NeuroImage 102 (2014) 3–10

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

General overview on the merits of multimodal neuroimaging data fusion

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ARTICLE INFO

Article history:
Accepted 8 May 2014
Available online 16 May 2014

ABSTRACT

Multimodal neuroimaging has become a mainstay of basic and cognitive neuroscience in humans and animals, despite challenges to consider when acquiring and combining non-redundant imaging data. Multimodal data integration can yield important insights into brain processes and structures in addition to spatiotemporal resolution complementarity, including: a comprehensive physiological view on brain processes and structures, quantification, generalization and normalization, and availability of biomarkers. In this review, we discuss data acquisition and fusion in multimodal neuroimaging in the context of each of these potential merits. However, limitations – due to differences in the neuronal and structural underpinnings of each method – have to be taken into account when modeling and interpreting multimodal data using generative models. We conclude that when these challenges are adequately met, multimodal data fusion can create substantial added value for neuroscience applications making it an indispensable approach for studying the brain.

Contents

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http://dx.doi.org/10.1016/j.neuroimage.2014.05.018

Forms of multimodal imaging and data fusion

What is multimodal neuroimaging?

The brain intrinsically is a highly active organ consuming ~20% of the energy in the entire body and its activity embodies sensation, perceptual inference, evaluation processes, action planning and execution. Structurally, the brain functions rely on different cell types (e.g. pyramidal neurons, interneurons, glia), and the distribution of these cells and their connections develop via predetermined biological pathways and under the influence of experience. Modern neuroimaging methods in humans probe these processes and structures on a meso- and macroscopic level in order to unravel the neuro-glial basis of cognition and behavior in healthy subjects and its dysfunctioning in patients.

Multimodal neuroimaging in a narrow sense typically combines two or more data sets acquired with different imaging instruments with the aim of improving our understanding of the structure and function of the brain by utilizing complementary physical and physiological sensitivities. In a wider sense, multimodal imaging also refers to the fusion of data contrasts obtained with the same physical instrument (e.g. combining perfusion- and diffusion-weighted MRI in stroke imaging).

Physical interactions

All imaging methods employ specific physical principles to interact with the tissue. The physical interactions determine which physiological processes and/or structures are measured and, together with the signal acquisition parameters of the method, determine the respective temporal and spatial resolution. Therefore, we briefly mention some examples of the physical interactions that characterize different techniques before discussing the physiological underpinnings.

Magnetic resonance imaging (MRI) probes brain structure and activity by manipulating and detecting the bulk magnetic moment of protons (Jezzard and Clare, 2001; Norris, 2006). Positron-emission tomography (PET) detects the γ-rays resulting from annihilation of positrons with electrons (radioactive β-decay of radiolabeled compounds) (Jones and Rabiner, 2012). Electro-encephalography and magneto-encephalography (E/MEG) passively record electric and magnetic changes induced by extra- and intra-cellular electric currents associated with neuronal activity (Hari and Salmelin, 2012; Michel and Murray, 2012). Finally, optical imaging methods, including functional near-infrared spectroscopy (fNIRS), measure changes in light scattering and absorption properties of the tissue following neuronal activity (Hillman, 2007; Kerr and Denk, 2008; Villringer and Chance, 1997).

Narrow and wide sense multimodal imaging, definition

The term 'multimodal imaging' in neuroscience is generally used in a **narrow sense** to describe the combination of data obtained with different instruments. For simultaneous acquisition, specific instrumentation has to be developed in order to permit data to be obtained with low or removable interference from the other modality. For example, EEG–fMRI combination uses an EEG instrument (cap, amplifiers etc.) combined with data from an MRI scanner, either simultaneously or non-simultaneously acquired (Rosenkranz and Lemieux, 2010). The novel instrumentation can range from a relatively simple arrangement, such as caps where EEG detectors and fNIRS optodes can be placed (Obrig et al., 2002), to additional complex technological innovations, such as electrical circuitry and amplifiers to allow simultaneous electrophysiology and MRI (Logothetis et al., 2001) or magnetic field insensitive photosensors for PET to allow simultaneous imaging with MRI (see overview of the technological development in Herzog et al., 2010). In some combinations, for example MEG–MRI, the physical interactions of the two instruments prevent simultaneous acquisition of data (although there are attempts to overcome this obstacle, see (Ilmoniemi et al., 2012)).

In a **wider sense**, multimodal imaging also includes the combination of non-redundant data (i.e. contrasts) acquired with the same instrument.[2] In this context, MRI is a very versatile imaging tool as it can actively manipulate the magnetization state of the tissue and therefore can produce different tissue contrasts depending on the timing and exact temporal profile of the electromagnetic pulses applied (Hennig, 1999; Jezzard and Clare, 2001).

