Psychophysiology-Informed (Multimodal) Imaging

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Abstract Electroencephalography (EEG) and magnetic resonance imaging are two popular methodologies for brain research. While EEG has a high temporal resolution, yet a low spatial resolution, MRI has the complete opposite, a high spatial resolution, yet a low temporal resolution. Obviously therefore, researchers have been searching for ways combining the two methodologies, for more than two decades. However, there are many issues that have to be solved before the methodologies can be successfully and, more importantly reliably, combined. Here, we give an overview of these issues, and present strategies that have been used over the past two decades to overcome them. We start with a general description of EEG and (f)MRI methodology, then present the difficulties involved in combining both methodologies, and lastly present and discuss the most popular strategies that have been used over the past two decades to solve these problems. We conclude that in spite of the many issues, the two methodologies can be combined successfully, provided that the correct procedures are followed.

Keywords EEG · (f)MRI · P50 suppression · Schizophrenia

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1 Introduction to EEG

Electroencephalography (EEG) is a methodology to assess electrical activity of the brain. It was first discovered by Hans Berger (Berger 1929; See also: Jung and Berger 1979). EEG makes use of the fact that neurons produce electricity (pre- and post-synaptic potentials) which spread throughout the brain until it reaches the scalp. This electrical activity can be measured by for instance placing electrodes on the scalp, by placing them on the brain tissue itself or, even more invasive, by inserting them in the brain (Niedermeyer and Lopes da Silva 2005). Obviously, the two last techniques are mostly used in animal research, although sometimes it is used in humans as well, e.g. when a patient needs brain surgery. From the scalp, it is not possible to assess the electrical activity of one single neuron. For this, the electrical current is simply too small. EEG recordings from the scalp generally consist of populations of neurons "firing" at the same time, in synchrony. Before the electrical activity arrives at the scalp, it usually has travelled through a number of brain tissues, including cerebrospinal fluids, dura mater, bone, skin, which all affect the signal: where cortical discharges can reach amplitudes up to 1.5 mV, typical activity recorded by scalp electrodes lies between 10 and 100 μV, but more generally do not exceed 50 μV (Niedermeyer and Lopes da Silva 2005). This means that the signals that reach the scalp need to be amplified, typically 10^5–10^6 times, to enable assessment. In clinical settings, EEG is most frequently investigated without further processing. Unprocessed EEG is for instance used to determine whether an individual suffers from epileptic seizures, or is used in sleep research (e.g. Keshavan et al. 1990). Unprocessed EEG can also be decomposed in frequency bands (e.g. alpha, beta, gamma bands) by means of Fourier transformation (Kooi et al. 1978; see also Fig. 1), from which certain psychological activities or mental states are commonly inferred (Barry et al. 2003a; Kiloh et al. 1972; Niedermeyer and Lopes da Silva 2005).

