COMBINED EEG AND FMRI STUDIES OF HUMAN BRAIN FUNCTION

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Combined electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies show great promise for helping researchers to develop a more comprehensive understanding of the neural basis of behavior, including brain function and dysfunction. The aim of this paper is to review current knowledge and research on the use of combined fMRI and EEG data. We briefly examine the complementary features of the two techniques, and we then describe ways to acquire the two types of data, the relative advantages and disadvantages of acquiring them simultaneously, and strategies and methods for

effectively combining them. We address topics related to both event-related and emergent neural activity.

I. Introduction

Understanding the neural basis of brain functioning requires knowledge about the spatial and temporal aspects of information processing. Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are two techniques widely used to noninvasively investigate human brain function. Neither of these technologies alone, however, can provide the information necessary to understand the spatio-temporal aspects of information processing in the human brain. fMRI yields highly localized measures of brain activation, with a good spatial resolution (about 2-3 mm) but a temporal resolution significantly longer than the time needed for most perceptual and cognitive processes. EEG has the necessary temporal resolution to study the dynamics of brain function, but its poor spatial resolution precludes identification of underlying neural sources. fMRI and EEG therefore represent complementary imaging techniques, and combining information from them is a particularly useful way to examine the spatial and temporal dynamics of brain processes (Babiloni et al., 2004; Dale et al., 2000; Liebenthal et al., 2003; Menon et al., 1997). In Section II we review the fundamental features of neural activity as indexed by EEG and fMRI, with a view to better understanding the principles of various methods and their strengths and limitations for combining the two types of data.

II. The Signals

A. EEG

A clear understanding of the basics of EEG signal generation and recording is necessary in order to effectively combine EEG with fMRI. We review some of the relevant issues here; for a detailed review of EEGs, however, the reader is referred to a comprehensive text on this topic (Niedermeyer and Lopes da Silva, 2004). EEG signals recorded on the scalp surface arise from large dendritic currents generated by the quasi-synchronous firing of a large number of neurons (Freeman *et al.*, 2003). At a finer spatial scale, these same currents are also responsible for local field potentials recorded extracellularly *in vivo* in both humans and animals (Steriade, 2001). The local field potential is generated by extracellular currents that pass through the extracellular space in a closed loop.

These currents induce voltage changes (in the uV range) that are smaller than action potentials but that last longer and extend over a larger area of neural tissue. The local field potential reflects the linear sum of overlapping sources (current flows from the intracellular to the extracellular space) and sinks (current flows from the extracellular to the intracellular space). Scalp EEG arises from the passive conduction of currents produced by the summating local field potentials over large neuronal aggregates. The columnar structure of the neocortex facilitates the summation of electrical activity distributed among multiple neuronal groups. EEG activity recorded on a scalp electrode corresponds to the sum of activity from regions near the electrode, but large signals originating from more distal cortical sites can make a significant contribution to the activity observed at a given point on the scalp (Liu et al., 2002). Furthermore, the domains of spatially correlated activity underlying perceptual and cognitive processing are about 2-3 mm in the neocortex; volume conduction by the scalp significantly increases coherence across several cm on scalp recordings (Freeman et al., 2003; Menon et al., 1996). More importantly, the problem of recovering sources of neuronal activity from scalp EEG is fundamentally ill posed (Nunez and Srinivasan, 2006).

Scalp-recorded EEG in healthy adults typically reaches a maximum amplitude of 75 μ V (Fig. 1); however, it can reach an amplitude of 1 mV or more in pathological situations such as epileptic seizures (Niedermeyer and Lopes da Silva, 2004). The temporal resolution of EEG is about 1 msec; by this we mean that events of short duration, such as epileptic spikes (which last about 1 msec), can be reliably recorded. Although normal EEG fluctuations have amplitudes of 75 μ V or more, the magnitude of useful brain signals buried in these fluctuations is often considerably smaller.

1. Evoked EEG Activity

The term "event-related potential" (ERP) refers to the electrical response of the brain to a specific stimulus or cognitive process. Much of the background EEG activity is not time locked to the stimulus. Typically, stimulus-evoked signals are in the range of a few microvolts, which implies that the signal-to-noise ratio is much smaller than 1. Thus, signals cannot often be identified by visual inspection, and signal averaging and other statistical or signal-analysis procedures are therefore needed to recover meaningful brain signals. Averaging the EEG time locked to the stimulus or response increases the signal-to-noise ratio, resulting in reliable detection of useful brain signals (Handy, 2005). For cognitive processes, typically 30–100 stimuli trials are needed to obtain reliable ERP components. The spatial resolution of scalp-recorded ERPs is, however, poor, and this further limits accurate determination of the location of neural sources.

ERPs have been widely used to examine the timing of distributed brain processes involved in perception and cognition (Regan, 1989; Rugg, 1995).

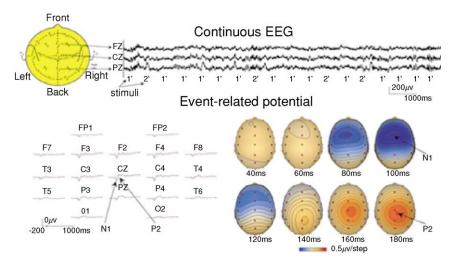


FIG. 1. Top: Raw EEG recorded at electrodes FZ, CZ, and PZ during the presentation of two different auditory tones, labeled "1" and "2." The EEG responses following the presentation of the tones are not visible on the raw EEG. Bottom left: Event-related potentials (ERPs) derived by averaging EEG segments following the presentation of the tones (e.g., stimulus 1 on the raw EEG). The N1 and P2 peaks are negative and positive deflections at 100 msec and 200 msec poststimulus, respectively. Bottom right: Topographical maps every 20 ms, from 40 ms to 180 ms poststimulus, presenting the N1 and P2 peaks of the ERPs.

ERP waveforms can be broken down into several basic components. A "component" is a positive- or negative-going fluctuation that can be visually identified in an ERP waveform. The components that occur prior to 100 ms are thought to reflect information processing in early sensory pathways. Cognitive electrophysiologists have been most interested in the so-called long-latency ERP components, including the P1, P2, P3, N1, N2, and N4 components. These components are named by their polarity (P for positive, N for negative) and either their ordinal position after stimulus onset (P1 is the first positive peak) or their latency after stimulus onset (N4 or N400 is a negative-going component peaking at 400 ms). In general, the mid-latency components occuring between 100 and 200 ms are thought to reflect late sensory and early cognitive processes, while those after 250 ms or so are thought to reflect higher-level cognitive processes (e.g., episodic memory).

