MEG and Multimodal Integration

Seppo P. Ahlfors

Abstract Functional brain imaging methods provide measures of various physiological processes with a range of spatial and temporal scales. Because the sensitivity properties of the imaging modalities differ, combining multimodal data is expected to provide more information about the brain activity than is available by a single method. In direct data fusion, multimodal data can be described as complementary or supportive. Complementary modalities have the same type of sources, such as electroencephalography (EEG) and magnetoencephalography (MEG), which are both generated by cortical primary currents, but with different sensitivity characteristics. Combination of EEG and MEG data can resolve ambiguities in data from only one of the modalities. In a supportive role data from one imaging modality guides the analysis and interpretation of another modality. Structural magnetic resonance imaging (MRI) provides supportive data for MEG source estimation, e.g., by indicating allowable locations and orientations of MEG source currents. Functional MRI (fMRI) can be used in a supportive role to suggest a likely source distribution for MEG among multiple alternatives. MEG and fMRI can also be considered complementary if the different source types, i.e., primary currents for MEG and blood oxygenation level dependent (BOLD) contrast for fMRI, are both derived from a common physiological model.

Keywords Magnetoencephalography (MEG) · Electroencephalography (EEG) · Functional magnetic resonance imaging (fMRI) · Multimodal · Data fusion

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1 Introduction

Different functional neuroimaging methods, often called imaging modalities, provide information about a variety of physiological processes related to brain activity, and have a range of spatial and temporal sensitivity characteristics (He and Liu 2008). Magnetoencephalography (MEG) and electroencephalography (EEG) detect electrical activity in the brain with millisecond temporal spatial resolution, but the inverse problem of determining the spatial distribution of the activity is challenging, and the accuracy depends among other things on the overall pattern of activity (Michel et al. 2009; Hansen et al. 2010). Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and optical near infrared spectroscopy (NIRS) detect hemodynamic phenomena; the time-resolution of these methods is limited by the relatively slow hemodynamic response. However, fMRI can provide millimeter-scale spatial resolution across the whole brain, without the kind of ambiguities inherent in the MEG and EEG source localization. The different sensitivity properties of the imaging modalities suggest that multimodal imaging can provide more information about brain function than is attainable by any single method alone.

In MEG, superconducting quantum interference device (SQUID) sensors are used to measure extracranial magnetic fields generated by neuroelectric currents in the brain (Cohen 1972). The main sources of the MEG signals are post-synaptic dendritic currents in cortical pyramidal cells (Lopes da Silva 2010). From the measured spatial pattern for the magnetic field outside the head, the spatiotemporal pattern of sources within the brain can be estimated (Ahlfors and Hämäläinen 2012). Both MEG and EEG originate from the same type of physiological sources, described as primary currents (Tripp 1983). The spatial sensitivity patterns to the primary currents are different for MEG and EEG, allowing them to provide complementary information about the same type of sources. In contrast, the physiological sources of fMRI (commonly the blood oxygenation level depend or BOLD contrast) and other hemodynamic signals are of a different type from those of MEG and EEG, thereby presenting various opportunities and challenges for multimodal imaging.

According to Horwitz and Poeppel (2002), three main approaches to combining data from multiple neuroimaging modalities are: converging evidence, direct data fusion, and computational neural modeling. Comparison of separately obtained results from different modalities to establish converging spatial or temporal patterns of brain activation is useful for the assessment of the obtained results, e.g., in clinical pre-surgical mapping studies. Many studies have examined the convergence of MEG and fMRI results, including (Beisteiner et al. 1995; Morioka et al. 1995; Sanders et al. 1996; Stippich et al. 1998; Inoue et al. 1999; Woldorff et al. 1999; Del Gratta et al. 2002; Mathiak et al. 2002; Singh et al. 2002; Moradi et al. 2003; Tuunanen et al. 2003; Rossini et al. 2004; Vartiainen et al. 2011; Swettenham et al. 2013); see also the reviews (Mathiak and Fallgatter 2005; Poline et al. 2010).