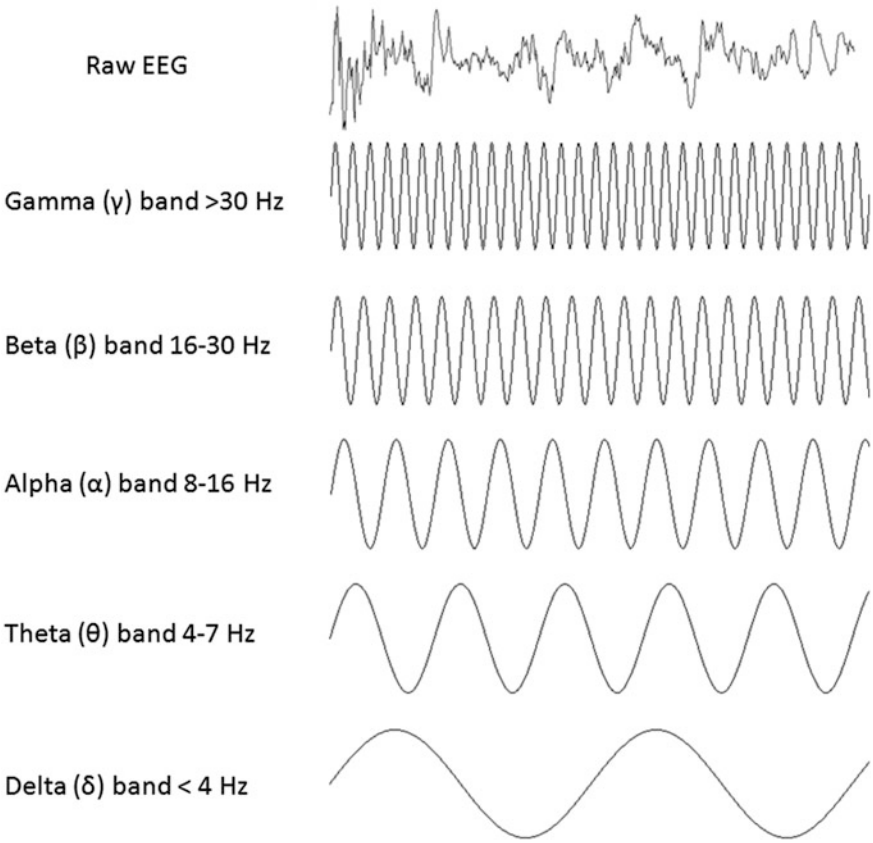

Fig. 1 Raw EEG decomposed with Fourier transformation, displaying the main frequency bands

However, EEG can also be processed: If identical sensory stimuli are presented a number of times, then so-called event-related brain potentials (ERPs, sometimes also referred to as evoked potentials, EPs) can be derived from them, by averaging the elicited EEG signals (e.g. Pfefferbaum et al. 1995). By averaging, one accomplishes that all randomly generated "noise" in the brain is cancelled out, because in contrast to the presented stimulus, the noise is not time locked to the EEG signal, thereby ensuring that the activity left is solely generated by the presentation of the sensory stimulus. Obviously, the more the trials are repeated, the more it will assure that the ERP is indeed generated by the stimulus in question, and the less it will be affected by randomly generated brain activity (e.g. Fabiani et al. 2000; Pfefferbaum et al. 1995). ERPs are for instance clinically used to determine the extent of auditory loss with so-called brain auditory evoked potentials (BAEPs) (Markand 1994) and also frequently used in research, such as research on schizophrenia or other psychiatric disorders (Aggernaes et al. 2010; Barry et al. 2003b; Coull 1998; Madsen et al. 2013; Näätänen 1990; Oranje et al. 2013; Sumich et al. 2006). An auditory

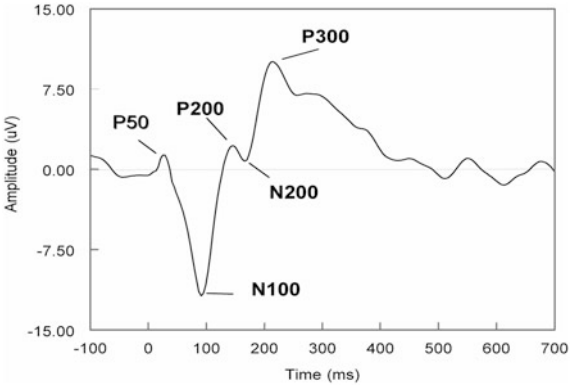

Fig. 2 Example of an ERP, following an auditory stimulus

stimulus can, also depending on the paradigm, among others elicit a P50, N100, P200, N200 and even later components such as a P300 ERPs, (see Fig. 2). About the nomenclature: the "P" and "N" stand for positivity, respectively negativity, the number stand for time in ms. Hence, P50 stands for a positive deflection in the EEG, 50 ms following stimulus presentation; N100 stands for a negativity appearing 100 ms post-stimulus, etc.

2 Introduction to (f)MRI

2.1 MRI

Magnetic Resonance Imaging (MRI) is presently favored over other imaging techniques for investigation of brain structure and function. This is primarily because MRI is a non-invasive methodology, uses no radioactive radiation, has relatively short acquisition times, and obtains high spatial resolution. A further advantage of MRI methodology is that both brain structure and function can be assessed in one single session. Inside an MRI scanner, there is a strong homogenous static magnetic field (B_0) usually ranging from 1.5 to 3 Tesla (T), although rather recently 7 T scanners have also become available for research. Nuclei with gyromagnetic properties (such as protons) will have a tendency to align the axis of their intrinsic spin along the B_0 field. The axis of the spins will precess, or "spin around", the direction of B_0 (z-direction) with a frequency, the "Larmor frequency", that is specific for each type of nuclei and dependent on the surrounding field strength. Imaging with magnetic resonance typically uses hydrogen atoms because the abundance of hydrogen in biological systems ensures a high signal. The alignment of the spins results in a net magnetization of the subject while he or she remains inside the field. With a radio frequency (RF) pulse in resonance with the Larmor frequency of the nuclei of interest (as mentioned before, usually

