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A sparse representation-based method for parcellation of the resting brain and its application to treatment-resistant major depressive disorder

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HIGHLIGHTS

- An elastic net-based (EN) parcellation method is introduced for fMRI data.
- Performance evaluated using simulation datasets and resting-state fMRI datasets.
- The proposed EN-based method achieved higher accuracy than LASSO-based method.
- No functional volumetric differences in insular subdivisions between MDD and HVs.
- Patients showed hypo-connectivity in medial temporal region with insular subdivision.

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ABSTRACT

Background: Parcellating brain regions into functionally homogeneous subdivisions is critical for understanding normal and abnormal brain functions.
New method: In this study, we developed a new sparse representation-based parcellation method for functional magnetic resonance imaging (fMRI) data, and applied the new method to investigate functional insular subdivisions in treatment-resistant major depressive disorder (MDD). Realistic simulations were implemented to demonstrate the feasibility of the method. Subsequently, the method was used to parcellate the insula in a sample of fifty-six MDD patients and thirty-six healthy volunteers (HVs). The optimal number of clusters was determined by an independent test-retest dataset. Finally, differences of the functional connectivity profiles of each insular subdivision between patients and HVs were inspected.
Results: The results from both simulated and test-retest fMRI datasets demonstrated the feasibility of the proposed elastic net-based (EN) method. With the proposed method, the insula was parcellated into four subdivisions (dorsal anterior dAI; ventral anterior vAI; middle, MI and posterior, PI). Whereas patients showed hypo-connectivity between vAI and right medial temporal lobe, there were no functional volumetric differences in insular subdivisions between MDD patients and HVs.
Comparison with existing method: Results from both simulated and real fMRI datasets showed that the proposed EN method achieved higher accuracy than least absolute shrinkage and selection operator-based (LASSO) method.
Conclusions: These findings suggest that EN-based parcellation has the potential to be a useful addition to the parcellation techniques for fMRI data, and provide evidence of decreased functional connectivity without functional volumetric changes of the insula in treatment-resistant MDD.
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1. Introduction

Brain parcellation divides the brain into a set of non-overlapping parcels that exhibit homogeneous characteristics within the parcel and heterogeneous characteristics between different parcels. By doing so, one gains a deeper understanding how different brain regions function together in perception and cognition processing (Eickhoff et al., 2015; Yeo et al., 2011). Moreover, the parcellation of the brain into distinct subdivisions provides a critical tool for understanding the brain pathology, and it may provide critical insights into the neurobiological underpinnings of neuropsychiatric disorders such as major depressive disorder (MDD) (Downar et al., 2014), obsessive-compulsive disorder (Dunlop et al., 2015) and autism (Nebel et al., 2014; Yamada et al., 2016). Human brain parcellation has been constructed using anatomical features, however, these studies were mainly based on post-mortem brains (Garey, 1994), which are different from in-vivo brains, or structural images (Cammoun et al., 2012; Fischl et al., 2004), which did not take account of the functional properties of the human brain. The results obtained by these modalities can hardly transferred to infer the function of the brain regions, since there is a limited correspondence between anatomical boundaries and those based on functional specialization of the brain. As a result, functional parcellation techniques have recently gained research momentum (Eickhoff et al., 2015). The advances of resting-state functional magnetic resonance imaging (fMRI) technique pave an avenue for delineating the brain's functional properties noninvasively. As parcellation of brain regions using resting-state fMRI data can be posed as a data clustering problem, several parcellation frameworks based on various clustering algorithms have been proposed for resting-state fMRI data (Eickhoff et al., 2015; Thirion et al., 2014).