Wide sense multimodal imaging, examples

Many cognitive neuroimaging investigations using MRI acquire T1- and T2-weighted anatomical, T2*-weighted functional, and diffusion-weighted data within the same session. However, clever MRI pulse design can sometimes combine two or more contrasts in the same acquisition. Notable in this respect is a recent paper by Griswold and colleagues that takes this multi-contrast approach to an extreme (Ma et al., 2013). They have proposed a new MR sequence approach, called MR fingerprinting, which varies MR sequence parameters pseudo-randomly within the acquisition. The signal obtained from each voxel can then be compared with theoretical simulations using the Bloch equation as a function of tissue electromagnetic properties (such as T1, T2*, proton density etc.). Performing the simulations for a range of realistic values of these properties and matching these with the measured signal in each voxel allow mapping of many quantitative MRI contrasts *simultaneously*.

PET can also acquire multiple contrasts by injecting different radioactive compounds (Jones and Rabiner, 2012). However, this only allows measuring the contrasts in a sequential manner as the β-decay from the different compounds typically produces γ-rays with the same energy (~511 keV). Optical imaging detects various contrasts by using exogenous contrasts agents, cell labeling and/or multiple wavelengths (Hillman, 2007; Kerr and Denk, 2008; Villringer and Chance, 1997).

Passive electrophysiological recording methods, such as EEG and MEG, are used for multimodal imaging in the wide sense by using non-redundant characteristics of the data, such as event-related potentials (ERPs) and event-related (de-)synchronization in specific frequency bands (Pourtois et al., 2008; Schroeder et al., 1995). In invasive electrophysiology, an electrode can record both multi-unit spiking and local field potentials separated by the frequency of the underlying physiological processes, which convey independent information on the information processing in the brain (Belitski et al., 2008). However, invasive electrophysiology often is limited to few recording sites. Electrocorticography (ECoG), an array of electrodes patched directly on the surface of the brain, provides both high spatial and temporal resolution for an extended part of the brain (e.g.Buffalo et al., 2011). Due to its invasiveness, this approach can only be applied in animals or specific human patient populations.

An important recent development is the invention of optogenetics, which allow modifying cell properties (e.g. ionic channels in neurons) using a specific virus enabling cell type specific neuroimaging and manipulation using light (Fenno et al., 2011). Optogenetics can be used for multimodal imaging (in the narrow sense) in combination with fMRI or electrophysiology or (in the wide sense) using multiple optically controllable cell modifications.

In this paper, we consider multimodal neuroimaging in both the narrow and wide sense and discuss its general merits and the challenges in leveraging them for neuroscience applications.[3] After discussing types of multimodal data acquisition and data fusion in the next section, we

[2] Note that the distinction between narrow- and wide-sense multimodal imaging is relative and depends on technological developments, e.g. PET and MRI acquisition are now being integrated into one physical instrument (Herzog, 2012; Sauter et al., 2010).

[3] Note that this article does not intend to present a comprehensive review on multimodal imaging studies but rather provides an overview on why and how multimodal imaging is used. The experimental examples mostly reflect the authors' expertise but they serve as an illustration of a general statement beyond the imaging methods used in the examples given. For overview of multimodal studies, we refer the interested reader to specialized reviews (e.g. Judenhofer et al., 2008; Laufs, 2012; Ritter and Villringer, 2006; Rosenkranz and Lemieux, 2010; Toga et al., 2006).

will successively focus on the main general merits: Improving spatial and temporal resolution, a more comprehensive physiological view on brain processes and structures, quantification, generalization and normalization, and the availability of biomarkers.

Data acquisition and fusion in multimodal imaging

Multimodal imaging typically requires specialized post-processing tools to merge data from the modalities because the "space" of meaningful qualities imaged is mostly different for each modality. Joint analysis of multimodal datasets has the aim to combine the complementary aspects (either in terms of underlying physiological processes or in spatiotemporal resolution) of each modality in such a way that there is an added benefit compared to analyzing and interpreting each dataset separately. Data can be separately recorded and analyzed, but interpreted together in the same template space, e.g. separate analysis of fMRI and diffusion MRI (dMRI) recorded in the same MRI exam (e.g. Khalsa et al., 2014-in press; Marques et al., 2013; Schmithorst et al., 2013). Alternatively, the data can be separately recorded (on the same subjects and with the same task paradigm) and jointly analyzed, e.g. fMRI-informed distributed source localization of independently recorded E/MEG data (Daunizeau et al., 2010; Valdes-Sosa et al., 2009). A necessary condition for this integration is that the data are transformed into the same spatial space (see section B.3. for extensive discussion of coordinate systems).