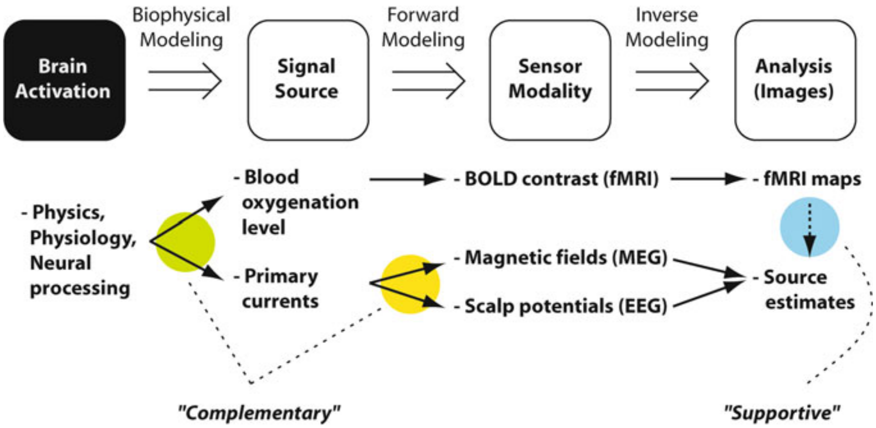

Fig. 1 Schematic diagram of stages involved in the construction of functional brain images. Biophysical modeling can be used to relate the physical and physiological neural processes associated with brain activation to the underlying sources of the brain imaging signals. Forward modeling describes the signal patterns generated by a given source distribution. Inverse modeling involves the estimation of the source distribution on the basis of the recorded signals. MEG and EEG record "complementary" (*yellow circle*) information about the same sources, i.e., primary currents. Functional MRI can be used in a "supportive" role (*blue*) in MEG source analysis. MEG/EEG and fMRI can also be considered complementary (*green*) since the sources of both signals originate from common neural processes

In direct fusion, data from different modalities are combined mathematically to estimate the sources of the measured signals (George et al. 1995; Dale and Halgren 2001). In computational neural modeling, different functional imaging modalities can be modeled within a common framework and the experimental multimodal data can be used to determine parameters of the computation model of the brain networks underlying cognitive tasks (Horwitz et al. 1999; David and Friston 2003; Riera et al. 2005; Babajani and Soltanian-Zadeh 2006; Valdes-Sosa et al. 2009; Plis et al. 2010; Bojak et al. 2011). Here we focus on the combination of MEG with EEG, anatomical MRI, and fMRI, mainly from the point of view of direct data fusion.

We suggest that in the direct data fusion approach, imaging modalities can be conceptually described as "complementary" or "supportive", depending on the nature of the signal sources and the role of the modalities in the interpretation of the multimodal data (Fig. 1). Complementary modalities provide information about the same type of sources. EEG and MEG are complementary modalities, which both detect the primary current distribution related to neural activity. A common source model greatly facilitates the fusion of complementary multimodal data. In a supportive role, data from one modality is used to guide and influence the analysis of the data from another modality. In the analysis of MEG (and/or EEG) signals, anatomical MRI provides important supportive data to constrain the allowable MEG source space. Functional MRI data can be combined with MEG in both supportive and complementary way. In a supportive role fMRI activation can be used, e.g., to constrain the locations of the MEG sources. However, special considerations are necessary when the sources of signals are of different type. Since both fMRI and MEG signals ultimately have their origin in brain activity, linked via neurovascular coupling, they can also be treated as complementary modalities.

2 MEG and EEG

Since the physiological sources underlying both MEG and EEG are of the same type, the benefits of combining MEG and EEG are based on the different sensitivity properties of these modalities. The spatial sensitivity patterns of MEG and EEG sensors are called lead fields. The set of lead fields is one way to express the forward model, which incorporates the available physical and structural information about the head and the instrumentation to establish the signal patterns that primary currents generate in a sensor array. The structure of the lead fields forms the basis on which source estimates (inverse solution) are constructed. The lead fields of MEG and EEG sensors differ in a non-trivial way from each other, thereby providing complementary information about the underlying primary current distribution in the brain (Cuffin and Cohen 1979; Cohen and Cuffin 1983; Malmivuo and Plonsey 1995; Mosher et al. 1999; Riera et al. 2006). The complementary properties of MEG and EEG can enhance the detection, dissociation, and localization of the neural sources of interest (Wood et al. 1985).

