Spatiotemporal mapping of brain activity by integration of multiple imaging modalities

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Functional magnetic resonance imaging (fMRI) and positron emission tomography measure local changes in brain hemodynamics induced by cognitive or perceptual tasks. These measures have a uniformly high spatial resolution of millimeters or less, but poor temporal resolution (about 1 s). Conversely, electroencephalography (EEG) and magnetoencephalography (MEG) measure instantaneously the current flows induced by synaptic activity, but the accurate localization of these current flows based on EEG and MEG data alone remains an unsolved problem. Recently, techniques have been developed that, in the context of brain anatomy visualized with structural MRI, use both hemodynamic and electromagnetic measures to arrive at estimates of brain activation with high spatial and temporal resolution. These methods range from simple juxtaposition to simultaneous integrated techniques. Their application has already led to advances in our understanding of the neural bases of perception, attention, memory and language. Further advances in multi-modality integration will require an improved understanding of the coupling between the physiological phenomena underlying the different signal modalities.

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Abbreviations

BOLD	blood-oxygenation-level-dependent
ECD	equivalent current dipole
EEG	electroencephalography
ERP	event-related potential
fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
MRI	magnetic resonance imaging
NIRS	near infrared spectroscopy
PET	positron emission tomography

Introduction

The past decades have shown revolutionary changes in our ability to non-invasively image human brain activity, with current spatial and temporal resolutions meeting standards previously reserved for invasive methods in animal models. In particular, the development of functional magnetic resonance imaging (fMRI) has enabled imaging of changes in blood oxygenation and perfusion, with a potential spatial resolution of a few hundred microns [1–4]. Similarly, advances in magnetoencephalography (MEG) and high-density electroencephalography (EEG) have enabled estimation of brain activity with a temporal resolution of the order of milliseconds [5–7,8•]. However, each of these signal modalities is limited either in terms of its temporal or spatial resolution. Hence, high-resolution spatiotemporal imaging of brain activity requires integration of information from multiple signal modalities [9–11].

In this review, we will first discuss what is known about the physical and physiological basis of the imaging signals and the coupling between the processes underlying the different techniques. Next, we will discuss various approaches that have been proposed for integrating information across multiple modalities. Finally, we will discuss future directions and remaining challenges in the field of multi-modality integration.

The physical and physiological basis of imaging signals

A major challenge for multi-modality integration results from the fact that distinct physiological mechanisms underlie the signal generation for different imaging modalities. Broadly speaking, the different imaging modalities can be divided into three main categories: first, EEG/MEG; second, optical imaging; and third, fMRI/PET (positron emission tomography).

EEG and MEG signals

The techniques of EEG/MEG are unique in that the observed signals are directly coupled to neuronal electrical activity [7,8•,12]. More precisely, EEG and MEG reflect the electric potential and magnetic field, respectively, resulting primarily from synaptic trans-membrane currents in neuronal dendrites [13]. These synaptic currents can be modeled as sinks (inward currents) and sources (outward currents) within a passive volume conductor made up of neuronal tissues, cerebrospinal fluid, skull and scalp [12]. Thus, the transmission of electrical activity within the brain to the EEG and MEG sensors is effectively instantaneous (limited only by the speed of light in tissue). The propagation of such electric and magnetic fields through the head, known as the bioelectric/magnetic forward problem, is relatively well understood, and efficient and accurate algorithms exist to predict the EEG and MEG signals [14]. Further incremental advances are still possible, especially incorporating information regarding conductance anisotropy within white matter and preferential current shunts resulting from skull defects and sutures [15,16•]. However, the so-called inverse problem of estimating the current sources and sinks on the basis of EEG and/or MEG recordings alone is fundamentally ill-posed. That is, for any distribution of EEG and MEG signals outside the head, there are infinitely many possible configurations of current sources and sinks within the brain that are consistent with those recordings — a principle

originally pointed out by Helmholtz [17]. In order to disambiguate the inverse problem, it is therefore necessary to impose additional constraints on the solution [9,18].

Optical signals

The physiological basis of the most common form of non-invasive optical imaging, known as near infrared spectroscopy (NIRS), is wavelength-specific absorption of photons by oxygenated and deoxygenated hemoglobin [19]. Thus, the contrast mechanism for NIRS signals is closely related to that of intrinsic optical imaging of exposed cortex using visible light [20]. The much lower baseline absorption levels at the longer wavelengths used in NIRS allow the light to travel further through skin, skull and brain tissue, thus allowing non-invasive imaging of hemodynamics, albeit with lower spatial resolution [21–23]. To a first approximation, the hemodynamic response to electrical activity can be modeled as the output of a linear low-pass filter applied to the neuronal response, effectively suppressing any signal power below 1 Hz [24]. Thus, although it is possible to sample optical signals quite rapidly (>1 kHz), the effective temporal resolution is limited by the indirect nature of the coupling of the hemodynamic processes affecting the optical signals and the underlying neuronal electrical activity [25].