Hydrogen), the net magnetization can be "pushed" out of equilibrium (excitation). The net magnetization will then precess while it returns to equilibrium (relaxation). This results in emission of radio waves with the Larmor frequency but only as long as there exists a magnetization component perpendicular to the B_0 field (along the xy-plane). These radio waves can be received as a signal. The relaxation is determined by two time constants T1 (spin-lattice relaxation time) and T2 (spin–spin relaxation time). Both T1 and T2 are dependent on the environment that the nuclei are part of and, therefore, specific for each type of tissue. T1 describes how the magnetization returns to equilibrium along the longitudinal axis (z-axis). T2 describes the loss of magnetization in the xy-plane due to dephasing of the spins as a result of molecular interactions. Inhomogenities in the field and susceptibility losses, e.g. due to the presence of deoxyhemoglobin or air/tissue boundaries, cause a faster loss of signal than the pure T2; the combined time constant is called T2*. The timing and strength of the excitation pulses, as well as the delay between excitation and signal reception, determines whether a sequence is more sensitive for T1 or T2.

When a gradient in the magnetic field is applied using an additional electromagnet, the Larmor frequency is also affected. This can be used for imaging. By applying a magnetic gradient superimposed on B_0 during the excitation, only the 2D-plane with Larmor frequency corresponding to the RF pulse is excited (slice selection). Applying a gradient along the excited plane determines the precession of the protons in a controlled way. This process is repeated with different gradients, varying the direction and gradient strength (each variation of direction and strength corresponding to a point or line in "k-space") in a predetermined sequence saving the signal each time. The selected 2D plane can then be imaged by a mathematical technique called Fourier transformation. For further information on the basic principles of MRI, the reader is referred to textbooks on the subject (e.g. Jezzard et al. 2008).

2.2 fMRI

In the early days of its use in brain research, MRI was predominantly used to study brain structure only. Nowadays, a number of equally ingenuous as advanced techniques have been developed, resulting in a variety of additional uses of MRI, such as determining structural brain networks with diffusion tensor imaging (DTI), functional brain networks by using regression approaches, or even biochemistry of the brain by means of spectroscopy. However, a discussion on these approaches is beyond the scope of this chapter. Besides these techniques, MRI can also be used to map changes in brain hemodynamics. This is termed functional magnetic resonance imaging or fMRI. The basis for performing fMRI is the Blood Oxygen Level Dependent (BOLD) signal, first used by Ogawa et al. (1990). The technique is based on the fact that oxyhemoglobin is diamagnetic while deoxyhemoglobin is paramagnetic. Paramagnetic molecules disrupt the homogeneity of the magnetic

field and decrease T2*. If blood flow increases due to increased cellular activity, and a comparable increase in oxygen consumption is not present, oxygenation increases. This measurable increase in signal is termed the BOLD contrast. Increased blood flow followed by neuronal activity in the brain is referred to as the hemodynamic response. The BOLD contrast is the sum of changes in the cerebral blood flow (CBF), cerebral blood volume (CBV) and oxygen metabolic rate that occurs in response to neural activity. It is still debated what kind of neural activity specifically determines these changes, although increasing evidence suggest that BOLD is more a measure of local field potential (LFP) changes rather than spikes in activity (Logothetis et al. 2001), i.e. the hemodynamic response follows the level of neuronal input to a given area more than the actual firing of the neurons (output) in the area. When measuring fMRI, the same sequence is repeated consecutively throughout the scan. Each of the repeated sequences images the whole, or a part of, the brain (termed a volume). It is then possible to detect changes in the BOLD response following different types of stimuli (conditions). These conditions, or responses, can be compared in a contrast, by subtracting one condition from another or by comparing a condition to baseline. The faster the repetition time (TR), the higher the temporal resolution becomes. This is why the so-called "echo planar imaging" (EPI) sequence is frequently used in fMRI, because this sequence can sample the entire two-dimensional k-space following a single RF excitation pulse. For more detailed information on BOLD imaging, please see reviews (e.g. Logothetis and Wandell 2004; Raichle and Mintun 2006) or textbooks on the subject (e.g. Jezzard et al. 2008).