2. Emergent EEG Activity

Although ERPs have been widely used in human brain research, they have significant limitations. Notably, averaging removes useful brain signals that are not time locked to the stimulus or the response. Cortical activity contains both

evoked and emergent patterns of stimulus-related activity (Freeman et al., 2003). Researchers like Walter Freeman have emphasized the importance of investigating both evoked and emergent EEG activity. For example, Ohl et al. (2003) examined evoked and emergent patterns in the primary auditory cortex (field AI). They showed that evoked patterns were focally organized at locations corresponding to the thalamically relayed input into the cortical tonotopic map. In contrast, emergent patterns could also discriminate responses to stimuli, but they were broadly distributed and held no apparent relationship to the tonotopic map. More recently, Makeig and colleagues (2002) have extended these ideas to human-scalp EEG data. They have shown that some components of the ERP are generated by stimulus-induced phase resetting of changes in ongoing EEG dynamics. More recent studies have shown unambiguously that averaging filters out much of the information about cortical dynamics available in the unaveraged single trials (Makeig et al., 2004). The combination of unaveraged EEG and fMRI data promises to open new vistas in the study of brain dynamics.

B. fMRI

The basic features of the fMRI signal have been described in Chapter 5 of this volume. Here, we will briefly describe the properties of the fMRI signal as it relates to combining EEG with fMRI. Unlike EEG, fMRI does not directly measure neural activity; instead, it relies on changes in oxygenation, blood volume, and flow (Logothetis and Wandell, 2004). During performance of perceptual and cognitive tasks, regions of the brain that are more active than others will have increased blood flow, resulting in increased oxygen levels. This localized increase in oxygen results in changes in the magnetic properties of the underlying tissue, which we can detect in scanners with high magnetic fields. Thus, we can quantify the amount of activity in given brain regions based on the extent and amount of blood flow to those regions over time. Because of the hemodynamic lag—the amount of time it takes for local blood-oxygen levels to rise and peak—the temporal resolution of fMRI is limited to several (1-6) seconds. One advantage of fMRI over EEG and MEG is that its spatial resolution is an order of magnitude better, allowing researchers to pinpoint where in the brain an operation is occurring, with a resolution approaching 1 mm at high fields (Formisano et al., 2003).

As with EEGs, the baseline fMRI signal shows spontaneous and continuous fluctuations even in the absence of external stimuli. But, unlike with EEGs, the origin of these fluctuations is poorly understood. Human cortical EEG activity has been intensively examined at frequencies ranging from 0.5 Hz to several hundred Hz. Recent studies have, however, demonstrated large-scale very slow fluctuations in the human cortex at frequencies ranging from 0.02 Hz to 0.2 Hz

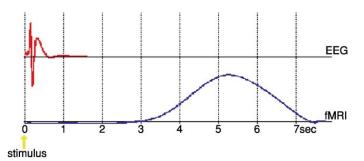


FIG. 2. Relative timing of EEG and fMRI responses following the presentation of a stimulus. The EEG response lasts about 1 second poststimulus, whereas the fMRI (blood oxygen level–dependent) response takes about 2–3 seconds to rise and reaches a maximum at about 5–6 seconds poststimulus.

(Vanhatalo *et al.*, 2004). The relation between these fluctuations and the fMRI baseline is not known, but such oscillations provide useful starting point for further investigations of the relations between the two signals.

Stimulus-evoked and task performance—evoked responses in the fMRI signal are somewhat better understood. When neuronal activity in a given brain region increases, metabolic demands result in an increase of oxygenated blood, which in turn is detected as an increase in fMRI signal intensity (Logothetis and Pfeuffer, 2004). Following onset of task-related neuronal activity, the fMRI signal takes about 2 seconds to increase and 4–6 seconds to reach its peak, and then it recovers to baseline in 12 seconds (Fig. 2). This change in signal, or the response to an impulse, is referred to as the hemodynamic response function (HRF). The form of the HRF has important consequences in terms of experimental design and interpretation of combined EEG and fMRI data acquisition.

III. The Relation Between EEG and fMRI Signals

Combined imaging and physiology experiments in monkeys have indicated that the fMRI signal is better correlated with the local field potential than with multiunit and single-neuron activity (Logothetis and Pfeuffer, 2004). In a seminal study combining microelectrode recording and fMRI in anesthetized monkeys, Logothetis *et al.* (2001) showed a linear correlation between the BOLD response and the stimulus-driven local field potential activity. At a fundamental level, this augurs well for combined EEG and fMRI studies of information processing in the human brain, since the EEG reflects spatially summed and volume-conducted local field potentials.

As we have already noted, EEG signals are directly related to neuronal processing, whereas fMRI responses arise from subsequent changes in blood-oxygenation levels. There are other important differences as well that are relevant for combining the two types of data. For neuronal responses to be recorded on the scalp EEG, it is necessary that sources be located in brain structures that can generate far-field potentials. Brain structures that have a laminar organization, such as the neocortex, can contribute significantly to the scalp EEG. On the other hand, neural sources in structures such as the thalamus and basal ganglia, which have a radial or noncolumnar organization, are less likely to make any significant contributions to the scalp EEG, even when large local field potentials can be recorded from them (Niedermeyer and Lopes da Silva, 2004). fMRI signals, on the other hand, are not directly dependent on the laminar or the radial neuronal organization; they have more to do with the structure of the underlying vascular bed. In the future it will be important to incorporate such constraints into more detailed biophysical modeling.

IV. Nonsimultaneous and Simultaneous EEG and fMRI Data Acquisition

Combined fMRI and EEG studies can be conducted with either simultaneously or nonsimultaneously acquired data. With the former method, EEG and fMRI data are acquired in the scanner; with the latter method, EEG is acquired outside the scanner in a separate session, and the order of the sessions is randomized across subjects.

A. Nonsimultaneous EEG-fMRI Acquisition

A number of brain-imaging studies have combined fMRI and EEG using data recorded in separate sessions (e.g., Ball et al., 1999; George et al., 1995; Heinze et al., 1994; Menon et al., 1997; Opitz et al., 1999; Snyder et al., 1995). An advantage of this approach is that the signal-to-noise ratio of EEG data obtained outside the scanner is usually much better than that of data obtained inside the scanner. Although data are recorded in two separate sessions, differences between the sessions can be minimal, especially those involving ERPs. This is certainly the case for several standard ERP paradigms, such as the oddball ("P300") paradigm and the semantic mismatch ("N400") paradigm, in both of which ERPs may, in fact, be better recorded outside the scanner. Methods for acquiring EEG and fMRI follow standard protocols and so are not discussed further here.