It should be noted, however, that there is some evidence that it may be possible to detect optical signals more directly related to neuronal activation [26–29]. The physiological basis of these event-related optical signals (EROS) is not well understood, but may include cell swelling or membrane polarization associated with neuronal activity, resulting in local light-scattering changes [25]. Thus, optical imaging may provide insights into both the electrophysiological (fast) and hemodynamic (slow) processes underlying other brain imaging signals. However, the spatial resolution afforded by optical methods alone is limited by the diffuse nature of photon transport through tissue [21].

PET and fRMI signals

In contrast to the signal modalities mentioned above, PET and fMRI provide unambiguous spatial localization of activity with a relatively high spatial resolution. PET is based on the measurement of paired photons that result from annihilation of positrons emitted by radioactively labeled markers [30]. PET has been used to measure blood flow, glucose utilization, and receptor density [31–33]. fMRI measures a blood-oxygenation-level-dependent (BOLD) response which reflects a number of factors, including the concentration of deoxygenated hemoglobin, blood flow, and blood volume [34,35]. With fMRI, it is in principle possible to image such hemodynamic changes with a spatial resolution essentially limited only by the signal-to-noise ratio. However, inferences about neuronal activity made on the basis of fMRI signals are again limited by the indirect nature of the coupling between the observed signals and the underlying neuronal electrical activity, with the achievable spatial and temporal resolution determined by the spatiotemporal point-spread function of the hemodynamic response [36,37].

In order to combine electrophysiological signals with those related to hemodynamics in a principled way, it is therefore essential to take into account both the modality-specific physics governing signal generation and propagation, and the coupling between hemodynamics and neuronal electrical activity. Although the physics of signal generation and propagation is generally well understood, the physiological coupling has not yet been well characterized. However, there is a growing body of evidence for a strong spatial correlation between local electrical activity and hemodynamic signals; such evidence is based on comparisons between maps obtained using voltage-sensitive dyes and using intrinsic optical signals [38], as well as comparisons between single-unit recordings and intrinsic optical signals [39]. The intrinsic signal itself is closely co-localized with the BOLD response [40]. Recent studies also indicate that the amplitude of the hemodynamic response correlates more or less linearly with electrophysiological measures, based on comparisons between the fMRI BOLD response and electrophysiological recordings in rat [41,42]. Further research is needed to enable the precise, quantitative characterization of the spatiotemporal coupling between electrophysiological and hemodynamic phenomena essential for optimal integration of information from different imaging modalities (see below).

Approaches to multi-modality integration

Efforts to arrive at a fuller understanding of neurocognitive processes by use of fMRI/PET for localization and MEG/EEG for timing have ranged from simple juxtaposition to truly integrated analyses. Simple juxtaposition has the advantage that the analysis does not assume that the signals in the different modalities are generated by the same or similar neural generators; however, this assumption is often implicit in the concurrent interpretation of the multimodal results. Recent examples of this approach include applications to attention [10], somatosensory activation [43], visual flow [44], novelty processing [45–47], and emotional judgements [48].

Equivalent current dipole models

The most common approach to multi-modality integration is to assume that the EEG/MEG signals are generated by a relatively small number of focal sources. Typically, both hemodynamic and electromagnetic modalities are recorded during the same task. The activation foci derived from PET or fMRI are used as initial guesses (or 'seeds') for dipole locations, and the positions of the equivalent current dipoles (ECDs) are adjusted using a non-linear fitting procedure ([18]; see also Figure 1a,b). The orientation and strength over time of the ECDs can then be estimated using a simple linear least-squares algorithm. In some cases, this technique of 'seeded dipoles' can lead to significant conclusions regarding neurocognitive processing mechanisms that cannot be