3 EEG and fMRI Combined

3.1 General

Although there have been many decades of research devoted to the behavioral and psychological processes behind ERPs, research on the generators of these ERPs in the brain is lagging behind. Initially, attempts were made to locate these generators by EEG source localization, using software such as BESA® (MEGIS Software GmbH, Gräfelfing, Germany; e.g. Scherg et al. 2002; Scherg and Picton 1991). Later, software was developed that could integrate EEG with MRI, such as Curry® (Compumedics, Neuroscan). Although source localization with EEG has high temporal resolution, its spatial resolution is rather poor: this resolution is approximately half of the average electrode distance, i.e. approximately 1 cm when 64 electrodes are used (Scherg 1990). In contrast to EEG methodology, fMRI has much higher spatial resolution, yet much lower temporal resolution, because the hemodynamic response is relatively slow—it peaks at approximately 6 s following a stimulus. In other words, the combination of EEG and fMRI methodology complements each other, i.e. potentially it could result in data with

both high temporal resolution due to the EEG part, and high spatial resolution due to the fMRI part. However, combined use of EEG and MRI methodology has many issues and although being performed for approximately a decade or two, it is still developing (Im et al. 2006). In this chapter, we shall predominantly focus on through electrophysiology informed MRI imaging techniques and the many issues that need to be dealt with when combining the two methodologies.

3.2 Issues

While a typical EEG environment is devoid of any other stimulation than the stimuli presented in the paradigms, the typical MRI environment is rather noisy. This noise is likely to interfere with the paradigms used in EEG settings, especially if they happen to make use of auditory stimuli. In addition, an MRI assessment frequently triggers anxiety, much more than is the case in a typical EEG assessment: the procedures are intimidating, the scanner space is claustrophobic and as mentioned before, rather noisy. This anxiety most likely impacts on the results. Another issue is that responses to stimuli in close temporal proximity of each other, such as in typical EEG paradigms, cannot be separated with fMRI, because the hemodynamic response is much slower than these interstimulus intervals. Moreover, some ERPs are rather small in amplitude, such as that of the P50 ERP (on average between 4 and 5 μV, e.g. Oranje et al. 2006) and hence its generators in the brain may be fewer, or at least much less active, than those of larger waveforms, such as the N100 or the P300. The generators of these larger waveforms may therefore dominate the results. A further issue is that metal can affect MRI images, i.e. the EEG electrodes or their wires can affect the quality of the MRI data. Finally, an MRI scanner produces huge electrical artefacts in EEG data when both techniques are used concurrently (see below for more detail). Over the years, several methods and strategies have evolved to overcome the above-mentioned issues. Broadly speaking, these strategies can be categorized into two approaches.

3.3 Associative Approach (Separate EEG and FMRI Assessments)

In this approach, EEG and (f)MRI are assessed separately from each other. Roughly, there are two strategies that make use of this approach. The first, based solely on associations, takes the least effort in preparation and data processing: It simply asks for testing the same individuals in an EEG setting and in an (f)MRI setting, after which the results of both techniques are analyzed for possible associations. This strategy has for instance been used to study associations between structural brain correlates and several electrophysiological parameters,

such as sensorimotor gating (assessed with a pre-pulse inhibition of the startle reflex paradigm or PPI) (e.g. Hammer et al., 2012; Kumari et al. 2005, 2008), sensory gating (assessed with a P50 suppression paradigm) (e.g. Arciniegas et al. 2001), mismatch negativity (e.g. Rasser et al. 2011) or P300 amplitude (e.g. Egan et al. 1994; Fusar-Poli et al. 2011; McCarley et al. 2002); an interesting variant of this approach is when so-called low-resolution electromagnetic tomography (LORETA) is coupled with MRI, such as for instance was used in the study of Pae et al. (2003) to locate generators behind the P300 amplitude.

This is currently the most widely used approach for pragmatic reasons; neither the compatibility between EEG and MRI equipment nor that of the paradigms used are relevant when using this approach. However, obvious disadvantages of this strategy are that it is still difficult to find the actual generators behind a specific ERP amplitude in the brain, because it will remain uncertain whether the MRI derived brain activations that correlate with a specific ERP of interest are not related to other (earlier or later appearing) ERPs, or to other processes behind the paradigm altogether.

