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Review

General overview on the merits of multimodal neuroimaging data fusion

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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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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).