Figure 1

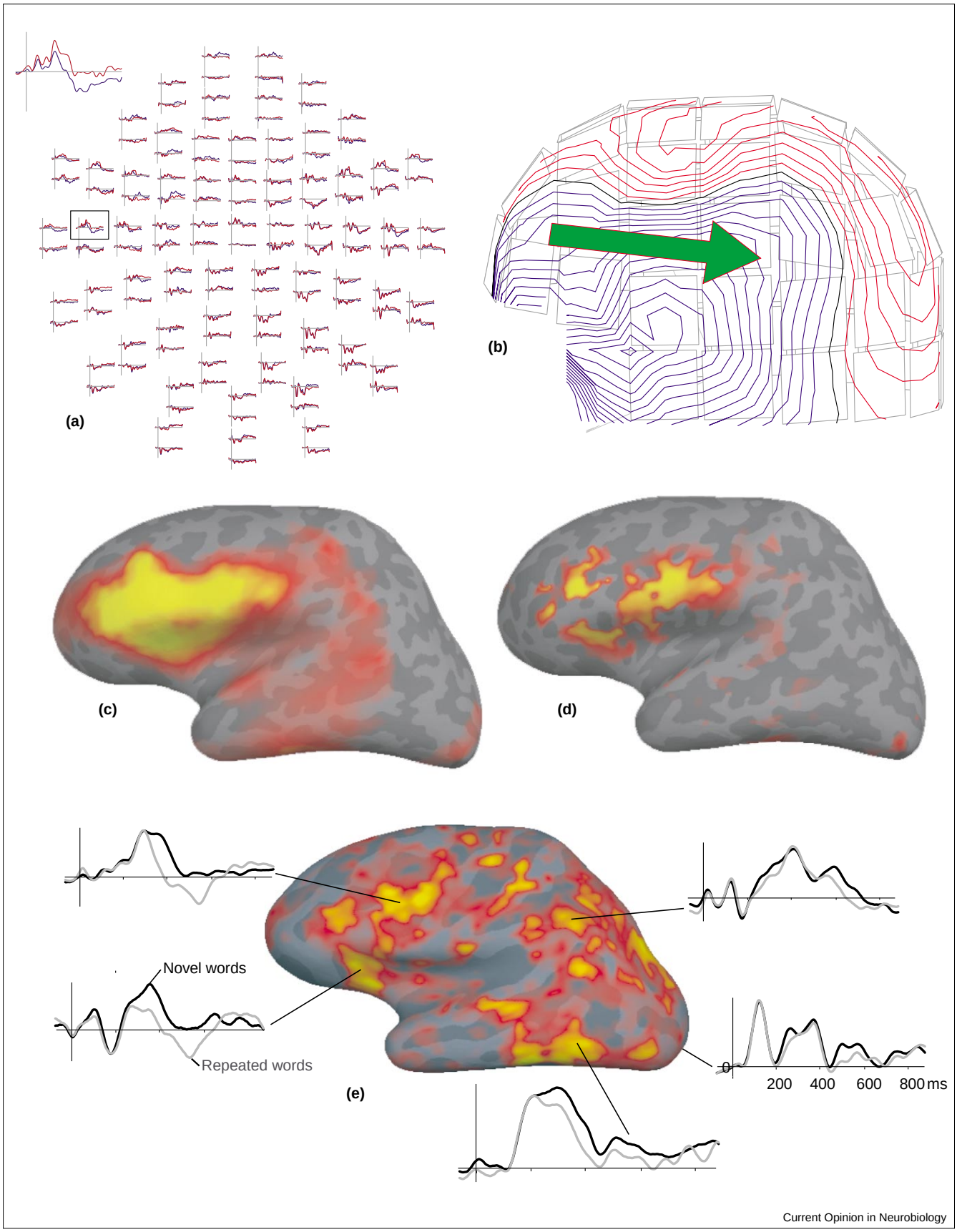
(a)
(b)
(c)
(d)
(e)
Novel words
Repeated words
0
200
400
600
800 ms
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Figure 1 legend

Examples of multi-modality integration methods applied to a visual size-judgment task, contrasting novel versus repeated words (see [8•] for details on the experimental design and analysis). (a) MEG waveforms recorded from 122 channels. The responses to novel and repeated words are shown in blue and red, respectively. (b) Result of fitting a single ECD to the repetition effect (novel minus repeated) at a latency of 540 ms post stimulus-onset, using the method described in [7]. The dipole location is indicated by the green arrow, superimposed on a contour plot of the measured magnetic field. (c) The corresponding statistical parametric map of cortical activity based on the anatomically constrained current estimation method described in [8•]. The activity map is displayed on an 'inflated' representation of the left cortical hemisphere [9]. (d) Activity map obtained by using both anatomical and fMRI-based constraints on the estimates. Note the increased spatial detail revealed by the integration of the fMRI constraint, relative to that obtained using (b) ECD fitting or (c) anatomical constraints alone. (e) Time course estimates for neural activity evoked by novel and repeated words at different cortical locations. The activity estimates (using both anatomical and fMRI-based constraints) were averaged across four subjects using a surface-based inter-subject registration procedure [66]. The background image shows a statistical parametric map based on inter-subject averaged fMRI activations in the same task and subjects.

obtained when using either hemodynamic or electromagnetic techniques in isolation [49,50,51•,52•,53].