An alternative strategy that deals with some of these issues makes use of functional instead of structural MRI, and in which identical, or at least very similar, paradigms are used in both the EEG and fMRI setting. The difficulty with this approach is that a typical EEG setting is quite different from a typical MRI setting (see Sect. 3.2). Where EEG is usually recorded in sound isolated and electrically shielded rooms, an MRI setting is quite the opposite: recording MRI images makes a lot of noise. For paradigms using visual stimulation, this may seem less of a problem. However, in the EEG setting, subjects are usually sitting upright, while subjects lie down in an MRI scanner, which means that visual stimuli are usually presented by mirrors or goggles. Paradigms using auditory stimulation call for more drastic procedures. In one of the strategies, scanner noise is as much avoided as possible by making use of so-called interleaved scanning: in this method, the MRI recordings are stopped a period just before and after a trial of a paradigm. During this "silent" period, the auditory stimuli of the trial can be presented. The MRI scanning then starts again before the expected peak of the hemodynamic response, which enables identification of the activated brain areas. This method was for instance used by Tregellas et al. (2007). Another strategy ingeniously made use of the scanner gradient coils to create auditory stimuli with a duration of 50 ms to locate sources of P50 suppression in the brain (Mathiak et al. 2011). Other researchers tried to reduce the noise of the scanner to such levels that it did not interfere with the auditory stimulation of the paradigm. This is rather difficult, due to the intensity of the scanner noise, which usually exceeds that of the auditory stimuli of the paradigms by manifold: typical intensities of auditory stimuli in EEG paradigms (PPI paradigms not included) are at most 90 dBa, whereas typical MRI scanner sequences may reach sound intensities up to 114 dBa or even beyond (Counter et al. 1997). This means that at most MRI noise can be reduced to such levels that the stimuli of the paradigms can be heard, yet the residual scanner noise could still very well have an impact on the results. There are several examples of studies that made use of this approach, with the investigators

frequently taking drastic additional steps to minimize the effects of residual scanner noise (e.g. Hazlett et al. 2001, 2008; Mayer et al. 2009).

Alternatively, stimuli of a different modality can be used altogether, e.g. by using visual or tactile stimuli instead of auditory stimuli. Frequently, these alternative paradigms are first validated in EEG sessions to verify that they yield similar results as their auditory versions. This strategy, together with often more advanced procedures, has been used in several studies (Bak et al. 2011, 2013; Kumari et al. 2003). Although this strategy is more accurate in relating EEG or EMG (electromyography) signals to fMRI derived sources in the brain than the first mentioned strategy, it still has several limitations. Importantly, it is not certain that the paradigms in the EEG and fMRI setting produce similar results, e.g. does P50 suppression or PPI of the startle reflex actually occur in both settings, and if so will it occur in similar levels. The results may after all still be influenced by non-paradigm related processes, such as anxiety due to MRI assessment or scanner noise. Another issue is that a certain ERP cannot be directly coupled to a specific activity in the brain due to the low temporal resolution of (f)MRI: An auditory stimulus gives not only rise to P50 amplitudes, but also to N100, P200, N200, etc. amplitudes; it is impossible with this approach to directly determine which ERPs are coupled with which activated areas in the brain as indicated by the fMRI scan; this can only be done by approximation, e.g. by applying associative statistical analyses. The next category of approaches go one step further, they assess EEG concurrently with MRI, effectively solving most of the above-mentioned issues.

3.4 Concurrent Approach (Simultaneous EEG and FMRI Assessment)

In this approach, the psychophysiological measurements are assessed concurrently with the imaging technique, i.e. EEG is assessed inside the MRI scanner. The most important advantage of assessing EEG and MRI concurrently is that one does not need to assume that the same paradigm triggers the same processes in the brain in the (f)MRI session as in the EEG session, as would be the case in the associative approach, but one can directly deduce from the data whether this is the case or not (see: Herrmann and Debener 2008; Huster et al. 2012; Ritter and Villringer 2006, for introductory reviews of concurrent EEG-fMRI). However, concurrent assessment is certainly not easy, given the many issues mentioned above: it not only sets limitations for the paradigms and even the EEG equipment that can be used in the MRI environment, but it also means more complicated processing of the data. The MRI scanner will produce serious artefacts in the EEG data that will need to be removed, and vice versa, the electrodes and cables necessary for EEG assessment can produce artefacts in the MRI images. Nevertheless, with the right equipment and appropriate processing of the data, EEG and EMG can actually be assessed concurrently with fMRI with only minor effects on the quality of the data.