Clearly, a major drawback of this approach is that single-trial EEG and fMRI cannot be combined to examine emergent brain responses which may

not be time locked to the stimulus or response. Even for ERPs, there may be significant subjective and experimental differences between the two sessions. For example, there may be differences in subjects' levels of attention, vigilance, motivation, and familiarity with the task. Using simultaneous EEG-fMRI acquisition, it has been shown that arousal levels are an important determinant of brain activation during cognitive tasks (Matsuda et al., 2002). In addition, we must consider that the two separate sessions do not provide the same environment, because during the fMRI session the subject is in a noisy environment, whereas during the EEG session the subject sits generally in a comfortable and quiet room. This is an important issue for combined EEG-fMRI studies of auditory processing.

B. SIMULTANEOUS EEG-fMRI ACQUISITION

The main advantage of acquiring EEG and fMRI data in the scanner is that the two types of data reflect the same neuronal processes. Simultaneous acquisition allows us to ensure that subjects use the same strategy for both kinds of data; this is an issue that is particularly important for tasks involving complex cognitive processing. For epileptic seizure localization, simultaneous EEG and fMRI is clearly important. There are other important clinical problems in which simultaneous EEG and fMRI is critical, particularly those cases where symptoms can change over short durations. For example, some patients with schizophrenia have problems distinguishing self-generated from externally generated percepts during hallucinatory episodes, which can wax and wane unpredictably.

Even outside the clinical domain, simultaneous EEG and fMRI recordings are becoming increasingly useful. Studies of single-trial EEG and fMRI in which researchers seek to better understand neuronal processing that is not necessarily time locked to external events (Makeig et al., 2004) will also benefit from simultaneous recordings. Studies of the resting state and attempts to better understand brain dynamics underlying intrinsic EEG rhythms (Goldman et al., 2002) and the default mode of brain function (Raichle et al., 2001) also rely increasingly on simultaneous EEG and fMRI recordings (Laufs et al., 2003a,b). Simultaneous acquisition is also preferable for clinical and developmental studies, as it cuts down on the total time necessary to acquire data. Finally, for studies where continuous EEG tracks various stages of sleep (e.g., REM/non-REM), simultaneous acquisition of EEG and fMRI data is imperative (Czisch et al., 2004).

There are practical reasons why simultaneous recordings may be necessary. For clinical studies and for studies of children and the aged, nonsimultaneous recordings may not be practical. Most of these subjects are not willing to participate in multiple sessions involving extended periods of time—this has certainly been our experience across many such subject groups. Furthermore, in clinical

studies that involve medication, it may not be feasible, reliable, or practical to conduct studies across multiple sessions. Thus, whereas normative studies on college-aged adults can be performed easily in two or more sessions, this is certainly more difficult in clinical and developmental studies. Also, even in normal healthy individuals, particularly in children, memory and learning paradigms involve extended stimulus exposure, which can interfere with encoding and retrieval.

In the past five years, several brain-imaging centers have developed and refined techniques for simultaneous acquisition of EEG and fMRI data (Bonmassar et al., 2001a; Krakow et al., 2000; Lemieux et al., 2001b; Salek-Haddadi et al., 2002) and have used them to detect EEG spikes, characterize resting-state EEG, and investigate the neural basis of ERPs (Bonmassar et al., 1999, 2001b, 2002; Christmann et al., 2002; Lazeyras et al., 2001; Liebenthal et al., 2003; Mulert et al., 2004; Nagai et al., 2004; Thees et al., 2003).

1. General Considerations

The procedures used to record EEGs inside the scanner are, for the most part, similar to those used outside the scanner. Figure 3 summarizes a basic setup for data acquisition. EEG data can be recorded in either a referential or a bipolar configuration. In the referential configuration, data for all electrodes are recorded with respect to a neurophysiologically "neutral" electrode that may, for example, be attached to the mastoid (behind the ear lobes). In the bipolar configuration, each electrode is recorded with respect to a neighboring electrode on the scalp. Both kinds of configurations have been used to acquire EEGs in the scanner. One advantage of bipolar electrodes' in a twisted configuration is this makes it possible to significantly reduce gradient noise (Goldman et al., 2000). However, it should be noted that some EEG signals of interest may not be clearly detectable in a bipolar montage. In this case, the bipolar montage can be transformed into a referential montage provided there is appropriate connectivity between electrodes in different head regions. In particular, it is necessary that at least one channel that connects left- and right-side electrodes be included in the bipolar montage (e.g., the C3-C4 channel) (Lagerlund et al., 2003).

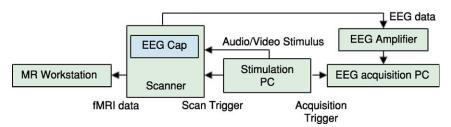


FIG. 3. Schematic diagram showing basic features of a combined EEG-fMRI data acquisition system.

Although 16- to 32-channel recordings have been commonly used, high-density EEG has been recorded with 64 and 128 channels (Scarff *et al.*, 2004). Increasing the number of recording electrodes from 64 to 128 improved the accuracy of the equivalent dipole source localization but decreased the signal-to-noise ratio (SNR) of MR images. This suggests that the 64-electrode setup may be optimal for use in simultaneous recording of EEG and fMRI data. However, spiral fMRI methods may not suffer geometric distortion, as echoplanar imaging methods do, due to off-resonance effects (Pfeuffer *et al.*, 2002).

A number of technical problems must be first overcome before the benefits of simultaneous EEG-fMRI acquisition can be fully realized. Concurrent acquisition of EEG and fMRI has proven to be challenging for a number of reasons, including those related to data quality (Allen *et al.*, 1998, 2000; Goldman *et al.*, 2000; Sijbers *et al.*, 1999, 2000). EEG data acquired in the scanner are contaminated by physiological and imaging artifacts (Ives *et al.*, 1993). These artifacts can reach amplitudes that are several hundred times larger than those of the EEG. Studies using simultaneous EEG-fMRI acquisition can be divided into two categories related to the type of fMRI acquisition: interleaved or fully continuous acquisition. Both of these acquisitions have specific advantages and disadvantages, which will be discussed in the following sections.