Two major differences between MEG and EEG lead fields are related to the orientation and the depth of the sources (Cuffin and Cohen 1979). Regarding the source orientation, MEG sensors are insensitive to radial source currents, whereas EEG sensors are sensitive to both radial and tangential sources. In the spherical head model, the sensitivity of MEG to radially oriented sources is zero (Baule and McFee 1965; Grynszpan and Geselowitz 1973). The insensitivity of MEG to one source orientation occurs also for realistic, non-spherical head models (Melcher and Cohen 1988; Haueisen et al. 1995; Ahlfors et al. 2010a). In a simulation study using a boundary element model for the head, the median value over cortical locations for the relative signal magnitude for the source orientation with the lowest versus the highest sensitivity was found to be 0.06 for MEG and 0.6 for EEG (Ahlfors et al. 2010a). The selective sensitivity of MEG to tangential source components can be helpful for the dissociation of multiple time-varying sources.

Regarding the source depth, both MEG and EEG are generally more sensitive to superficially located sources than to deep sources. However, the relative sensitivity of MEG diminishes faster as a function of depth than that of EEG (Cuffin and Cohen 1979; Hillebrand and Barnes 2002). In the spherical head model, the sensitivity of MEG is zero at the center of the sphere, whereas EEG signal can be generated by sources at any location. Assuming the primary currents are oriented perpendicular to the cortical surface, only very narrow strips at the crest of gyri are expected to have the radial orientation that the MEG cannot detect; therefore, the depth-dependency appears more important in the comparison of sensitivity patterns of MEG and EEG than the orientation dependence (Hillebrand and Barnes 2002).

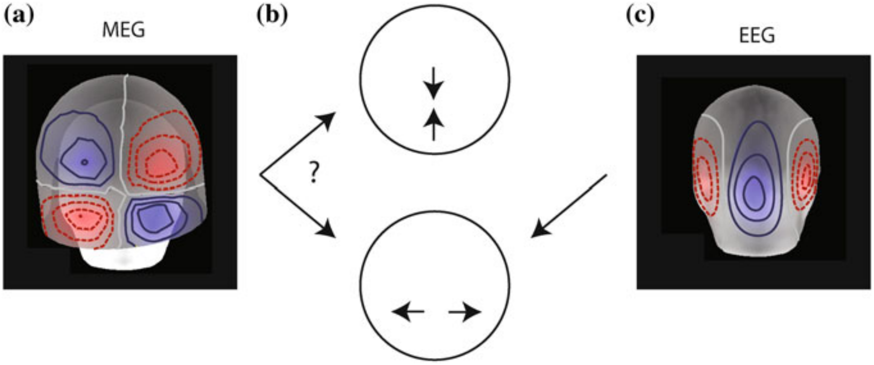

Fig. 2 An example of complementary properties of MEG and EEG signals that can, in combination, help disambiguate the source distribution. The quadrupolar pattern of the extracranial magnetic fields (MEG) (**a**) could be generated either by two near-midline dipoles in the parietal and occipital regions (**b**, *top*) or by two bilaterally located occipital dipoles (**b**, *bottom*). However, the corresponding topography of scalp potentials (EEG) would be quite different for these two configurations; here the EEG pattern for the two occipital bilateral dipoles is illustrated (**c**). Thus, the combination of MEG and EEG can resolve source configurations that can be ambiguous in one of the modalities. Analogous examples can be easily constructed in which MEG resolves source patterns that are ambiguous on the basis of EEG topography only. Adapted from (Ahlfors et al. 2010b)

Selective cancellation of signals from tangential source components on opposite walls of a sulcus or a gyrus tends to make extended source patches look radial (Eulitz et al. 1997; Freeman et al. 2009; Ahlfors et al. 2010b), with potentially important implications to the relative signal-to-noise ratio (SNR) of MEG and EEG and the detectability of e.g., epileptic activity (Goldenholz et al. 2009; Ebersole and Ebersole 2010).