Simultaneous and separate data acquisition

The choice of separate or simultaneous recording is pivotal, since there are both costs and benefits of simultaneous recording to consider. The costs often include degraded data quality in terms of signal-to-noise and increased artifacts compared to separate recording. For instance, the well-known MRI gradient and cardio-ballistic artifacts in EEG simultaneously recorded with fMRI limit the data quality, even though significant progress has been made in post-processing correction routines for these artifacts (Ritter and Villringer, 2006; Ritter et al., 2007; Vulliemoz et al., 2011). Conversely, the magnetic field distortions caused by the EEG electrodes, though spatially relatively confined, cause distortions and dephasing of the local MR signal in adjacent brain tissue. In MR-PET, the components of the MRI scanner (e.g. patient table, RF coil) can lead to signal degradation in PET (Herzog et al., 2010), and references therein). Finally, subject discomfort and set-up time can contribute to the costs of multimodal imaging since it can be increased during simultaneous acquisition. Nevertheless, in many cases the benefits of simultaneous functional multimodal imaging can strongly outweigh the costs (see below sections B.).

If the data of interest are the average responses to a task and the responses are assumed to be stereotypical, then multimodal data can be acquired sequentially. If, however, neuronal events to the same task and their imaging correlates are state-dependent and vary with context, then it is mandatory that the data are simultaneously acquired (Debener et al., 2005).

Symmetric and asymmetric data fusion

Multimodal data analysis approaches generally aim at a high degree of integration in the joint analysis of the different modalities. Here a distinction can be made between symmetric and asymmetric data fusion (Daunizeau et al., 2010; Valdes-Sosa et al., 2009). In *asymmetric* integration approaches, information from one modality is given higher importance or lower uncertainty than the other, for instance in treating information derived from one modality as the cause of, or constraint on, the other modality. Examples are (distributed) E/MEG source localization constrained by fMRI contrast maps or using time–frequency power of EEG as a predictor in fMRI General Linear Modeling. In *symmetric* data fusion, both modalities are used on an equal footing, with appropriate concern of their spatial and temporal resolution and, possibly, their indirect relation to neuronal activity and the uncertainty in that relationship. In MR-PET, for example, metabolic and molecular imaging data obtained with PET is merged with the structural information of soft tissue contrast (T1-, T2*-weighted, MRS and diffusion MRI) obtained with MRI (e.g. in tumour imaging, see Neuner et al., 2012). In turn, symmetric fusion approaches can be divided into *hypothesis-driven* approaches (often in a model-based setting and called *model-driven*, see below), and *data-driven* approaches, such as independent component analysis, often belonging to the class of (semi-)blind source separation methods (Sui et al., 2012).

Generative models

Model-driven symmetric fusion can be achieved through generative model inversion, which has the potential to explicitly incorporate both the physiological and spatio-temporal complementarities of different modalities (Daunizeau et al., 2010; Valdes-Sosa et al., 2009). A generative model is a dynamical model that has a physiologically and physically realistic account of the forward causal chain of events from neuronal activity to the observed data (see Fig. 2). The model can contain multiple unobserved variables relating to neuronal and vascular processes that are linked to observations e.g. net primary current densities from pyramidal postsynaptic potentials for EEG and mediators of neurovascular coupling triggered by pre- and postsynaptic potentials for BOLD fMRI (e.g. Valdes-Sosa et al., 2009). If combination of multiple generative models can generate (i.e. simulate) multimodal data from the same modeled neuronal activity, the inversion (i.e. identification by estimating its parameters) of this model corresponds to model-driven multimodal data fusion. In the model-driven fusion context, EEG and MEG present us with an ill-posed *spatial* deconvolution problem, and fMRI confronts us with an underdetermined *temporal* deconvolution problem (Buxton et al., 2004; Roebroeck et al., 2011a). Model-based symmetric fusion by joint analysis of the two datasets has the aim to constrain each inverse problem with information from the other modality (Daunizeau et al., 2010; Deneux and Faugeras, 2010; Valdes-Sosa et al., 2009). In addition, imaging modalities differ in their physiological sensitivities (see below), e.g. E/MEG predominantly reflect synchronous neuronal activity, whereas fMRI is sensitive to the hemodynamic consequences of neuro-glial metabolic changes.[4]

In a generative model, measured variables (e.g. EEG-data) and their relations and exogenous input variables (outside of the system, e.g. stimulus functions) are modeled through unobservable state variables (which represent the neuronal population activity). These so-called state–space representations generally consist of two sets of equations. The transition equations or state equations describe the evolution of the dynamic system over time, capturing relations among the not directly observed, hidden state variables themselves and the influence of exogenous inputs on the state variables. The observation equations or measurement equations describe how the observed measurement variables are obtained from the hidden state variables.