2. Interleaved Acquisition

Most studies to date have used interleaved EEG-fMRI acquisition protocol, in which EEG data are required continuously and fMRI data are acquired intermittently. fMRI data are acquired using a clustered procedure, whereas EEG data are recorded continuously. Following stimulus presentation, 1 to 2 seconds of the EEG data are first acquired without fMRI scanning (the MRI scanner is quiet during this time interval), followed by a few seconds of fMRI data acquisition (Fig. 4). This is similar to the "clustering" procedure used to acquire fMRI data in auditory experiments (Hall et al., 1999), where it is important that auditory stimuli be heard without interference from scanner noise. Most of the useful stimulus-related EEG is therefore not contaminated by scanner noise, since the neurophysiological response starts a few milliseconds after the stimulus onset and lasts no more than 1 to 2 seconds, depending on the cognitive processes involved in the task. Starting the fMRI data acquisition 1 to 2 seconds after stimulus onset allows us to estimate the BOLD response without contamination from gradient artifacts. The EEG recorded in this manner still has artifacts related to cardiac pulsation. These ballistocardiogram (BCG) artifacts must be removed in order for single-trial EEG data to be useful (see Section V.A for more). The extent to which BCG artifacts are synchronized to stimulus and response is currently not known. It is likely that for tasks that do not involve a strong affective response, the BCG and stimulus-related responses are not synchronized, so that at least for ERPs it is not absolutely necessary to remove the

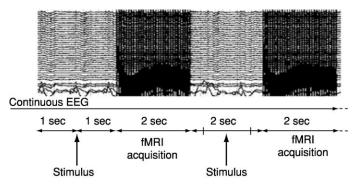


FIG. 4. EEG data from an interleaved EEG-fMRI acquisition in which the fMRI data are is acquired using a clustered procedure, with 2 seconds of EEG acquisition without MRI scanning followed by 2 seconds of fMRI data acquisition (note that the EEG is continuously acquired). In this case, the stimulus (either a tone or a flashing checkerboard) was presented 1 second after the end of each fMRI acquisition interval (TR).

BCG artifacts if a sufficiently large number of trials is used. The main disadvantage of interleaved acquisition is that the rate of stimuli presentation has to be reduced, often almost doubling the length of the experiment (cf. Liebenthal *et al.*, 2003). The interleaved acquisition is currently a good method for EEG—fMRI acquisition, particularly for recording ERPs, since the problem of gradient-artifact removal has not yet been satisfactorily solved. For single-trial EEG, the interleaved acquisition is, however, not optimal.

3. Fully Simultaneous Acquisition

In this case, both fMRI and EEG data are acquired continuously. This is useful for both cognitive and clinical studies. For one, rapid event-related studies require the added sampling afforded by simultaneous recordings. For shortlived and unpredictable events such as epileptic spikes, also, this is preferable and can greatly increase the statistical power. However, fully simultaneous acquisition is even more challenging than interleaved acquisition because of the large artifacts in the EEG during fMRI data acquisition (see Section V.B). It is necessary to have EEG amplifiers with large dynamic range so that the amplifiers do not saturate during the fMRI acquisition. Sophisticated algorithms are necessary for removing gradient artifacts. The first studies using fully continuous acquisition sought to determine seizure foci (Benar et al., 2002; Lemieux et al., 2001a). This method has rarely been used for ERP studies (Nagai et al., 2004), partly because ERP signals have low SNR and partly because many experimental paradigms can be successfully implemented with the interleaved acquisition. Procedures to record EEG inside the scanner are similar to those used outside, except that the removal of gradient artifacts requires that EEG data be recorded at a sampling rate of 10 kHz/channel or higher. This is considerably higher than the 1 kHz/channel sampling typically used in standard EEG recordings. This is necessary both to prevent aliasing of scanner artifacts into the EEG signal and to detect and remove gradient artifacts that contaminate the EEG.

C. fMRI Data Acquisition

Anatomical and functional MRI acquisitions have been performed at scanner strengths of up to 3 Tesla (T) with minimal artifacts from the EEG setup and data acquisition on MRI or fMRI images. Normal imaging protocols are used to acquire fMRI data, except in the case of the interleaved EEG-fMRI acquisition, where standard clustering procedures can be used. These procedures are not described here; for details, the reader is referred to Huettel et al. (2004).

V. Artifact Reduction in Simultaneous EEG-fMRI Data Acquisition

A. BCG ARTIFACTS

The BCG artifact is a consequence of the electromotive force (EMF) produced on the EEG electrodes due to small head movements, such as those caused by cardiac pulsation, inside the scanner magnetic field. As pointed out by Sijbers et al. (2000), there are three major sources of BCG artifacts: (1) small but firm movement of the electrodes and the scalp due to expansion and contraction of scalp arteries between the systolic and diastolic phases; (2) fluctuation of the Hall voltage due to the pulsatile changes of the blood in the arteries; and (3) small cardiac-related movements of the body (Fig. 5). The cardiac pulse generates artifacts with amplitudes considerably larger than those of EEG signal fluctuations. It is therefore important to develop methods to identify and remove these artifacts in a robust manner. Most methods of eliminating BCG artifacts have focused on either (1) averaged artifact subtraction (AAS), in which a BCG artifact template is estimated by averaging over the intervals of EEG signal that are corrupted by the artifact and subsequent subtraction of the template from the corrupted segments to obtain a clean signal (Allen et al., 1998) or (2) adaptive filtering techniques, which make use of correlations between a reference ECG channel and the EEG channels to estimate the contribution of the BCG artifact in the EEG signals, which is then subtracted to yield clean signals.

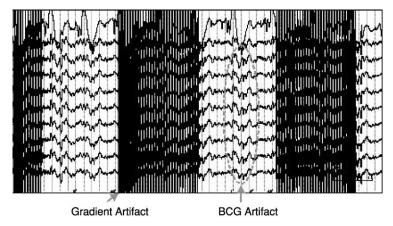


FIG. 5. EEG traces from an interleaved EEG-fMRI data acquisition showing the gradient (imaging) artifact and the ballistocardiography (BCG) (physiological) artifacts. Both artifacts are clearly visible on the EEG data at every electrode.

Currently, the AAS procedure is the most commonly employed method for removing the BCG artifact from EEG data. In this procedure, first, the QRS peaks in the ECG signal are detected, and then EEG activity time locked to these peaks is averaged to give an estimate of the pulse artifact (Allen et al., 1998). The average artifact is then subtracted from the EEG. Goldman et al. (2000) have used a method that is conceptually similar to the AAS procedure but that differs in the weights that are applied to data segments prior to averaging. These weights vary inversely with the temporal displacement from the current sample to compensate for the slow changes in the BCG artifact. Along similar lines, Sijbers et al. (2000) have used ORS onset detection to create a template of the BCG artifact based on adaptive filtering. They point out that simple averaging would not lead to a satisfactory template, as the ECG is not a stationary signal and hence the rate and duration of BCG artifacts might vary over time. In their approach, median filtering was performed to obtain an artifact template, because it adapts to changes in ECG signals over time. Bonmassar et al. (2002) used motion information recorded from a piezoelectric sensor placed on the temporal artery to estimate the motion-artifact noise (originating mostly from BCG), followed by adaptive filtering to subtract the artifact. Srivastava et al. (2005) showed that independent components analysis (ICA) is useful for removing BCG artifacts. ICA consistently showed five to six components representing the BCG artifact. Following removal of these components, a significant reduction in spectral power at frequencies associated with the BCG artifact was observed. Preliminary results suggest that ICA-based procedures may be significantly better than other noise-cancellation methods.

