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Statistical testing and power analysis for brain-wide association study

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ABSTRACT

The identification of connexel-wise associations, which involves examining functional connectivities between pairwise voxels across the whole brain, is both statistically and computationally challenging. Although such a connexel-wise methodology has recently been adopted by brain-wide association studies (BWAS) to identify connectivity changes in several mental disorders, such as schizophrenia, autism and depression, the multiple correction and power analysis methods designed specifically for connexel-wise analysis are still lacking. Therefore, we herein report the development of a rigorous statistical framework for connexel-wise significance testing based on the Gaussian random field theory. It includes controlling the family-wise error rate (FWER) of multiple hypothesis testings using topological inference methods, and calculating power and sample size for a connexel-wise study. Our theoretical framework can control the false-positive rate accurately, as validated empirically using two resting-state fMRI datasets. Compared with Bonferroni correction and false discovery rate (FDR), it can reduce false-positive rate and increase statistical power by appropriately utilizing the spatial information of fMRI data. Importantly, our method bypasses the need of non-parametric permutation to correct for multiple comparison, thus, it can efficiently tackle large datasets with high resolution fMRI images. The utility of our method is shown in a case-control study. Our approach can identify altered functional connectivities in a major depression disorder dataset, whereas existing methods fail. A software package is available at https://github.com/weikanggong/BWAS.

1. Introduction

The human brain connectome is usually modeled as a network. In the brain's network, accurately locating the connectivity variations associated with phenotypes, such as clinical symptoms, is critical for neuroscientists. With the development of neuroimaging technology and an increasing number of publicly available datasets, such as the 1000 Functional Connectomes Project (FCP) (Biswal et al., 2010), Human Connectome Project (HCP) (Glasser et al., 2016) and UK-Biobank (Miller et al., 2016), large-scale, image-based association studies have become possible and should help us improve our understanding of human brain functions.

Using a priori knowledge of brain parcellation (e.g. Automated Anatomical Labeling atlas, Rolls et al., 2015) or an adoption of data-driven parcellation (e.g. Independent Component Analysis, Beckmann and Smith, 2004) to analyze the human connectome is the most popular approach, and many statistical methods have been designed for them (Zalesky et al., 2012; Kim et al., 2014). However, methods that designed specifically for voxel-level connectivity analysis are still lacking. Therefore, in this paper, a statistical framework for brain-wide association study (BWAS) is proposed (Cheng et al., 2015a; 2015b; 2016). It directly uses *voxels* as nodes to define brain networks, and then tests the associations of each *functional connectivity* with phenotypes.

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To conduct a systematic, fully-powered BWAS, two main issues should be carefully addressed. First, a multiple correction method to control the false-positive rate of massive univariate statistical tests should be developed. Second, a power analysis method to estimate the required sample size should be designed. One may ask whether the methods widely used in region-level studies can be directly generalized to connexel-level studies. Two issues hinder such a direct generalization. First, the statistical tests have more complex spatial structures in BWAS. Therefore, as shown in our analysis, some widely-used multiple correction methods, which do not utilize the spatial information of data (e.g. Bonferroni correction and false discovery rate (FDR), Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001), may not be powerful enough to detect signals. Second, although non-parametric permutation methods (Nichols and Holmes, 2002) may account for the complex structures among hypothesis tests to provide a valid threshold, they are computationally very expensive in connexel-wise studies, owing to the requirement of performing billions of statistical tests. Therefore, an accurate and efficient method for multiple comparison problem and power analysis is needed.

Random field theory (RFT) is an important statistical tool in brain image analysis, and it has been widely used in the analysis of task fMRI data (Penny et al., 2011) and structure data (Ashburner and Friston, 2000). Statistical parametric maps (SPM) are usually modeled as a discrete sampling of smooth Gaussian or related random fields (Penny et al., 2011). The random field theory can control the FWER of multiple hypothesis testings by evaluating whether the observed test statistic, or the spatial extent of clusters exceeding a cluster-defining threshold (CDT), is large by chance, which is known as peak-level and cluster-level inference respectively. Since Adler's early work on the geometry of random field (Adler, 1981; Adler and Taylor, 2009), theoretical results for different types of random fields have been obtained, such as Gaussian random field (Friston et al., 1994; Worsley et al., 1996), t, χ^2, F random fields (Worsley, 1994; Cao, 1999), multivariate random field (Taylor and Worsley, 2008), cross-correlation random field (Cao et al., 1999). Among them, only the cross-correlation field is designed for connectivity analysis. In that framework, the voxel-level functional network is modeled as a six-dimensional cross-correlation random field, and the maximum distribution of the random field is used to identify strong between-voxel connections. Different from the above works, the aim of BWAS is to identify connectivities that are associated with phenotypes. To the best of our knowledge, no previous works have addressed this problem. In this paper, we show that the statistical map of BWAS, under the null hypothesis, can be modeled as a Gaussian random field with a suitable smoothness adjustment. Therefore, topological inference methods, such as peak intensity and cluster extent, are generalized from voxel-wise analysis to functional connectivity analysis.