Starting with the concept that the quality of the MRI data could be affected by the wires and electrodes of the EEG cap, there are studies showing that this impact can be minimized provided suitable equipment is used (Krakow et al. 2000; Mullinger et al. 2008). The impact of the MRI scanner on EEG signals, however, requires more attention. Back in 1824, William Sturgeon was the first to show that a coil of wire that is moved inside a magnetic field produces an electric current. Indeed, the shifting magnetic gradients that are necessary for fMRI produce artefacts in the EEG data due to the induced electrical current in the wires from the electrodes. Fortunately, these magnetic gradients are applied in a controlled and specific pattern, determined by the fMRI sequence. Due to this repetitiveness, the artefacts can be removed by averaging the EEG signal from the volumes. Typically, this is done by using a sliding average, and subtracting this average from the original data (Allen et al. 2000). However, movement of a subject also creates artefacts. Besides disturbing the MRI images, these movements will induce electrical currents in the wires of the electrodes, due to the same principles as mentioned above: moving conductive materials in the ever present steady state, magnetic field of an MRI scanner produces currents. Usually, these movement artefacts can be minimized by securing the wires from the electrodes and by preventing head movement as much as possible, e.g. by fixation of a subject's head in the head coil together with strict instruction of the subject. Nevertheless, even the small movements due to the heartbeat will produce EEG artefacts: movement of blood (a conductive fluid) through vessels creates pulse-related (cardioballistic) artefacts. Again, due to their repetitiveness also these artefacts can be relatively easy removed (Allen et al. 1998). By properly applying these procedures, all scanner artefacts can be quite efficiently removed (see Fig. 3): even information on ERP level is preserved, showing virtually no differences between EEG assessed in an EEG setting, or assessed in an MRI scanner (Bregadze and Lavric 2006). As an example of this strategy, we will describe the approach we recently used in our laboratory, where we made an attempt to locate the sources of P50 suppression with concurrent EEG and fMRI methodology. We started by adapting a typical auditory P50 suppression paradigm to an fMRI friendly version, among others by replacing the auditory stimuli with somatosensory stimuli. This somatosensory paradigm was first validated for showing actual P50 suppression in a pilot study, in which healthy subjects were assessed in a normal EEG setting. Following this validation study, subjects were assessed with the fMRI friendly paradigm first in a normal EEG setting (assessing only EEG) and later in an MRI setting, where both EEG and fMRI was assessed concurrently. Following the above described removal of MRI artefacts (see Fig. 3), we first statistically compared the EEG results of the two settings with each other.

After validating that these data sets did not significantly differ from each other, we first located by proxy, the generators of P50 suppression in the EEG data with BESA software. In the fMRI data, a contrast depicting differences between a trial type with suppression and one without was calculated. Following this, we imported the through EEG-derived sources in the fMRI recordings, and searched for significant clusters in the contrast that overlapped with these sources. This enabled us to