The power of dipole-seeding is in providing an objective initial guess for the ECD locations, thus alleviating the problem of local minima inherent in non-linear fitting procedures. There are, however, several potential problems with this approach. Most cognitive tasks involve many spatially extensive brain areas. Even simple visual stimuli activate a large number of distinct occipital, temporal, and parietal cortical areas [54,55]. Cognitive tasks typically involve an even more extensive network of sensory, motor, and association areas, as revealed using fMRI [56] as well as intracranial recordings [57–59]. The 'seeded dipole' approach requires the somewhat arbitrary partitioning of these extended activation regions into discrete foci to be represented by the individual ECDs. Furthermore, simulation studies have shown that constraining all generators of EEG and MEG to co-localize with the hemodynamic activation foci may result in significant estimation error if some of the ECD locations are incorrectly specified [60].

Continuous current estimates

These considerations have led some to explore continuous, weighted estimates of activation over the entire cortical surface using a continuous estimation approach [9,61•,62•]. In this approach, the cortical surface is partitioned into a large number of small patches, with each patch represented by an ECD in the middle of the patch, thus approximating any arbitrary spatial distribution of synaptic currents within the cortex. Data from fMRI or PET can then be used to spatially bias the EEG/MEG inverse solution towards locations that are hemodynamically active during a specific task [9,11]. In order to avoid potential mismatch between the activity measured by the different modalities, it is important to use identical experimental designs and stimulus conditions for each. The recent development of event-related analysis methods enables the use of identical rapid, randomized experimental designs with EEG/MEG and fMRI [63–65]. Using this approach, it is possible to obtain continuous spatiotemporal maps (or movies) of brain activity ([60]; see also Figure 1c,d). A further refinement of this method is achieved by normalizing the spatiotemporal estimates for noise sensitivity, thus yielding dynamic statistical para-metric maps of brain activity (for further details, see [8•]). The spatially continuous nature of such estimates also allows for averaging of activity across individual subjects, after aligning the sulcal–gyral patterns across individuals ([8•,66]; see also Figure 1e).

It should be noted, however, that even when using hemodynamic data to bias the inverse solution, some ambiguity remains. One approach to quantifying this uncertainty is to calculate the influence of activity at one location on the estimated activity at another location, or so-called 'crosstalk' [60]. A more general approach, suggested by Schmidt *et al.* [67], calls for an explicit characterization of the space of possible solutions, by sampling the *a posteriori* probability distribution given measurement data and *a priori* information.

Remaining challenges and future directions

In order to more accurately integrate EEG/MEG and fMRI, a better understanding of the coupling between the signals and the underlying neuronal activity is needed. Using fMRI and/or optical imaging methods in humans and animals along with electrophysiological recordings, it may be possible to obtain a more precise, quantitative model of this coupling [68,69,70•,71]. Recordings using multi-contact laminar electrodes and two-dimensional surface grids can also provide a better understanding of the spatiotemporal patterns of synaptic current flow in the cortex at microscopic and mesoscopic scales [72•,73,74]. Because the observed MEG/EEG signals are directly related to these synaptic current flows (the dipole moment is the first non-vanishing term of the multipolar expansion of the laminar current source density distribution), this information could lead to greatly improved constraints on the spatiotemporal activity estimates [7,74]. An important question that can be addressed using such invasive recordings is the degree to which the hemodynamic response is related to the phase-locked (evoked) component of the electrophysiological activity, or to the non-phase-locked component, which is eliminated by standard averaging techniques [75,76].

A closely related question, essential to an appropriate physiological interpretation of fMRI imaging results, is the

extent to which the BOLD effect reflects excitatory and/or inhibitory neuronal activity. Early studies using 2-deoxyglucose in animal models showed that strong inhibition could be associated with increased glucose uptake [77]. However, indirect evidence has recently accumulated suggesting that inhibition may not be associated with increased local cerebral blood flow [78,79].

Ultimately, it should be possible to relate the observed electric/magnetic, optical, and MRI signals to biophysical models of neuronal circuitry. Because these imaging methods have a finite resolution, the resulting signals reflect the integrated activity of thousands or millions of neurons. This suggests the use of spatially coarse-grained modeling approaches, in which local populations of neurons are treated as statistical ensembles [80,81]. Combining such modeling approaches with the modality-specific forward solutions, specifying the coupling between the imaging signals and the relevant biophysical parameters of the model at the appropriate spatial scale, it may be possible to relate non-invasive imaging signals to information processing at the neuronal circuit level.

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