Several studies have demonstrated complementary properties of EEG and MEG in detecting epileptic discharges, such that some are detectable in EEG only or in MEG only, but not necessarily in both (Sutherling et al. 1991; Yoshinaga et al. 2002; Zijlmans et al. 2002; Lin et al. 2003; Rodin et al. 2004; Knake et al. 2006; Ramantani et al. 2006; Ossenblok et al. 2007). Differences in source detectability can be understood in terms of the expected SNR for different sources, which depends on the sensor lead fields, signal noise, the source magnitude, and the background brain activity (de Jongh et al. 2005; Goldenholz et al. 2009; Huiskamp et al. 2010). Prominent differences between MEG and EEG have also been demonstrated, for example, in sleep data (Dehghani et al. 2010).

Combining MEG and EEG data can sometimes be useful for resolving source configurations that are ambiguous on the basis of the signal topography in a single modality. Figure 2 shows simulated MEG data from a bilateral pair of occipital current dipoles. In this case, the quadrupolar MEG topography (Fig. 2a) is consistent in the presence of uncertainty due to measurement noise with two very different two-dipole models, either laterally located horizontal dipoles or medially located vertical dipoles (Fig. 2b). The EEG topography, however, would be very different for these two scenarios: the EEG map shown in Fig. 2c suggests horizontally oriented dipoles. Bilateral activation of auditory cortices is a well-know example of topographies that can be potentially ambiguous in terms of source areas: two tangential supra-temporal lobe dipoles typically generate a large mid-frontal maximum in EEG that could be mis-interpreted as being due to a radial frontal source (Vaughan 1982), whereas in MEG the two auditory cortex sources are typically readily dissociable (Mäkelä et al. 1993); however, these sources may also generate a dipolar looking MEG signal pattern over the parietal lobe (Hämäläinen et al. 1995).

Combined MEG and EEG inverse modeling is facilitated by the common source model. Indeed, incorporating signals from both EEG and MEG sensors is not different, in principle, from incorporating different types of MEG sensors, such as gradiometers and magnetometers. An important practical issue is how to adjust the relative weighting of the different sensors in the source estimation procedures to take into account the expected SNR for each sensor (Fuchs et al. 1998; Baillet et al. 1999). Determining the SNR is challenging, however, because of the various types of uncertainties that should be incorporated, such as those related to co-registration, head model, sensor calibration, and background physiological noise. Enhanced source estimation results obtained by combining EEG and MEG data have been demonstrated in several studies of experimental and simulated data (Stok et al. 1990; Mosher et al. 1993; Phillips et al. 1997; Fuchs et al. 1998; Muravchik et al. 2000; Pflieger et al. 2000; Babiloni et al. 2001; Liu et al. 2002; Sharon et al. 2007; Molins et al. 2008).

3 MEG and Structural MRI

MEG source estimates are commonly visualized by superimposing them on high-resolution structural MRI, thereby relating the MEG results to brain anatomy. Structural MRI also provides essential supportive information for the inverse modeling of MEG signals. Anatomical information from MRI can be used to determine the permissible MEG source locations (often called the source space) to be within the cranial volume or the cortical gray matter (George et al. 1991; Dale and Sereno 1993). In addition, the source orientation can be constrained to be strictly or nearly perpendicular to the cortical surface (Dale and Sereno 1993; Lin et al. 2006; Chang et al. 2013). Typically, anatomical constraints are imposed on the individual subject level, but atlas-based approaches are possible as well (Hillebrand et al. 2012).