Currently, the most prominent form of generative modeling in neuroimaging is Dynamic Causal Modeling (Friston et al., 2003) which – by applying a modality specific generative model – can be applied to fMRI (Friston et al., 2003), E/MEG (David et al., 2006) and LFPs (Moran et al., 2009). In fact, it is exactly the physiologically realistic generative model and its inversion which distinguish DCM from other causal modeling approaches such as Granger causality, although combinations of these approaches are possible (Roebroeck et al., 2011b; Valdes-Sosa et al., 2012).

The biophysical generative models are motivated by experimental findings typically obtained from animal studies, and they have to be constantly adapted to novel experimental insights. That is, ground truth validation studies need to be performed to establish the validity of generative models. Such studies will largely take the form of

[4] Note that this does not mean that neurovascular coupling is achieved by metabolic byproducts of neuronal activity but rather that mediators of neurovascular coupling ensure that a specific relationship between metabolic and hemodynamic changes is preserved during neuronal activity.

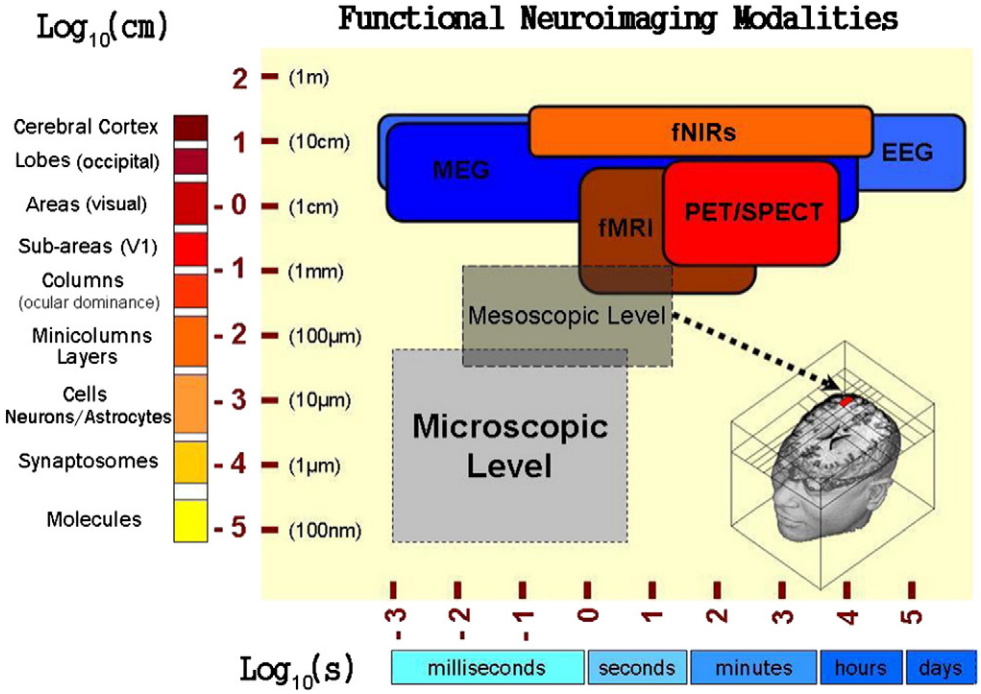

Fig. 1. The spatiotemporal resolution profile of the most used non-invasive functional neuroimaging modalities. Temporal resolution is on the horizontal axis and spatial resolution on the vertical axis, both on a logarithmic scale, with indications of relevant time periods and brain structures.

multimodal investigations in which a ground truth validating modality is used to investigate sensitivity and specificity of the target modality.

Benefits of multimodal imaging

Improving spatial and temporal resolution

Illustrated in Fig. 1 are the spatial and temporal ranges for the most popular non-invasive functional imaging methods used in humans.[5] Non-invasively, the functional imaging method with the highest spatial resolution is functional MRI, currently capable of imaging hemodynamic processes on the laminar and columnar level of the human cortex (i.e. submillimeter) at ultra-high magnetic field strengths albeit with low temporal resolution compared to neuronal population dynamics (i.e. typically a few seconds for whole brain coverage). EEG and MEG measure electrical and magnetic changes on a millisecond time scale but with a spatial resolution/uncertainty of at least several millimeters (Hari and Salmelin, 2012; Michel and Murray, 2012). Although the microscopic level of neuroscience typically is beyond reach with non-invasive imaging techniques (see Fig. 1), the mesoscopic level in humans (i.e. neuronal assemblies in columnar-laminar level) is currently investigated by ultra high-field MRI (e.g. Olman et al., 2012; Zimmermann et al., 2011). One obvious merit of combining different imaging methods is, therefore, improving the spatio-temporal resolution of characterization of brain processes. Typically, multimodal imaging is performed to take advantage of this spatio-temporal complementarity: One modality's superior temporal resolution is combined with the superior spatial resolution of the other modality. In cases of similar spatio-temporal resolution, the combination of data is called validation (such as cerebral blood flow measured with ASL MRI and water-PET, Zhang et al., 2014).

