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Review

Function–structure associations of the brain: Evidence from multimodal connectivity and covariance studies

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ABSTRACT

Despite significant advances in multimodal imaging techniques and analysis approaches, unimodal studies are still the predominant way to investigate brain changes or group differences, including structural magnetic resonance imaging (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI) and electroencephalography (EEG). Multimodal brain studies can be used to understand the complex interplay of anatomical, functional and physiological brain alterations or development, and to better comprehend the biological significance of multiple imaging measures. To examine the function–structure associations of the brain in a more comprehensive and integrated manner, we reviewed a number of multimodal studies that combined two or more functional (fMRI and/or EEG) and structural (sMRI and/or DTI) modalities. In this review paper, we specifically focused on multimodal neuroimaging studies on cognition, aging, disease and behavior. We also compared multiple analysis approaches, including univariate and multivariate methods. The possible strengths and limitations of each method are highlighted, which can guide readers when selecting a method based on a given research question. In particular, we believe that multimodal fusion approaches will shed further light on the neuronal mechanisms underlying the major structural and functional pathophysiological features of both the healthy brain (e.g. development) or the diseased brain (e.g. mental illness) and, in the latter case, may provide a more sensitive measure than unimodal imaging for disease classification, e.g. multimodal biomarkers, which potentially can be used to support clinical diagnosis based on neuroimaging techniques.

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Introduction

There is increasing evidence that instead of focusing on the relationship between physiological or behavioral features using a single imaging modality, multimodal brain imaging studies can help provide a better understanding of inter-subject variability from how brain structure shapes brain function, to what degree brain function feeds back to change its structure, and what functional or structural aspects of physiology ultimately drive cognition and behavior.

Many studies try to address the aforementioned issues by comparing specific subject groups, e.g. those with a specified mental disorder to healthy controls, in terms of either brain structure or function, thereby only enabling indirect conclusions on putative structure–function relationships. In contrast, direct associations can be inferred when more than one measurement modality has been utilized in a given study (Schultz et al., 2012); however, it is not necessary for these modalities to have been measured simultaneously or have later been processed in a concurrent fusion model. Yet, the availability of several modal measurements allows the application of a number of statistical approaches, including (but not being limited to) correlational analyses (Skudlarski et al., 2008), data integration (Arndt and Loffeld, 1996; Savopol and Armenakis, 2002) or data fusion based on higher-order statistics and/or modern machine learning algorithms (Sui et al., 2012a).

A key motivation for jointly analyzing multimodal data is to take advantage of the cross-information of the existing data, thereby potentially revealing important variations that may only partially be detected by a single modality. Combined analysis of multiple modalities is typically performed either by data integration or data fusion (here we do not consider 'overlay' approaches which have also been called data fusion but do not directly incorporate the information about multiple modalities beyond visual co-registration). Data integration approaches use data from one modality to enhance the other, and can be considered an asymmetric approach. In this case, one modality can be constrained by features derived from a second modality to obtain a generative model in order to improve brain activity estimates. In contrast, we define data fusion as a symmetric approach in which multiple modalities contribute jointly to the solution (Calhoun and Adali, 2009). More specifically, data fusion involves exploratory discovery of joint relationships among multiple data sets, which are typically not possible to identify by evaluating each data set separately. Such approaches can provide a wealth of information, enabling researchers to more confidently draw conclusions about normal variability in aging, disease, cognition, and behavior. A number of efficient fusion approaches have been developed to assess the joint information provided by multiple imaging techniques (mostly based on cross-modal covariance). In addition to these more recent methodological developments, we also reviewed more classical approaches for combining structural and functional information in the context of connectivity studies.

There is increasing evidence from multimodal studies that patients with mental disorders exhibit unique morphological characteristics, connectivity patterns, and functional alterations. Applying classification techniques to these characteristics could identify biomarkers for psychiatric diseases. This could expedite differential diagnosis, thus leading to more appropriate treatment and improved outcomes for patients with mental disorders. Therefore, in this review paper we reviewed several machine learning methods that were able to identify features from multiple imaging modalities, providing significant discrimination between patients and controls, which could possibly be applied to the early detection of psychiatric diseases.

The most common structural imaging modalities are structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI). Functional MRI (fMRI) and electroencephalography (EEG) are the two most prevalent methods for functional imaging. In this paper, we selectively reviewed a number of multi-modal neuroimaging studies that concurrently utilize at least one structural and one functional modality of the aforementioned ones. Behavioral relevance of the assessed physiological features will be mentioned whenever possible. We will discuss approaches for doing two–way combinations first, followed by a 3-way or N-way fusion applications, and also provide some comparison of the strengths and limitations of the different approaches when possible.

Prevalent brain imaging modalities

High-resolution T1-weighted imaging (which we will refer to as sMRI from now on), is the most common method for depicting structural properties of the brain, which enables the assessment of differences in the local concentration or volume of gray matter (GM) and white matter (WM) at each voxel, by using approaches such as voxel-based morphometry (VBM) (Ashburner and Friston, 2000), voxel-based cortical thickness (VBCT) (Haier et al., 2009), or higher order morphometric and shape changes through programs such as FreeSurfer (Fischl, 2012). DTI, on the other hand, for a given voxel, measures the directional diffusion of water molecules. Common parameters derived from DTI are fractional anisotropy (FA) and mean diffusivity (MD), which refer to the overall strength of water diffusion and its directedness regardless of its specific orientation, respectively. Note that tractography based on DTI cannot directly image multiple fiber orientations within a single voxel. Because if a diffusion tensor is calculated, only one direction for the fiber is obtained in the voxel given by the principal eigenvector, and the orientation distribution function (ODF) is a delta function. To address this limitation, a number of methods have been proposed to measure ODF's based on the angular resolution requirement to resolve closely aligned fiber bundles. Among others, these methods include diffusion spectrum imaging (DSI) (Wedeen et al., 2005), Q-ball imaging (Tuch, 2004), and a probabilistic method based on Monte-Carlo simulations (Behrens et al., 2003). Particularly, DSI and related methods were developed to image complex distributions of intra-voxel fiber orientation (Johansen-Berg and Rushworth, 2009). DSI relies on more accurate assumptions regarding the typical structure of white matter, thus enables looking at crossing or kissing fibers (Tefera et al., 2013), and has shown structural basis of functional cerebellar circuits in the human cerebellum in vivo (Granziera et al., 2009). Structural imaging can also be performed with diffusion-weighted imaging (DWI) and fiber tractography, which use the passive diffusion of water molecules to infer properties of the surrounding tissue (Roberts et al., 2013). Recently, DWI has been increasingly used for its ability to assess WM microstructure and pathways of the whole brain in vivo (Jones, 2008). In this paper, we use diffusion MRI (dMRI) to denote all abovementioned diffusion imaging methods.

In the functional domain, fMRI measures dynamic changes of the hemodynamic response related to neural activity in the brain. Using blood oxygenation-level dependent (BOLD) imaging, changes in regional

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