4 MEG and Functional MRI

Functional MRI and other hemodynamic imaging data can be used in a supportive role in MEG (and EEG) data analysis to suggest a likely spatial distribution for the sources of MEG signals (George et al. 1995; Simpson et al. 1995; Dale and

Halgren 2001). One possibility is to place equivalent dipoles at the locations of foci of fMRI activation (Heinze et al. 1994; Ahlfors et al. 1999; Korvenoja et al. 1999; Torquati et al. 2005). A powerful application of fMRI-guided MEG source estimation is to use information from fMRI-based mapping of the retinotopic representation of the visual field to constrain the locations of equivalent dipoles in multiple visual areas (Hagler et al. 2009). For distributed MEG source models, such as the minimum-norm estimate (MNE) (Hämäläinen and Ilmoniemi 1994), fMRI can be used as an a priori weighting for the inverse solution (Liu et al. 1998; Dale et al. 2000). This is implemented by adjusting the diagonal elements of the source covariance matrix (Liu et al. 1998).

Because of the different physiological nature of the origin of fMRI and MEG signals, it is important to minimize potential adverse effects from a mismatch between the locations of activity seen in fMRI and the actual source locations of the MEG signals (Dale and Halgren 2001). "False positive" fMRI locations refer to cases in which activation in fMRI does not correspond to an MEG source, whereas "false negative" fMRI refers to the lack of fMRI activity at the location of a true MEG source (Liu et al. 1998; Ahlfors and Simpson 2004; Im et al. 2005; Im and Lee 2006; Liu et al. 2006). In general, both of these types of mismatches can be due to the differing physiological properties of the signal generation in the two modalities. There is encouraging experimental evidence of the BOLD contrast typically observed in fMRI being closely correlated with post-synaptic currents (Logothetis et al. 2001). However, it is likely that details of the local neural circuitry and the neural and vascular morphology can result in differences in the properties of the signals in the different imaging modalities. Mismatches may also be caused by differences in the experimental design in fMRI and MEG data acquisition and analysis. Event-related fMRI paradigms make it possible to use similar cognitive task designs that are commonly used in MEG (Rosen et al. 1998). However, it is important to critically evaluate the similarity of the baseline conditions and design contrasts used in each modality. In addition, false negative fMRI locations can result from susceptibility artifacts or partial-only coverage of the head in the fMRI data. False positive fMRI can occur when MEG is insensitive to some activity, e.g., when the corresponding primary currents are radially oriented or located deep in the brain. Furthermore, false positive fMRI is bound to happen in the analysis of individual time points of the MEG data: because of the slow time course of the hemodynamic response, a single fMRI map usually shows areas whose activity in the millisecond time scale may only partially overlap in time, and therefore only a subset of the activated areas in fMRI is expected to contribute to the MEG signal at any given time instant.

Ideally, an approach for incorporating a priori constraints from a supportive modality would give improved source estimates when the a priori information is compatible with the actual source distribution, while also being insensitive to incompatible priors (Liu et al. 1998; Vauhkonen et al. 1998; Ahlfors and Simpson 2004). False positive fMRI constraints in MEG source modeling are typically well-behaving, i.e., the contribution to the MEG inverse estimates is usually small for the false positive fMRI locations, especially if the true and false locations are far apart from each other (Liu et al. 1998; Fujimaki et al. 2002). False negative fMRI constraints are expected to be more problematic than false positive ones (Liu et al. 1998; Ahlfors and Simpson 2004; Im et al. 2005), although simple false negative fMRI may actually have only little effect (Babiloni et al. 2003). In particular, if the assumed MEG sources are strictly restricted at the locations of fMRI activation only, MEG signals originating from other locations may be erroneously assigned to the assumed source locations (Liu et al. 1998; Ahlfors and Simpson 2004). Therefore, it is important that the source estimation algorithm allows the MEG sources to be also at non-fMRI locations.