The prime example for multimodal neuroimaging to improve spatio-temporal resolution is the combination of EEG and fMRI. Historically, simultaneous EEG–fMRI recording has mainly been driven by epilepsy research (Rosenkranz and Lemieux, 2010). The aim was to use simultaneously recorded fMRI to help localize epileptic foci by appropriately correlating it to interictal epileptiform discharges (IED) characterized by EEG. The IED have also been used to trigger the fMRI image acquisition.[6]

Another important application of simultaneous EEG–fMRI in neuroscience, made possible by the complementarity of their resolution characteristics, is the investigation of spatial sources of neuronal oscillations (Goldman et al., 2002; Laufs et al., 2003), both during tasks and rest. These studies have taken an asymmetric analysis approach in which the power in frequency bands of the EEG signal is used as the independent variable or regressor in statistical parametric mapping analysis of concurrently recorded fMRI data (Ritter and Villringer, 2006).

Effective and nominal resolution

In discussing the increase in spatio-temporal resolution by multimodal imaging, it is not the nominal resolution of each modality that solely is relevant. Rather, we have to consider the effective resolution of each modality alone and the additional effect on the resolution of combining the multimodal data. The nominal resolution is determined by the physical acquisition parameters (e.g. sampling rate). The effective resolution, in contrast, is described by the information content of the data. For example, in fMRI the nominal spatial resolution is given by the field-of-view in k-space (or voxel size in the image space) (Buxton, 2002); the effective spatial resolution, however, can be considerably larger due to the physiological spread of the hemodynamic response and the specific vascular weighting of the fMRI sequence (Shmuel et al., 2007). The same is true for the temporal resolution in fMRI: the nominal resolution is given by the repetition rate TR but the

[5] Note that this illustration does not include all non-invasive imaging methods and only provides approximate ranges for spatial and temporal resolutions.

[6] Note that in this example, it is crucial to acquire the data simultaneously as the exact and unpredictable timing of the IED has to be known in order to be correlated with the fMRI signal. Although advances in source localization of unimodal high density scalp EEG recordings (i.e. electrical source imaging, ESI) are also a promising endeavor in this respect, simultaneous EEG–fMRI has the potential for more precise localization, especially of deep brain structures (Grova et al., 2008; Rosenkranz and Lemieux, 2010).

effective resolution is lower due to the slow evolution of the hemodynamic response prohibiting the detectability of independent neuronal events in fast succession, i.e. temporal convolution (Buxton et al., 2004).

Electrophysiological methods typically have a nominal temporal resolution in the millisecond range. However, statistical detectability and the slow evolution of neuronal field potentials can rather limit the effective resolution to the level of tens or hundreds of milliseconds. In addition, for evoked potentials in E/MEG, many repetitions might be necessary to achieve a detectable signal, whereas in fMRI a single stimulus often evokes a detectable hemodynamic response in the sensory areas. Having said this, single-trial EEG analysis is possible (Jung et al., 2001), even when simultaneously recorded with fMRI (Jung et al., 2001). In summary, the information content specific to each application, and not only the acquisition parameters of the instruments, determine the effective spatio-temporal resolution of multimodal data fusion. However, quantitative assessment of the task- and analysis-specific effective spatio-temporal resolution of multimodal approaches has not yet been widely attempted.

Comprehensive physiological view on brain processes and structures

Often overlooked, imaging methods are not only characterized by their spatial and temporal resolution but also by their specificity to certain physiological processes and tissue structures. Fig. 2 illustrates how some of the imaging modalities are related and/or caused by elementary neurophysiological processes in the tissue. As can be seen, neuronal activity is composed of many physiological processes and not only of spiking activity. These processes are associated with or elicit electromagnetic, metabolic and vascular changes detected by neuroimaging techniques. Consequently, each method provides a physiologically and physically filtered view on one or more brain processes of interest. Thus, another general merit of combining imaging methods is to get a more comprehensive physiological view on brain processes than with just one imaging method alone. Very promising in this regard is the combination of functional-structural MRI data with different contrast (such as T1, T2*, MRS diffusion and perfusion MRI) and molecular specificity of PET (Herzog et al., 2010; Neuner et al., 2012). In addition, constant perfusion of radioactive ligands in PET allows simultaneous imaging of functional MRI and processes associated with neuro-transmitters and –modulators.