Inspired by the success of using sparse representation for signal and pattern analysis in the machine learning and pattern recognition fields (Wright et al., 2010), sparse representation has been used to help decode the functions of the human brain (Li et al., 2014) by analyzing spontaneous blood oxygenation level-dependent (BOLD) fluctuations of brain activity measured with fMRI. However, these studies mainly focused on inferring brain networks with sparse representation methods (Ge et al., 2016, 2015; Lv et al., 2015; Yu et al., 2017). It has also been proposed that sparse representation could be used for clustering with high-dimensional datasets (Elhamifar and Vidal, 2009, 2013). To the best of our knowledge, only two studies (Zhang et al., 2015, 2016) have investigated the feasibility of applying sparse representation to functional brain parcellation. These studies took advantage of the merit of robustness to noise of the sparse representation methods, and introduced two promising approaches to partition brain areas by the least absolute shrinkage and selection operator (LASSO) algorithm (Tibshirani, 2011). The employment of a sparse representation method was reasonable because the representation coefficients were intrinsically sparse: voxels within a particular area were highly correlated due to the functional communications (De Luca et al., 2006) between these voxels and/or spatial smoothing, averaging effect of BOLD signals; thus one voxel could be effectively represented by a small portion of voxels which were highly correlated with themselves and, accordingly, the representation coefficients were sparse. Although LASSO-based method exhibited better performance over other commonly used methods, it has limitations. One limitation is intrinsic to the LASSO technique (Zou and Hastie, 2005). The scenario is that if there is a group of variables (voxels) among which the pairwise correlations are very high, LASSO tends to select only one variable from the group and enforce coefficients corresponding to other voxels to be zero. For fMRI data at conventional voxel sizes and field strengths, a typical brain area usually has hundreds of voxels and, for those voxels sharing similar functions, the correlations between them can be high. The ideal sparse representation method should be able to eliminate the trivial voxels and select the related grouping voxels. LASSO lacks the ability to reveal the grouping information, and is therefore not an ideal method. The elastic net (EN) method follows a similar formulation as the LASSO with an additional penalty term to encourage variable grouping and a more stable solution (Zou and Hastie, 2005). Consequently, the EN should have better performance than LASSO in partitioning brain areas into functional distinct subdivisions.

Recent advances in fMRI-based parcellation methods have led to the detailed examination of the functional architecture of specific brain regions. Among these regions, the insula has been of particular interest, as it is involved in diverse brain functions, including cognition, emotion, and sensory perception (Kurth et al., 2010). In spite of several studies functionally parcellating the insula, the question of whether there exist differences in insular functional architecture in psychiatric disorders remains to be addressed. Furthermore, there exist no work on insular functional architecture in treatment-resistant MDD specifically. The insular cortex is increasingly conceptualized as a limbic integration cortex abundantly and reciprocally with limbic structures such as the hippocampus, the amygdala, and the cingulate cortex (Augustine, 1996). In light of increasing evidence about the involvement of insular cortex in the pathophysiology of MDD (Sliz and Hayley, 2012), we were interested in parcellating the insula into functional subdivisions, to investigate if their functional arrangement and patterns of functional connectivity to the rest of the brain are altered in MDD patients. In the current study, we introduced a novel brain parcellation method that operates by quantifying the similarity between brain regions using the regularized sparse representation. We tested the feasibility of this method on simulated data and test-retest data, and then used this data-driven method to determine if the volumes and the functional connectivity (FC) of insular subdivisions differs in patients with treatment-resistant MDD compared with healthy volunteers (HVs).

2. Materials and methods

2.1. Parcellation framework

The time series of each voxel $y_i \in R^{Ti}$, $i = 1, \ldots, V$ (Fig. 1) within the target region for each subject was extracted, where Ti is the number of time points and V is the number of voxels over the target region. The sparse representation of the k-th voxel by all the other voxels could be represented by the following EN minimization problem:

$$\boldsymbol{\beta}_k = \underset{\beta}{argmin} \sum \left(y_k - \boldsymbol{X}_k \boldsymbol{\beta} \right)^2 + \lambda \left[(1-\alpha) ||\boldsymbol{\beta}||_2^2/2 + \alpha ||\boldsymbol{\beta}||_1 \right] \quad (1)$$

where $y_k \in R^{Ti}$ is the time series vector of k-th voxel; $\boldsymbol{X}_k = [y_1, \ldots, y_{k-1}, y_{k+1}, \ldots, y_V] \in R^{T_i \times (V-1)}$ is the residual feature matrix consisting of time series of all voxels within the target region by eliminating the k-th voxel; $\boldsymbol{\beta}_k = \left[\beta_{1,k}, \ldots, \beta_{j,k}, \ldots, \beta_{(V-1),k} \right]^T \in R^{V-1}$ is the representation coefficient vector; $\lambda \geq 0$ is a complexity parameter, and $0 \leq \alpha \leq 1$ is a compromising parameter between the ℓ_1 and ℓ_2 constraints, where ℓ_1 constraint is defined as the ℓ_1-norm of the coefficient vector: $||\boldsymbol{\beta}_k||_1 = \sum_j |\beta_{j,k}|$ and ℓ_2 constraint is defined as the square of the ℓ_2-norm of the coefficient vector: $||\boldsymbol{\beta}_k||_2^2 = \sum_j |\beta_{j,k}|^2$. It should be noted that λ and α together determine the trade-off between the accuracy of the linear regression, sparsity and "grouping effect" of the coefficient vector $\boldsymbol{\beta}_k$ (Zou and Hastie, 2005). Eq. (1) would degrade as a LASSO problem with $\alpha = 1$ and a conventional linear regression problem with $\lambda = 0$. To solve the EN-based minimization problem, we used the Glmnet (http://

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