B. GRADIENT ARTIFACTS

The gradient artifact is caused by EMF induction on the EEG leads due to the rapidly switching magnetic-field gradients during fMRI acquisition. This is a periodic artifact with multiple spectral lines in the Fourier spectrum, and the fundamental frequency is governed by scan parameters like repetition time (TR) and number of slices. The standard deviation of this artifact is about 30-50 times as large as that of the EEG signal (Fig. 5), and hence the signal-to-artifact ratio (SAR) is negative: -20 to -30 dB. The current methods to remove this artifact include (1) using short EEG leads for scalp measurements with optical data transmission inside the MR scanner bore to prevent the gradient artifacts from saturating the amplifier; (2) estimating the individual responses of the G_x , G_y , G_z gradients and subtracting the sum of these responses from the actual EEG data to recover just the physiological signal recorded on the scalp (Felblinger et al., 1999); (3) estimating the power spectrum of the gradient artifact through combined median filtering of different noisy sections of the data and using the spectrum as a template for removing the gradient noise through adaptive filtering techniques (Sijbers et al., 1999); (4) straight time averaging of noisy sections of each EEG channel to obtain a template gradient-artifact waveform, subtracting the template from the channel, and cleaning the residual noise using adaptive techniques (Allen et al., 2000).

Most of the commercially available MR-compatible EEG acquisition system do not reduce the gradient artifact to attenuate at the acquisition stage. This leads to small EEG signals and large artifacts. The gradient artifacts have large power in the EEG frequency range, and, hence, conventional low-pass or bandpass filtering cannot be employed to clean the artifact without severely compromising the quality of EEG signals. The power in the gradient artifact is concentrated in very narrow spectral spikes, and, hence, it is useful to use notch filters with very narrow stop bands and large attenuation so that only the power at spike frequencies is suppressed, and therefore there is no significant effect on the power in the neighboring EEG frequency range. However, explicitly designing such notch filters is difficult and, moreover, may result in removal of significant EEG power in the alpha, beta, and mu bands. Advanced signal-analysis procedures such as adaptive noise cancellation will be necessary to satisfactorily remove these artifacts.

VI. Task-Design Issues

Although early fMRI studies used blocked designs, which provide a better SNR, both fMRI and EEG research have converged on event-related designs. In a blocked fMRI design, subjects are presented with alternating task conditions

that last about 15-30 seconds each. Blocked designs are efficient for estimating generalized task-related fMRI responses, but they are not optimal for parsing specific component processes and therefore can be combined with EEG only for tasks involving minimal cognitive processing. In event-related fMRI designs, each stimulus (or trial) corresponding to specific task conditions is presented randomly. In slow event-related designs, successive trials are spaced in time so that their evoked BOLD responses do not overlap. In contrast, rapid eventrelated fMRI designs use shorter intertrial-intervals (ITIs) of about 1–7 seconds. This allows faster data acquisition and also reduces the impact of cognitive processes associated with long ITIs. In this design, the BOLD response to successive trials can overlap, but "jitter" and randomized sequences (Burock et al., 1998; Dale, 1999) can be used to reduce this confound (Friston et al., 1998). Most EEG-fMRI studies, both simultaneous and nonsimultaneous, have used fast event-related designs (Table I). Rapid event-related presentations have been the mainstay of EEG studies over the past 40 years. The performance of most experimental designs for EEG is near optimal, since EEG signals have a rapid decorrelation time and since, if the contribution of slow potentials is small enough, the carryover into trials separated by 2 seconds (the time typically required to acquire whole-brain fMRI data) is quite small. Care, however, must be exercised if the experimental paradigm induces long-lasting slow waves such as the contingent negative variation (Brunia and van Boxtel, 2001). In most studies of perception and cognition, this is not an issue. For fMRI, the task-design issues are much more critical.

The performance of an experimental design for fMRI can be characterized by its estimation efficiency, which is the ability to make an estimate of the hemodynamic response; its detection power, which is the ability to detect brain activation; and its conditional entropy, which is a measure of the randomness of the design (Liu, 2004). The properties of event-related sequences depend on the specific design chosen (e.g., m-sequence designs, clustered m-sequence designs, or mixed designs). There are tradeoffs among efficiency, power, and entropy for each sequence. An event-related design that is high in efficiency may not have the best detection power. For details of the theoretical results and their practical implications for the optimal design of fMRI experiments with multiple trial types, the reader is referred to the excellent papers by Liu and colleagues (Liu and Frank, 2004; Liu et al., 2001). Here, we focus on their relevance to combined EEG-fMRI studies. These considerations apply equally to simultaneously and nonsimultaneously recorded EEG-fMRI data. Whether the efficiency or the detection power is maximized depends on the type of modeling used to integrate EEG and fMRI data. For predictive and correlational analysis of continuous EEG-fMRI data and for more detailed biophysical modeling that relies on current source imaging, estimating the hemodynamic response is important. In such cases, a design that maximizes estimation

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 ${\bf TABLE~I}$ Summary of Some Recently Published Event-Related EEG-fMRI Studies

Reference	Task (no. of subjects)	Sequence parameters	No. of epochs	Scanner and EEG systems (strength in Tesla)	Ballistocardiography artifact removal	Gradient artifact removal	ERP components and analyses	Relation BOLD– ERP
Bonmassar et al., 1999	Visual task, checkerboard reversing at 4 Hz (N unknown)	Interleaved 1-sec fMRI, 1-sec EEG	Not provided	3T, 64 EEG channels, referential montage	Design of filter w that maximizes the ratio of projection of signal and noise onto w	None	Visual N75, P100	Not investigated
Bonmassar et al., 2001b	Visual task, checkerboard reversing at 2 or 4 Hz (2 subjects)	Interleaved 30-sec fMRI, 30-sec EEG (15 sec of checkerboard, 15 sec of uniform gray field)	epochs acquired, average on 500 epochs	1.5T, 32 EEG channels, bipolar montage	Short epoch (125–250 ms) compared to BCG pulsatility (~1 sec) leading to a low probability of corrupted epochs	None	Visual N75, P100 fMRI constraint EEG source localization	Not investigated
Bonmassar et al., 2002	Visual task, checkerboard at 4 Hz (15 subjects)	Interleaved 1-sec fMRI, 1-sec EEG	Average 100, 250 epochs	1.5T, 32 EEG channels, bipolar montage	Adaptive filtering using a piezoelectric transducer motion detector	None	N75, P1, comparison outside, static 1.5T field and interleaved acquisition	Not investigated
Christmann et al., 2002	Somato- sensory task (6 subjects)	Interleaved 2.5-sec fMRI, 2.5-sec EEG	2000 epochs acquired	1.5T, 26 EEG channels, referential montage	Not specified	None	N20-P30- P60, (ERPs not shown) fMRI seeded dipole modeling	Not investigated

