ms. These quasistable and unique distributions have been termed “microstates.” [37] Microstates reflect the summation of concomitant neuronal activity across brain regions rather than activity specific to any frequency band. Alterations in microstates have been demonstrated in several psychiatric disorders such as schizophrenia.[38] Using simultaneous EEG-fMRI, several authors have now described the relationship between EEG microstates and BOLD resting-state networks.[39-41]

Another very interesting approach will be the investigation of the relationship of EEG coherence patterns and fMRI connectivity. Recently, in monkeys using the combination of fMRI and invasive electrophysiological measurements, the relationship between interareal BOLD correlations and neural oscillations was investigated.[42] Here, coherence in low frequencies (<20 Hz) predominantly contributed to fMRI connectivity patterns in the task-free state, although gamma oscillations (30-100 Hz) have been shown before to be especially tightly linked to the BOLD signal. In the future, similar analyses integrating EEG coherence analyses and fMRI connectivity analyses might be performed using simultaneous EEG-fMRI and EEG source analysis in humans.

Conclusion

After several years of development, EEG-fMRI is now routinely performed in many MRI centers and both safety and signal quality issues can be addressed sufficiently. An appealing aspect of the combination of these methods is the fact that both EEG and fMRI are overlapping in their sensitivity to synaptic processing and accordingly brain function can be assessed by means of simultaneous EEG-fMRI with high temporal and high spatial resolution. One of the most promising applications for EEG-fMRI today is the characterization of brain network structure and dynamics. ❑

Electroencefalograma y resonancia magnética funcional simultáneos: hacia la caracterización de la estructura y dinámica de las redes cerebrales

El progreso en la comprensión del funcionamiento cerebral normal y alterado depende de manera fundamental de la aproximación metodológica que se aplique. El electroencefalograma (EEG) y la resonancia magnética funcional (RMf) son métodos altamente eficientes para la evaluación de la función cerebral humana. El recurrir específicamente a la combinación se relaciona con el hecho que ambos métodos son complementarios en términos de los aspectos básicos: el EEG es una medición directa de la actividad de la masa neural y permite una alta resolución temporal. La RMf es una medición indirecta de la actividad neural, se basa en cambios hemodinámicos y ofrece una alta resolución espacial. Ambos métodos son muy sensibles a los cambios de la actividad sináptica, lo que sugiere que con EEG y RMf simultáneos el mismo acontecimiento neural puede ser caracterizado con una alta resolución temporal y espacial. Ya que las oscilaciones neurales que pueden ser evaluadas con el EEG constituyen un mecanismo clave para la comunicación de múltiples sitios en el cerebro, la combinación EEG-RMf puede ofrecer nuevos conocimientos acerca de los mecanismos de conectividad de las redes cerebrales.

EEG et IRMf simultanés : vers la caractérisation de la structure et de la dynamique des réseaux cérébraux

Mieux comprendre les fonctions cérébrales normale et pathologique dépend essentiellement de la méthodologie choisie. L'électroencéphalogramme (EEG) et l'imagerie par résonance magnétique fonctionnelle (IRMf) sont des méthodes extrêmement efficaces pour évaluer la fonction cérébrale humaine. L'attrait particulier de cette association réside dans la complémentarité des deux méthodes dans leurs aspects fondamentaux : l'EEG mesure directement l'activité de la masse neuronale avec une résolution temporelle élevée. L'IRMf mesure indirectement l'activité neuronale avec une résolution spatiale élevée basée sur des modifications hémodynamiques. Les deux méthodes sont très sensibles aux variations de l'activité synaptique, ce qui sous-entend que le même événement neuronal peut être caractérisé avec une résolution élevée à la fois temporelle et spatiale en utilisant simultanément l'EEG et l'IRMf. Les oscillations neuronales évaluées par l'EEG étant un mécanisme clé de la communication multi-sites dans le cerveau, l'EEG-IRMf simultanés ouvrent une nouvelle réflexion sur les mécanismes de connectivité des réseaux cérébraux.

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