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Editorial

Toward a Meta-Analytic Synthesis of the Resting-State fMRI Literature for Clinical Populations

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Coordinate-based meta-analysis (CB-meta) is playing an important role in identifying spatially consistent findings for targeted questions in the neuroimaging literature, by quantitatively aggregating independent results reported in a standard coordinate space [1]. CB-meta has been widely used in voxel-based magnetic resonance imaging (MRI) studies, including task functional MRI (fMRI), where either patterns of within-group activation or patterns of between-group activation differences can be aggregated across studies. Given that variations in task design can introduce confounds into such pursuits, researchers work to limit any effort to the inclusion of studies using highly similar tasks. Task fMRI CB-meta papers have been published in most brain disorders.

Resting-state fMRI (RS-fMRI) does not require cognitive task probes, and its design is inherently similar across studies. From this perspective, it is ideally suited for CB-meta. However, while an array of analytic methods have emerged to characterize different aspects of resting brain activity, not all of them are suitable for CB-meta. This likely explains the relatively small number of RS-fMRI based CB-meta published to date [2–8].

The analytic methods for RS-fMRI can be divided into two categories, one for depicting functional relationships between remote brain regions and another for local activity (for a systematic review, see [9]). The widely used methods in the former category include seed-based functional connectivity, spatial independent component analysis (sICA), and graph theory. The latter has two widely used methods, namely, regional homogeneity (ReHo) and amplitude of low frequency fluctuation (ALFF)/fractional ALFF (fALFF).

Seed-based functional connectivity is one of the most widely used analytic methods in RS-fMRI studies. Typically, a region of interest (ROI) is predefined and then linear correlation or linear regression analysis is performed between the mean time series of this ROI and the time series of each voxel in the brain. The results are of course dependent on the location of seed ROIs and therefore are not suitable for CB-meta. Most of the 8 CB-meta RS-fMRI papers aforementioned did not include seed-based functional connectivity studies.

Spatial independent component analysis (sICA) decomposes the RS-fMRI data into multiple networks (components), among which only about 10 networks are psychophysiologically interpretable [10]. "Spatial independent" means spatially nonoverlapping. Therefore, sICA papers should not be taken into a CB-meta study, unless different papers have focused on the same component (e.g., the default mode network). A few CB-meta RS-fMRI studies have included sICA RS-fMRI papers [2, 4, 6, 8]. However, few explicitly mentioned the limitation of sICA for CB-meta.

Graph theory has been widely used for exploring the topological organization of complex brain networks in RS-fMRI studies. Unlike seed-based functional connectivity and sICA, which focus on a specific functional system(s), graph theory usually explores the topological properties, such as small-world, modular structure and highly connected hubs, of the entire brain. From this point of view, RS-fMRI studies using graph theory are also well suitable for meta-analysis. However, due to the high computational cost, most graph-based RS-fMRI studies have chosen a limited number of brain regions or ROIs, rather than brain voxels, as network nodes. Such results do not provide the coordinate information needed to support CB-meta. Degree centrality is one of the simplest and least computation-demanding measures for graph theory complex networks. Several RS-fMRI toolboxes (e.g., DPARSF (http://www.restfmri.net/; http://rfmri.org/) and Gretna (https://www.nitrc.org/projects/gretna/)) have included voxel-based degree centrality measurement [11, 12]. Some studies have applied voxel-based centrality to brain disorders including depression [13–15] and Alzheimer's disease [16]. In light of recent increases in computational capacity, more complicated measurements of graph theory will be implemented in a voxel-wise manner, thereby increasing the suitability of graph theory for CB-meta.

ReHo and ALFF are two methods widely used for characterizing local spontaneous activity of RS-fMRI data. ReHo measures the local synchronization of the time series of neighboring voxels [17] whereas ALFF/fALFF measures the amplitude of time series fluctuations at each voxel [18, 19]. Although both ReHo and ALFF/fALFF measure the local activity of each voxel, many studies used the two measurements and suggested that the two methods reveal different aspects of brain function and abnormalities arising in clinical populations [20–23]. For nearly all of the existing CB-meta RS-fMRI studies, researchers have combined across these methods for characterizing local activity (ReHo and/or ALFF), despite known differences in their properties. A CB-meta RS-fMRI study of depression by Iwabuchi and colleagues for the first time included RS-fMRI papers using the same analytic method (ReHo) [5]. This approach markedly reduces discrepancies in analytic methods. However, only 10 of the 200+ RS-fMRI papers on depression to date met the inclusion criteria of that CB-meta study.

Clinical studies always face the challenges of high heterogeneity and limited sample size in patient groups. Therefore, meta-analysis is critical for drawing congruent conclusion across studies carried out with similar settings and techniques. Few techniques for clinical studies enable the application of the broad range of analytic methods that RS-fMRI does in an effort to reveal the functional complexity of the human brain from multiple aspects. Although some analytic methods are not suitable for CB-meta, the strength of RS-fMRI is that its design is inherently similar across studies. Therefore, each dataset could be reanalyzed by using analytic methods being suitable to perform CB-meta. The current special issue was launched to encourage RS-fMRI studies on brain disorders by reanalyzing the published data with methods supporting future CB-meta.

In the current issue, a paper from Dr. Chunshui Yu's group in Tianjin Medical University is of particular interest (see Y. Xu et al., "Altered Spontaneous Brain Activity in Schizophrenia: A Meta-Analysis and a Large-Sample Study"). The authors not only performed two CB-meta RS-fMRI studies, in which only RS-fMRI papers using methods for local activity (ReHo and ALFF, resp.) were included, but they also validated the CB-meta results in their own dataset obtained from a relatively large sample of schizophrenia patients. One of the congruent results was that ALFF was reduced in the primary visual and primary sensorimotor cortex (see details in Y. Xu et al. "Altered Spontaneous Brain Activity in Schizophrenia: A Meta-Analysis and a Large-Sample Study"). The limitation of this study, like other CB-meta RS-fMRI studies, is the small number of eligible RS-fMRI papers. Only 6 ALFF papers and 4 ReHo RS-fMRI papers were included.

We hope this special issue will draw attention to the need for and value of CB-meta in the RS-fMRI research field. If your dataset has not been analyzed with a method that facilitates future CB-meta, please try it. Future CB-meta efforts need large numbers of studies for inclusion to enable more definitive conclusions, upon which models for the prediction or diagnosis of brain disorders can be developed. Additionally, accurate localization of abnormal spontaneous brain activity may help to guide intervention therapies (e.g., deep brain stimulation, transcranial magnetic stimulation, or transcranial ultrasound stimulation).

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