Mulert et al., 2002	Auditory oddball task (10 subjects)	Interleaved 2-sec fMRI, 1-sec EEG	not provided	1.5T, 29 EEG channels, referential montage	No specific BCG artifact removal	None	N1 and P3	Not investigated
Liebenthal et al., 2003	Passive auditory oddball task (7 subjects)	Interleaved 2-sec fMRI, 8-sec EEG (blocks of 16 stimuli)	Average on at least 190 epochs	1.5T, 30 EEG channels, referential montage	Averaged pulse artifact subtraction followed by adaptive filtering	None	Mismatch negativity (MMN)	Correlation between BOLD and MMN
Thees et al., 2003	2 somato- sensory tasks (6 subjects)	Interleaved l-sec fMRI, l-sec EEG	125, 175 epochs acquired, average 100, 140 epochs	1.5T, 32 EEG channels, referential montage	None	None	Dipole modeling	Not investigated
Foucher et al., 2003	Visual oddball task (5 subjects)	Interleaved 2.4-sec fMRI, 1.6-sec EEG	35 epochs acquired (rare stimuli), average on 26 trials	2T, 10 EEG channels, referential montage	Orthogonalization of the EEG data with respect to ECG signal	None	Visual N200 and P300, event-related gamma oscillations	Discussed but not directly tested
Mulert et al., 2004	Auditory oddball task (10 subjects)	Interleaved 2-sec fMRI, 1-sec EEG	Average on at least 40 epochs	1.5T, 27 EEG channels, referential montage	No specific BCG artifact removal	None	Auditory N1, P2 and P3; comparison inside/outside scanner; current density sources	Not investigated
Nagai <i>et al.</i> , 2004	Auditory CNV task (5 subjects)	Continuous	Average on 40 epochs	2T, 10 EEG channels, referential montage	Average pulse artifact subtraction followed by adaptive filtering	Average artifact subtraction, adaptive filtering	Auditory CNV	Correlation ERP– fMRI signals

efficiency should be emphasized. For dipole modeling and group-wise correlational analysis, on the other hand, the detection power is more important. In these cases, it is also important to verify that the task design is optimal for detection of the specific effect of interest. A design that is optimal for estimating the differential activation to two stimulus types, for example, may not be optimal for estimating the activation to each stimulus individually.

VII. Integrating fMRI and ERP Data

Table I summarizes the ERP components examined in several recent EEG—fMRI studies. Currently, two methods are widely used to integrate ERP and fMRI data; one relies on using ERPs as predictors of fMRI response, and the other uses dipole-based biophysical modeling to integrate ERPs and fMRI data. These methods are equally applicable to simultaneously and nonsimultaneously acquired EEG—fMRI data. Several researchers are now developing newer, more biophysically rigorous methods for integrating ERP and fMRI data. One such approach involves calculating three-dimensional volume currents at each voxel in the cortex from the surface measurements. In these distributed source models, the current density is estimated along the cortical surface and thresholded using statistical parametric analysis to generate dynamic maps of cortical response. A discussion of these methods is beyond the scope of this chapter, the interested reader is referred to Dale *et al.* (2000) and Kiebel and Friston (2004).

A. CORRELATION OF fMRI AND ERP DATA

One method for combining fMRI and ERP data is to use correlation analyses. In this approach, fMRI activation is correlated with the amplitude of a specific ERP component. The analysis can be performed either at the group level or at the individual-subject level. In the former, the amplitude of the ERP response and one task-related contrast image per subject are subjected to a correlational analysis. The amplitudes of the ERPs are measured either at the maximum peak of the component or in a time window that can include one or several ERP peaks. This method has the advantage of mapping brain responses that are specifically correlated with a specific and reliable ERP signal, but the correlational analysis provides little information about the temporal profile or temporal order of responses that led to the specific ERP component.

The individual subject-level analysis is a more powerful approach to combining event-related EEG and fMRI data. Here, windowed ERP amplitudes

from a parametric manipulation are used as covariates in a general linear modelbased analysis of the fMRI data. For example, Liebenthal et al. (2003) used such an approach to examine brain generators underlying mismatch negativity (MMN) (Naatanen, 1995). The MMN is elicited when subjects listen passively to a sequence of two different tones, one presented less frequently than the other. The presentation of the infrequent tone evokes an increased negative deflection at about 150 ms following stimulus onset. This negativity is thought to index automatic detection of stimulus deviancy. Liebenthal et al. (2003) used ERP amplitudes from three conditions—standards, small deviants, and large deviants-in a correlational analysis of fMRI data, and they found that restricted regions of the left and right superior temporal gyri, Heschl's gyri, and planum temporale showed significant correlation with the amplitude of the MMN. This approach and its extensions, using unaveraged EEG data, are likely to be widely used in the next few years as the first stage in the integration of fMRI and EEG data. It is expected that these methods will eventually be supplanted by more detailed biophysical modeling, once they are sufficiently validated and tested.

B. fMRI-Constrained Dipole Modeling

A more general method for combining EEG and fMRI data has been to use spatial information based on structural and functional MRI data to constrain the location of ERP sources (Fig. 6). One common approach uses dipoles to model the neural activity; this method is useful and reliable when the approximate locations of the ERP sources are known (Scherg and Von Cramon, 1985). Dipoles are a good model of the distal electrical fields generated by specific neural sources that are active above the background EEG. Single or bilaterally symmetric dipoles are often used when neuronal activity is confined to primary sensory regions. Beyond this, the main problem is to determine the location of the cortical sources and to then model the time course of activity in each location source.

fMRI activations, if used with the appropriate neuroanatomical and neurofunctional constraints, can be extremely effective in specifying initial dipole locations. These models require information about the geometry and conductivities of the different layers of the head, including the cortex, the skull, and the scalp. The contribution of each cortical source to the scalp-recorded signals can then be computed, and best-fitting dipole orientations and strengths can be estimated from a linear inverse solution (Babiloni et al., 2003; Liu et al., 1998; Scherg and Von Cramon, 1985). This analysis also yields the expected time course for each dipole. To the extent that the signals are high at latency windows that correspond to the peak latency of given ERP components and are low outside of those windows, this technique provides strong evidence for localizing

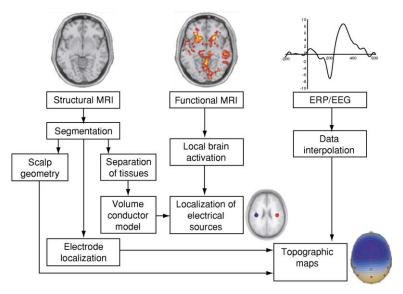


FIG. 6. Schematic overview of some of the steps involved in biophysical modeling of EEG data using constraints derived from structural and functional MRI data.

the source of the scalp-recorded ERP component. The orientation and strength of the dipoles can be fitted on the entire ERP window or on a window of specific components of the ERP. Finally, to investigate the relationship between the ERP and fMRI activation, correlations between dipole strength and the height and extent of fMRI activation can be examined. For further details on dipole modeling, the reader is referred to a recent review by Darvas et al. (2004).