Although it is probably true that standard multimodal data fusion yields valid results, there is no *a priori* reason why data from different imaging modalities have to be suitable for coherent combination (Nunez and Silberstein, 2000). Hence, caution has to be exercised whenever multimodal data are combined as one physiological process might evoke a response in one modality but not in the other. We give some recent prominent examples of such dissociation of neuronal activity measurements:

1) In the study of Sirotin and Das (2009), an *anticipatory hemodynamic response* uncorrelated to neuronal changes has been proposed to exist. That is, it has been hypothesized that even though there is no increase in neuronal activity (measured with invasive electrophysiology), an increase in blood flow and oxygenation occurs (measured with intrinsic optical imaging) in *expectation* of an increase in neuronal activity due to entrainment.[7] Thus, the data proposed a hemodynamic response independent of neuronal activity. However, in this context, there is an ambiguity of the term 'neuronal activity'. Does this term refer to all intra- and extra-cellular events (see Fig. 2) associated with synaptic activity or just to the action potentials and local field potentials (multi-unit activity, MUA, and local field potentials, LFP)? Thus, it is conceivable that neuronal activity did indeed change, for example, due to activation of interneurons or glial cells, which are typically not characterized by standard invasive and non-invasive electrophysiology (Logothetis, 2010). In this case, fMRI would have sensitivity to certain tissue processes consuming energy (see Fig. 2) but standard electrophysiology would not. Therefore, an absence of MUA and LFP changes does not necessarily imply that the neuronal status of the tissue did not change.
2) In the vascular system, there are fluctuations independent of the local neuronal activity, for instance blood oxygenation and volume changes due to heartbeat, respiration or autoregulation (Bianciardi et al., 2009; Triantafyllou et al., 2005). Although this issue is easily appreciated for systemic vascular changes, it is difficult to decide whether some fMRI signal changes are neuronal or vascular in origin or are caused by imaging artifacts. For example, part of resting state fluctuations in fMRI has been shown to be related to respiration (Bianciardi et al., 2009; Birn, 2012). Or: The post-stimulus fMRI signal undershoot has been suggested alternatively to be purely vascular, purely neuronal or of mixed origin (Buxton et al., 2004; van Zijl et al., 2012). These examples illustrate that integrating all changes in multimodal data might result in misleading conclusions.

In summary, it is important to realize that data from different imaging modalities have both specific (from an origin invisible to the other modality, neuronal or not) and shared aspects (which both are sensitive to, though perhaps by other mechanisms). Thus, data from imaging modalities might not be just spatial or temporal convolutions of each other, which is an implicit assumption made in many multimodal studies. In principle, well formulated and validated generative models, as described above, have to represent these specific and shared aspects (Daunizeau et al., 2010). Thus, the chain of physiological and physical events leading to the observations has to be clarified and formalized in the form of generative models (see A.2. for discussion). Although this may complicate multimodal data analysis, it also allows examining the brain process more thoroughly than with one modality alone justifying the additional efforts of multimodal imaging and modeling. That is, apparent discrepancies in the results of the imaging methods should not be easily dismissed but rather taken as a valuable source of insight into brain processes and have to be carefully examined (e.g. recent examples in Bartels et al., 2008; Lippert et al., 2010). Dissociations might be as informative as associations.

Quantification, generalization and normalization

Quantification

Generative models and multimodal imaging also are indispensable to quantify imaging signals in terms of underlying physiology. Most imaging modalities are non-quantitative and have to be complemented by other data to normalize the signal and obtain absolute units and/or to allow inter-subject comparison. For example, the fMRI signal is a result of complex physiological and physical processes and the same level of neuronal activity in different subjects or brain areas can evoke different fMRI signals (Buxton et al., 2004). The amplitude of the fMRI signal is, thus, not an absolute marker for neuronal activity, which poses a problem for inter-areal and inter-subject comparisons. Studies have found that the same CBF change is associated with different fMRI signals in different brain areas, or in persons of different age or in healthy subjects as compared with patients (Ances et al., 2008). Thus, the fMRI statistical maps are biased towards voxels, which have high fMRI signal sensitivity (for instance due to high blood volume, low blood oxygenation and/or high RF coil sensitivity). To account for the ensuing sensitivity differences, several approaches have been proposed; the most widely used being the so-called calibrated BOLD approach (Blockley et al., 2013; Chiarelli et al., 2007; Hoge, 2012).

[7] This study has received criticism because of suboptimal analysis and assumptions regarding the physiological sensitivity of invasive electrophysiology (Handwerker and Bandettini, 2011a, 2011b; Logothetis, 2010; Sirotin and Das, 2009). However, for the sake of the discussion (i.e. that imaging modalities can reflect different tissue processes), we assume that these or similar effects in principle can exist and we refer the reader to the references to get details on this topic.