Besides controlling the type I error rate, estimating power and the required sample size for BWAS are also important. In genetics, for example, a high-quality GWAS analyzing one million single nucleotide polymorphism (SNP) usually requires tens of thousands of samples to reach adequate statistical power. In contrast, previous BWAS analyses of schizophrenia, autism and depression have only had sample sizes less than one thousand (Cheng et al., 2015a; 2015b; 2016). Therefore, compared to GWAS, it is natural to ask if BWAS, which is usually based on a limited sample size, can withstand the rigors of a large number of hypothesis tests. In this regard, most existing power analysis methods are designed for voxel-wise fMRI studies, including, for example, the simulation based method (Desmond and Glover, 2002), the non-central distribution based method (Mumford and Nichols, 2008), and the method based on non-central random field theory (ncRFT) (Hayasaka et al., 2007). Among them, the ncRFT-based method can both take into account the spatial structure of fMRI data and avoid time consuming simulation. Therefore, to analyze the power of BWAS, we adopted a methodology similar to that of the ncRFT-based method (Hayasaka et al., 2007). The signals at functional connectivities are modeled as a non-central Gaussian random field, and the power is estimated by a modified Gaussian random field theory.

In this paper, a powerful method to address the multiple comparison problem is proposed for BWAS (Fig. 1). This method uses Gaussian random field theory to model the spatial structure of voxel-level connectome. It can test the odds that either the effect size of every single functional connectivity (peak-level inference) or the spatial extent of functional connectivity clusters exceeding a cluster-defining threshold (cluster-level inference) is large by chance. The performance of the method is tested in two resting-state fMRI datasets, and in both volume-based and surface-based fMRI data. Our method can control the false-positive rate accurately. Compared with Bonferroni correction and false discovery rate (FDR) approaches, our method can achieve a higher power and filter out false-positive connectivities by utilizing the spatial information. In addition, we develop a method to approximate the power of peak-level inference by a modified Gaussian random field theory (Fig. 2). Power can be estimated in any specific location of connectome efficiently, which can help to determine the sample size for BWAS. The utility of our method is shown by identifying altered functional connectivities and estimating the required sample sizes in major depression disorder. The software package for BWAS can be downloaded at https://github.com/weikanggong/BWAS.

2. Material and methods

2.1. Connexel-wise general linear model

The popular general linear model approach is used in BWAS. Briefly, a voxel-level functional network is estimated for each subject using the fMRI data, and the association between each functional connectivity and phenotype of interest is tested using the general linear model.

In detail, the individual functional network is constructed first by calculating the Pearson correlation coefficients (PCC) between every pair of voxel time series. Let m be the number of voxels, s be the subject, and $R^{(s)} = [r_{ij}^{(s)}]_{m\times m}$ be the $m \times m$ functional network matrix for subject s. Each element of $R^{(s)}$ is the correlation coefficient between voxel time series i and j for subject s. An element-wise Fisher's Z transformation is then applied as $Z^{(s)} = [z_{ij}^{(s)}]_{m\times m} = \left[\frac{1}{2}\log\left(\frac{1+r_{ij}^{(s)}}{1-r_{ij}^{(s)}}\right)\right]_{m\times m}$, so that $z_{ij}^{(s)}$ will approximate a normal distribution. For every functional connectivity, a general linear model (GLM) is fitted by

$$Y_{ij} = XB_{ij} + \epsilon_{ij}$$

where, $Y_{ij} = (z_{ij}^{(1)}, z_{ij}^{(2)}, \ldots, z_{ij}^{(n)})$ is an $n \times 1$ vector of functional connectivities between voxel i and j across n subjects, X is the common $n \times q$ design matrix, $B_{ij} = (\beta_{ij}^1, \beta_{ij}^2, \ldots, \beta_{ij}^q)$ is a $q \times 1$ vector of regression coefficients, and ϵ_{ij} is an $n \times 1$ vector of random error, which is assumed to be an independent and identically distributed Gaussian random variable $N(0, \sigma_{ij}^2)$ across subjects. The ordinary least square estimator for B_{ij} is $\hat{B}_{ij} = (X'X)^{-1}X'Y_{ij}$, and for σ_{ij}^2, it is $\hat{\sigma}_{ij}^2 = (Y_{ij} - X\hat{B}_{ij})'(Y_{ij} - X\hat{B}_{ij})/(n-q)$. Then, a Student's t-statistic at functional connectivity between voxel i and j can be expressed as:

$$T_{ij} = \frac{\mathbf{c}\hat{B}_{ij}}{(\mathbf{c}(X'X)^{-1}\mathbf{c}'\hat{\sigma}_{ij}^2)^{\frac{1}{2}}}$$