The possibility of a mismatch in the spatial distribution of activation detected by MEG and fMRI raises a dilemma concerning the use of fMRI in a supportive role to guide the MEG source estimation. On the one hand, if we cannot be certain that the underlying patterns of activity are the same, the fMRI may provide an erroneous bias to the MEG source estimate. On the other hand, if the source analysis of MEG without the fMRI constraint indicates that the source locations of a particular set of MEG data indeed are identical to those seen in the corresponding fMRI, then there would be no need for the fMRI constraint. In other words, converging evidence of source locations from the comparison of MEG and fMRI data is useful in confirming MEG source localization results, but once this has been established, fMRI does not provide additional information for the supportive data fusion. The suggested resolution to this dilemma is that fMRI data should be used to indicate likely solutions among the set of all possible solutions allowed by the non-uniqueness of the inverse problem. The Bayesian approach provides a general formalism for these types of problems (Baillet and Garnero 1997; Friston et al. 2002; Jun et al. 2008; Auranen et al. 2009; Wipf and Nagarajan 2009; Henson et al. 2010). The principle can also be expressed geometrically in the source space (Ahlfors and Simpson 2004), leading to the same weighted MNE solution in which fMRI information is incorporated in the diagonal elements of the a priori source covariance matrix (Liu et al. 1998).

Figure 3 illustrates an example of visual motion related activity in which fMRI data suggested a likely solution among two possible ones for an ambiguous MEG topography (Ahlfors et al. 1999). The averaged visual evoked MEG signal showed a spatial pattern with four extremes (Fig. 3a). This topography suggests at least two sources, one occipitotemporal and one frontal (Fig. 3b, top). However, the dipolar pattern formed by the pair of extremes in the middle raises the question whether a third source, located in between the other two contributed to these MEG data (Fig. 3b, bottom). The fMRI data obtained using a similar stimulus paradigm indeed showed activity in the posterior part of the superior temporal sulcus, in accordance with the location of the putative third source (Fig. 3c). Thus, the fMRI suggests that a three-source model may be more likely here for the MEG than the two-source model. However, it is important to acknowledge that both solutions are consistent with the observed experimental MEG data. Note the difference between the case of combining EEG and MEG in Fig. 2, where the complementary data about the same type of sources was able to disambiguate between the two possible models for the MEG-only data because the EEG data was inconsistent with one of the models.

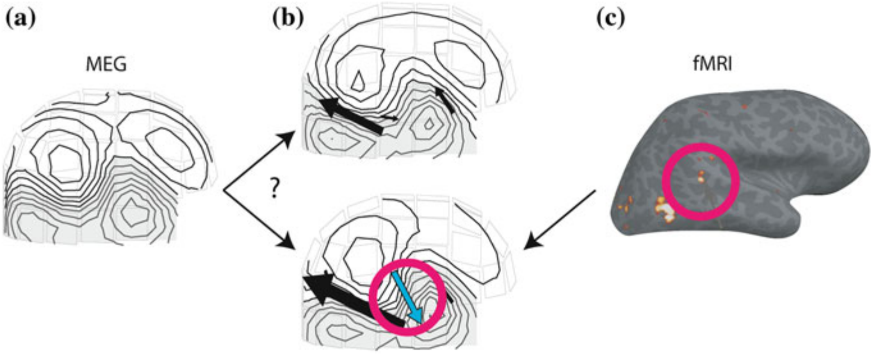

Fig. 3 An example of how fMRI data can suggest a likely MEG inverse solution among possible solutions. Averaged visual evoked MEG response at the latency of 170 ms after the reversal of the direction of the motion of concentric *circles* showed an ambiguous topography with four local extremes (**a**). This topography suggest two underlying dipole sources (*black arrows*), one at the visual motion sensitive middle temporal area and one near the frontal eye field (**b**, *top*). However, the measured topography would also be consistent with a third source in between the other two, contributing to the dipolar pattern of the two extremes in the middle of the topography (**b**, *bottom*). FMRI data recorded on the same subject indicated activation in posterior superior temporal sulcus (*red circle*) that matches the hypothesized third source location for the MEG (**c**). Thus, the fMRI suggested that the three-dipole model may be more likely that the two-dipole model; however, both models are possible solutions for the observed MEG topography. Adapted from (Ahlfors et al. 1999)

Examples of specific situations in which combining fMRI and MEG could provide helpful qualitative information about the neural activation patterns are illustrated in Fig. 4. The source currents of MEG and EEG are vector quantities, whose orientation and direction, in addition to the magnitude, can provide useful information that is not obtainable by fMRI. MEG is well suited to detect accurately the physical orientation of the tangential component of a source, because the whole topographic map of the extracranial signal will rotate if the source rotates tangentially. A change in the source orientation indicates that the neural sources contributing to the measured signals are not constant over time. This property may be useful for the detection of the presence of more than one neural population, even if the fMRI shows only a single extended focus of activity (Fig. 4a).