Various approximations are used to integrate fMRI activations into the source-localization procedures. One approach is to use Talairach coordinates of fMRI activation to be entered into a three-shell model of the cortex, skull, and scalp (Zanow and Peters, 1995). This approach obviates complex problems with fMRI and EEG coregistration and has been widely used to localize ERP sources (Fuchs et al., 2004; Liotti et al., 2000; Menon et al., 1997; Opitz et al., 1999; Pouthas et al., 2000; Tarkka et al., 1995; Wang et al., 1999; Woldorff et al., 2002). The use of individual subject MRIs to construct more accurate head models is, however, becoming increasingly common (Fuchs et al., 2004).

Regardless of the models used, prior information about possible and impossible sources needs to be incorporated into the analysis. For example, brain areas that do not have the layered organization (including elements such as the thalamus and basal ganglia) needed to generate far fields that can be recorded on the scalp (Nunez, 1999; Pedley and Traub, 1990) should not be included in the dipole model.

We now describe two examples from our research that help explain these ideas. In one study, we used fMRI and ERP with an auditory oddball task to investigate the neural bases of directed attentional processing (Menon et al., 1997). During this task, subjects were asked to detect deviant target stimuli presented randomly within trains of standard stimuli. Event-related fMRI and EEG data were acquired from the same subjects during performance of identical tasks. We combined the two types of data to investigate the neural generators of the P300. Target detection elicited significantly greater activation bilaterally in the temporal-parietal cortex, thalamus, and anterior cingulate cortex (ACC). Spatio-temporal modeling of ERPs based on dipole locations derived from the event-related fMRI indicated that bilateral sources in the temporal-parietal cortex are the main generators of the P300 (Fig. 7). The findings provide convergent fMRI and EEG evidence of significant activation of the temporal-parietal cortex in the interval from 285-610 ms after stimulus onset during target detection. The methods developed in the study provided a novel multimodal neuroimaging technique by which to investigate the spatio-temporal aspects of processes underlying brain functioning.

In a recent study, we extended this analysis and used combined ERP and fMRI to investigate the timing of early, modality-specific, attentional modulation by the ACC. The ACC has been reported to modulate responses in higherorder-association cortices; however, it is not known whether the ACC has a modulatory effect on early sensory processing regions. We used fMRI and effective-connectivity analyses to examine activation and connectivity of the ACC using fMRI data along with fMRI-constrained dipole modeling of ERPs obtained from subjects who performed auditory and visual oddball attention tasks. fMRI activation showed that the ACC response was similar for auditory and visual tasks; however, effective-connectivity analyses showed modality-specific effects with increased ACC influence on the precuneus during the visual task and on the Heschl's and superior temporal gyri during the auditory task (Fig. 8). ERP data recorded using the same oddball tasks showed large N2 and P3 components in response to the target stimuli in both modalities. Dipole modeling of the whole ERP segment was based on source locations determined from fMRI activations; we created one dipole model for the auditory task and another for the visual task. When the fMRI activations were similar in the two tasks, the dipole was placed at the same coordinates in both. This analysis showed that the ACC is the major generator of the N2b-P3a attention-related components in both modalities and that the primary sensory regions generate a small mismatch signal about 50 msec prior to feedback from the ACC. Responses in these sensory regions are significantly enhanced 60 msec after feedback from the ACC. Taken together, these results provide converging neuroimaging and electrophysiological evidence of top-down attentional modulation of early sensory processing by the ACC. Our findings suggest a model of attentional control based on dynamic

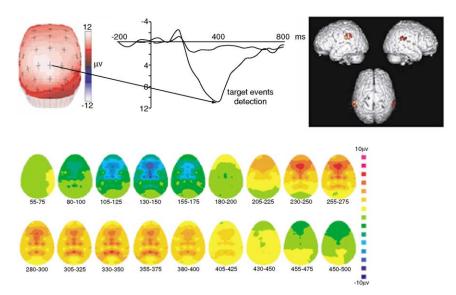


FIG. 7. Top left: Topography and time course of event-related potentials (ERPs) from normal adults during an "oddball" target detection task. The P300 component elicited during target detection has maximum amplitude over the parietal cortex approximately 300–400 ms after onset of the deviant stimulus. Top right: Event-related fMRI responses during target detection. Activated regions include the left and right temporo-parietal cortex 1. Bottom: Spatio-temporal dynamics of brain potentials acquired during target detection.

bottom-up and top-down interactions between the ACC and primary sensory regions.

VIII. Integrating fMRI and (Single-Trial) EEG Data

There is growing interest in combining single trial, or non-phase-locked, EEG with fMRI. These signals are related to perceptual and cognitive processing, but they may or may not be locked to an external stimulus. Combined EEG-fMRI techniques have been used to identify the neural correlates of clinically or behaviorally important spontaneous EEG activity, such as interictal spikes, the alpha rhythm, and sleep waves. The area where the greatest progress has been made is epileptic-seizure localization. The common method of integrating EEG and fMRI data here is to transform EEG data into a physiologically meaningful covariate to be used in a voxel-based general linear model (Salek-Haddadi et al., 2003).

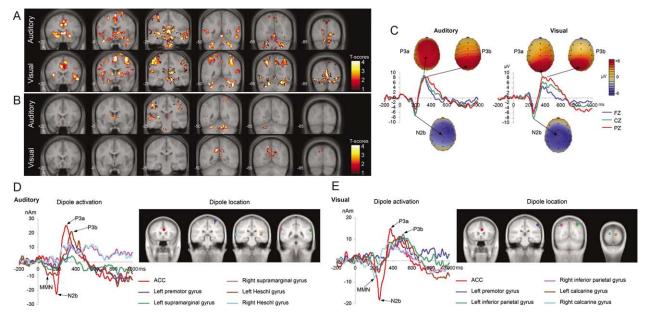


FIG. 8. (A) Brain areas that showed significantly greater activation during auditory (top) and visual (bottom) target detection. (B) Brain regions that showed significantly greater connectivity with the anterior cingulate cortex (ACC) during target detection. (C) Difference waveforms (targets minus standards) of the auditory and visual ERPs at electrodes FZ, CZ, and PZ. The topographical maps shown for the N2 and P3 components, however, reveal very little useful information. (D and E) The fMRI-derived dipole model of the ERPs, however, shows a large contribution by the ACC to the N2b–P3a components in both auditory and visual modalities.