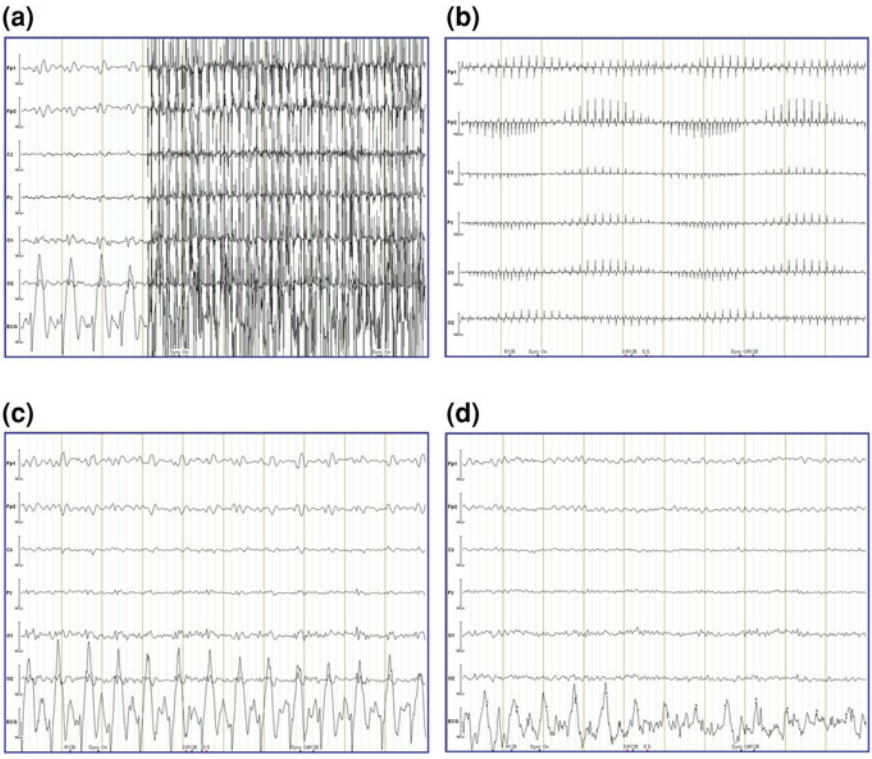

Fig. 3 Removal of MRI artefacts from EEG data during pre-processing. For simplicity, only six EEG channels are shown: FP1, FP2, Cz, Pz, O1, and O2. The channel below the EEG channels (in **a**, **c** and **d**) represents recording of ECG. **a** Representation of the beginning of MRI scanning in the EEG recording, showing the huge artefacts that this causes (*note* the scale represents 500 μV). **b** Representation of the EEG signal during the MRI scan (*note* the scale represents 5,000 μV), revealing the repetitiveness of the gradient artefacts. **c** The same data as **b**, with the gradient artefacts removed (same scale as in **a**); note that the contribution of the heartbeat and pulse can still be observed in the six channels. **d** In this last step, also the pulse artefacts are removed (same scale as **a** and **c**); the data is now ready for the usual further processing of EEG data

determine which of the many brain activations that followed the presentation of a trial were actually time locked to the P50 ERP. As such, we could successfully locate the generators of P50 suppression, first in healthy subjects (Bak et al. 2011) and later in the aberrant P50 suppression of patients with schizophrenia (Bak et al. 2013). An interesting alternative to this approach is to combine the above-described interleaved approach with concurrent EEG and fMRI assessment. The advantage of this is that the EEG artefacts due to the shifting magnetic gradients can be avoided. However, the shape of the hemodynamic response cannot be detected with this method, and the above-described cardioballistic artefacts still need to be removed. This procedure has for instance successfully been used to locate sources of PPI (Kumari et al. 2003) and P300 amplitude (Mulert et al. 2004).

Summarized, these studies show that it is possible to deal with the many issues that are involved in concurrent scanning of MRI and EEG, but it also shows that the procedures are quite laborious and challenging.

Attempts to extract more and more information out of the concurrent EEG and fMRI measurements have moved the field into yet another interesting area, directed towards incorporating single EEG trials in the statistical analysis of the data sets, rather than the averaged ERPs. This method requires additional expertise in the more advanced mathematical and computational models involved. A growing number of reports within this field have emerged over the last decade. A popular method is using specific components based on amplitudes of the waveforms from a specific electrode and entering these as explanatory variables in the general linear model (GLM) of the MRI analyses (e.g. Benar et al. 2007; Debener et al. 2005; Fuglo et al. 2012; Mobascher et al. 2012). This is presently only feasible for larger, robust components in the EEG signals, such as the N100 or P300 amplitudes, because they can be detected in single trials. A variant on this method makes use of an algorithm to identify components in the EEG signal corresponding to parts of the ERP. This can be done with independent component analysis (ICA) as suggested by Debener et al. (2006) but in principle any algorithm to extract relevant components or factors from the EEG signal could be used. Components representing artifacts can then be discarded, while all the relevant components can be used as predictors in the GLM analysis of the fMRI data or integrated with results from a similar approach based on performing parallel ICA, i.e. on both fMRI and EEG data and hemodynamic deconvolution (Eichele et al. 2009). The advantage of this strategy is that more complicated tasks can be analyzed in depth or specific parts of an ERP can be modelled. However, only part of the brain activity can be used in the fMRI analysis; therefore, components should be chosen to address the specific research question.

4 Conclusion

Obviously, the associative approach is by far the less laborious of the two approaches. An additional advantage of this approach is that the resulting EEG data can be compared to those of previous EEG studies. The assumption that the ERP is correlated with the average hemodynamic response is reasonable, even though EEG and fMRI measures represent different aspects of neuronal activity. However, the associative approach does not make optimal use of the strengths of the EEG and (f)MRI methodology, i.e. combining the high temporal resolution of EEG with the high spatial resolution of MRI, such as can be achieved by concurrent assessment of EEG and fMRI. Although this last (concurrent) approach is definitely preferable, it is also rather complicated and laborious. Nevertheless, when properly executed, the results are equally spectacular as reliable.

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