Since the primary currents generating the MEG signals are expected to be oriented locally perpendicular to the cortical surface, the physiological direction of the source can be described as inward (towards the white matter) or outward (Lopes da Silva 2010). However, the physical orientation, as detected by MEG and EEG, can be highly variable for a source within the convoluted cerebral cortex. In determining the physiological direction of the source current, fMRI can be particularly helpful in suggesting from which side of a sulcus or a gyrus the source is located. Figure 4b depicts a case in which uncertainty in the MEG source localization allows both walls of a sulcus as possible sites of the source. MEG can reliably determine the physical direction of the source, but the physiological

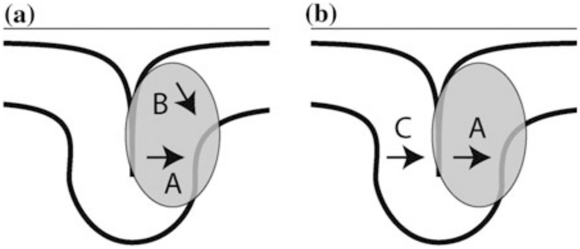

Fig. 4 Schematic illustration of helpful information that can be obtained by combining MEG and fMRI data. **a** A change in the MEG source orientation over time (from "*A*" to "*B*") reveals the presence of more than one neural population contributing to the activity, even when the spatial resolution of MEG as such may not be high enough to dissociate the locations of the source components, and the fMRI may show a single extended region of activation (*gray region*). **b** Uncertainty in the exact location of the source of the MEG signals can result in erroneous physiological interpretation of the source current direction if the source is mis-localized into the opposite wall of a sulcus. Using fMRI to identify the location of activity within the sulcus can help to determine the physiological direction of the MEG source. Here, the physical direction of both "*A*" and "*C*" is the same; however, the physiological direction is inward for "*A*" but outward for "*C*" with respect to the cortical surface

direction (outward vs. inward) depends on which side of the sulcus the source is located. Thus, using fMRI information to identify the likely location of the source will also help to determine the physiological direction of the source.

MEG and fMRI can also be considered complementary modalities, if the sources of both types of signals are taken to be related to a common pattern of neural activation. In this case, computational neural modeling is essential to relate the pattern of activity within brain networks capable of performing the cognitive task under study, as well as of generating the multimodal neuroimaging signals (Horwitz et al. 1999; David and Friston 2003; Riera et al. 2005; Babajani and Soltanian-Zadeh 2006; Daunizeau et al. 2007; Valdes-Sosa et al. 2009; Plis et al. 2010; Bojak et al. 2011).

5 Summary and Future Prospects

Multimodal data can provide information about brain activation patterns that is not attainable by a single method alone. In the analysis of MEG data, the role of other imaging modalities in the direct data fusion approach can be described as complementary or supportive, depending on whether the sources of the signals in the different modalities can be considered to be of the same type or not. This framework can encompass also other existing and emerging imaging modalities. Simultaneous acquisition of multimodal data has obvious advantages over sequential recordings, e.g., by ensuring that the state of the brain was the same for each modality, and enabling multimodal recording of events that are difficult to repeat in a controlled way, such as epileptic activity. MEG and scalp EEG are commonly recorded simultaneously. Because EEG is better suited than MEG for simultaneous data acquisition with hemodynamic imaging modalities, the similarity of the state of the brain during sequential recordings of MEG and other modalities can be evaluated by examining the concomitantly recorded EEG data. Promising prospects for multimodal integration in the future are expected from further developments in computational neural modeling of the brain processes that underlie the signals of all the imaging modalities.

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