A. EEG AND EPILEPSY SEIZURE LOCALIZATION

The recording of EEG during fMRI has opened up new avenues in epilepsy research. In fact, initial applications of single-trial EEG and fMRI have, until very recently, been limited to seizure localization. Interictal discharges underlying epileptogenic neural activity can be readily detected on scalp EEG; however, the origin of this activity cannot be inferred except in terms of lobes and hemispheres. This work differs from most applications of EEG–fMRI in that each patient has a different spatial and temporal distribution of the epileptogenic activity, and signatures of this activity need to be determined with relatively high accuracy and efficiency.

In the past few years, the simultaneous measurement of EEG and fMRI has been used by several groups to study interictal activity in patients with epilepsy (Aghakhani et al., 2004; Archer et al., 2003; Krakow et al., 2001; Lazeyras et al., 2000; Lemieux et al., 2001a). Although early studies used the EEG spikes to trigger fMRI acquisition (Krakow et al., 1999; Lazeyras et al., 2000; Seeck et al., 1998), use of continuous EEG and fMRI data is now common (Lemieux et al., 2001b). In either case, these studies have benefited from the relatively high amplitude of epileptogenic activity, which, at about 100 μ V, is visible on scalp EEG-standing in contrast to perceptual and cognitive ERPs, which have amplitudes of about 5-10 μV after averaging over several trials. However, in some patients, the events are usually not very frequent and of limited duration (from a fraction of a second to [rarely] more than 10 seconds) (Bagshaw et al., 2005), making the study of interictal epileptiform events extremely challenging in these cases. Major applications of fMRI in epilepsy include the localization of task-correlated language and memory function and the localization of ictal and paroxysmal phenomena (Detre, 2004). For example, research from several laboratories has shown that language lateralization by fMRI provides results comparable to those from intracarotid amobarbital testing (Waites et al., 2005). Recent studies have also shown that widespread regions of the cerebral cortex and thalamus underlie generalized spike and wave (GSW) or polyspike and wave bursts in patients with idiopathic generalized epilepsy (Aghakhani et al., 2004). Interestingly, both activation and deactivation were observed in relation to the GSW; activation predominated over deactivation in the thalamus, whereas the opposite was seen in the cerebral cortex. The presence of a thalamic BOLD response in most human patients converges on the thalamic involvement seen in animal models. Findings such as these provide further assurance of the usefulness of the combined EEG-fMRI approach to better understand the brain systems underlying various forms of epilepsy. For further details, the reader is referred to Lemieux (2004).

B. EEG AND RESTING-STATE fMRI

fMRI studies in humans have revealed task-specific increases in brain activity that are associated with various mental activities. Many of these studies also show task-independent decreases, especially when tasks with high-level cognitive load have been compared to a passive state, such as simple fixation or closed eyes. These decreases have raised the possibility that there might be a baseline or resting state of brain function involving a specific set of mental operations (Gusnard et al., 2001). The "default-mode" hypothesis of brain function (Raichle et al., 2001) proposes that there is a specific neural network whose activity predominates in the relaxed, resting state and that activity in this default-mode neural network decreases during the performance of a demanding externally cued task. This hypothesis is supported by fMRI studies of the conscious resting state (Greicius et al., 2003) and cognitively undemanding tasks (Greicius and Menon, 2004), which have shown strong temporal coherence of neural activity among brain regions implicated in the default mode. Changes in ongoing EEG activity unrelated to any specific externally mediated tasks have also been well known. For example, the alpha rhythm in the EEG increases when subjects stay relaxed with their eyes closed, and the beta rhythms are prominent when individuals are alert and attentive (Niedermeyer and Lopes da Silva, 2004). Resting-state fMRI and EEG have been used to examine the neural bases of these dynamic changes in baseline state as well as to examine their relation to default-mode networks.

Here, the analytic approach is to correlate ongoing EEG fluctuations with changes in the resting-state fMRI signal. For example, the spectral power of the EEG in the alpha range can be used as a covariate in a standard general linear model. Using this approach, several studies have examined the neural bases of the alpha rhythm using data from simultaneous EEG-fMRI recordings (Goldman et al., 2000, 2002; Laufs et al., 2003a,b). In these studies, the amplitude of the EEG in the alpha band (8-12 Hz) is computed over a moving window that steps about every 30 seconds across a total recording interval of 5 to 8 minutes. The resulting waveform is convolved with the HRF and used as a covariate in a conventional analysis of fMRI data. Goldman et al. (2002) found that the alpha rhythm was correlated with fMRI response in the thalamus. On the other hand, Laufs et al. (2003a) reported that there was little positive correlation of resting-state brain activity with alpha power (8-12 Hz), but strong and widespread negative correlation was observed in the lateral frontal and parietal cortices, which are known to support attention and working memory. Power in a 17- to 23-Hz range of beta activity was positively correlated with activity in retrosplenial, temporo-parietal, and dorsomedial prefrontal cortices, regions that overlap to some extent with the default-mode network identified in fMRI studies. These findings raise the possibility that beta rhythms may index spontaneous

cognitive operations during conscious rest. It is likely that simultaneously recorded, multichannel beta- and gamma-band EEG might assist in the interpretation of task-related fMRI data, since high beta and gamma EEG amplitudes both imply high rates of energy utilization (Freeman, 2004a,b).

IX. Conclusion

In the past 5 years, considerable progress has been made on several fronts in combined EEG and fMRI studies of human brain function. These include optimal study design, data acquisition, and data analysis. As better methods for removing artifacts in MRI scanning become available, it is to be expected that fully continuous EEG—fMRI recordings will become the mainstay of multimodal functional brain imaging. An area that clearly needs further research is the development, and validation, of procedures and algorithms for biophysical modeling of EEG and fMRI signals. Such models will help researchers to better integrate spatial and temporal information in fMRI and EEG. Validation of procedures for artifact reduction is also necessary; this can be easily accomplished using computer simulations, but very little research has been performed in this area. Finally, we note that although clinical applications have thus far been limited to epilepsy, in the future combined EEG and fMRI studies will also provide new insights into the dynamical bases of psychiatric, neurological. and neurodevelopmental disorders.

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