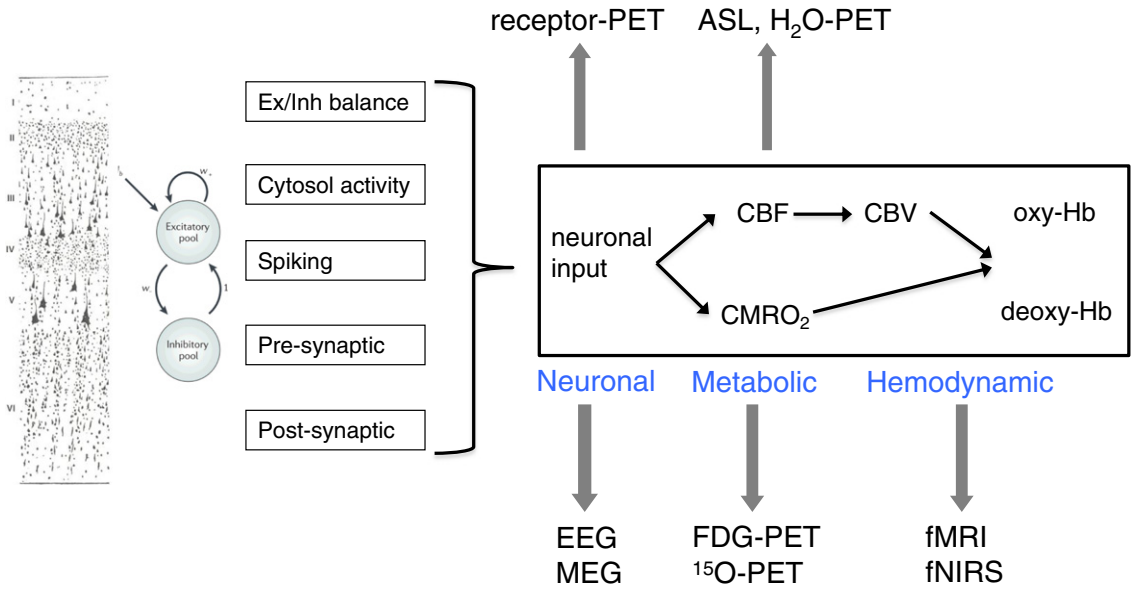

Fig. 2. An illustration of the different specificity of functional neuroimaging modalities to physiological processes involved in neuronal activity, cerebral metabolism and hemodynamics. Left: Some relevant aspects of neuronal activity are shown in boxes. Right: electromagnetic, receptor activity, metabolic and hemodynamic processes that follow from neuronal activity. Functional neuroimaging modalities are shown in black.

A prominent multimodal absolute quantification approach is the PET/CT combination where CT provides structural data on bone as the main absorber for the γ-rays. Without the attenuation correction, it is not possible to absolutely quantify the number of radioactive decays (Acton et al., 2004; Zeeberg et al., 1988). Currently, using ultra-short echo MRI sequences, it is under investigation whether MRI can substitute CT in this role. In MR-PET, bone and other structural information obtained with specific MRI sequences (such as UTE sequences) might be utilized to perform accurate attenuation correction necessary for absolute quantification of metabolites obtained with PET (Herzog et al., 2010). In general, normalization and calibration of imaging signals require additional, non-redundant data (hence, a genuinely multimodal approach) in combination with a biophysical forward (i.e. generative) model.

Coordinate systems and Generalization

An important application of both narrow and wide sense multimodal data is to improve the capacity to generalize results from one (or sometimes more) of the modalities allowing for general conclusions beyond individual subjects. The data of main interest are registered to other data resulting in easier comparability of imaging data among subjects. A prime example is the alignment of functional MRI images to an anatomical coordinate system, a standard practice to achieve standardization of reported results and comparability with other studies. Often used are anatomical coordinate systems derived from post mortem brain analysis (as in the Talaraich and MNI atlas) or from in vivo MRI. Currently, the MNI brain is utilized in MRI (Lancaster et al., 2007; Mazziotta et al., 2001), EEG (Pascual-Marqui et al., 2011) and fNIRS (Tsuzuki and Dan, 2014) as a standardized stereotaxic brain coordinate system. Templates in combination with atlases themselves have undergone steady development towards detailed multimodal information, allowing macroscale anatomical localization, e.g. by Brodmann's century-old classification, to be complemented with more detailed cyto-, myelo and receptor-architectonic information (Toga et al., 2006), and large white matter tract location (Catani and Thiebaut de Schotten, 2008; Wakana et al., 2004). This allows assigning functional or structural information to further characterize the brain structure involved in a task (Eickhoff et al., 2007; Frost and Goebel, 2013). There are also coordinate systems specialized for different age ranges and subcortical anatomy. These standardized templates and atlases are now part of analysis softwares used for multimodal data integration.

Improving data quality

Multimodal imaging also has the benefit of improving data quality of one modality with the help of data from the other modality. An example, steadily gaining a foothold in field of functional MRI and diffusion MRI, is distortion correction of EPI images (Oh et al., 2012; Viard et al., 2008). Echo planar imaging has revolutionized the human neuroimaging field and has become the standard read-out module for most fMRI and dMRI acquisitions, because of its unrivaled acquisition speed. However, even with the use of parallel acquisition methods, such as SENSE (Pruessmann et al., 1999) and GRAPPA (Griswold et al., 2002), EPI data suffer from geometric distortions and signal dropouts caused by off-resonance effects and dephasing mostly near tissue-air interfaces. These geometric distortions can be corrected in post-processing by use of wide-sense multimodal data, particularly the acquisition of a B_0 field map immediately after or before the EPI acquisition (Oh et al., 2012; Viard et al., 2008) or EPI acquisition with different parameters (Andersson et al., 2003). An emerging new example in MR-PET is the incorporation of movement information for PET reconstruction using high-temporal resolution MRI data.

Biomarkers

Multimodal imaging might also be useful even in circumstances when the researcher is interested in the results of only one modality and the data from both modalities are not integrated in the same framework. Data from the other modality serve to constrain the interpretation of the primary data. Thus, the purpose of multimodal imaging would not be to merge data but to allow informed judgment on the context of the data. The auxiliary data can yield biomarkers to assess the state of the brain tissue, which might account for intra- and inter-subject variability usually not accounted for. For example, EEG can inform about the drowsiness of the subject, skin conductance, heart rate and other peripheral data on the arousal state (e.g. (Rosenkranz and Lemieux, 2010) and references therein).

This is especially important for non-repeatable and non-standard experiments. As a case in point, simultaneous EEG–fMRI has also found its way into cognitive neuroscience investigations (Herrmann

and Debener, 2008), where it is especially useful when subject performance (vigilance, trial-by-trial evaluation processes, errors, learning) must be equal or learning and order effects must be avoided or exactly controlled. The presence of a subject performance requirement can outweigh the costs of simultaneous recording discussed above and even make simultaneous recording a necessity. Although EEG is often used as the biomarker in EEG/fMRI studies, it is interesting to consider a reversal of the multimodal analysis asymmetry. For instance, De Martino et al. (2010) used multivariate prediction methods to predict single-trial EEG responses from whole-brain fMRI data. One of the most striking recent findings enabled by concurrent EEG–fMRI is the modulation of human cortical responses during behavioral tasks by the state of ongoing oscillations (Becker et al., 2011; Scheeringa et al., 2011), paralleling earlier findings in animal studies.

Conclusion

Multimodal neuroimaging can serve different purposes and merits for studying brain processes and structure depending on the processing of the data. Many of the functional studies employing two (or more) imaging modalities utilize it to achieve the best spatial and temporal resolution available for each method, under the assumption that the imaging signals have the same neuronal origin. However, imaging methods might differ not only in the acquisition parameters but also in which and how neuronal processes and structures contribute to the image contrasts. This poses, on the one hand, a difficulty in combining data without a generative model describing the chain of physiological and physical events leading to the imaging signals. On the other hand, it allows one to get a more comprehensive physiological view on the brain processes measured. Thus, exploring sources of discrepancy in multimodal imaging promises to reveal a novel view on cognitive processes and tissue composition than with any imaging modality alone. To that end, generative biophysical models have to be formulated to resolve the apparent discrepancies. Multimodal imaging is also useful if one is only interested in the results of one modality as the other modality can constrain the interpretation of the data (i.e. using biomarkers derived from one modality), especially in cases when variability of brain states cannot be avoided (e.g. in learning experiments). Finally, multimodal imaging is utilized to *quantify and normalize* imaging data, mandatory to generalize individual subject's data. Although multimodal data acquisition and fusion pose many challenges (i.e. additional software, set-up time, subject discomfort etc.), the merits of multimodal imaging make it a valuable and an indispensable tool to investigate brain structure and function. The number of studies utilizing multimodal imaging will continue to grow, especially considering that acquisition techniques and analysis methods for integrating the data have dramatically improved in the last two decades.

Acknowledgments

We thank Peter de Weerd for comments on an earlier version of the manuscript and Pedro Valdes-Sosa for allowing to use Fig. 1.

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