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Predicting Cortical ROIs via Joint Modeling of Anatomical and Connectional Profiles

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Abstract

Localization of cortical regions of interests (ROIs) in structural neuroimaging data such as diffusion tensor imaging (DTI) and T1-weighted MRI images has significant importance in basic and clinical neurosciences. However, this problem is considerably challenging due to the lack of quantitative mapping between brain structure and function, which relies on the availability of multimodal training data including benchmark task-based functional MRI (fMRI) images and effective machine learning algorithms. This paper presents a novel joint modeling approach that learns predictive models of ROIs from concurrent task-based fMRI, DTI, and T1-weighted MRI datasets. In particular, the effective generalized multiple kernel learning (GMKL) algorithm and ROI coordinate principal component analysis (PCA) model are employed to infer the intrinsic relationships between anatomical T1-weighted MRI /connectional DTI features and task-based fMRI-derived functional ROIs. Then, these predictive models of cortical ROIs are evaluated by cross-validation studies, independent datasets, and reproducibility studies. Experimental results are promising. We envision that these predictive models can be potentially applied in many scenarios that have only DTI and/or T1-weighted MRI data, but without task-based fMRI data.

Keywords

DTI; T1-weighted MRI; fMRI; connectivity; functional cortical ROIs

1. Introduction

With the wide availability of multimodal T1-weighted MRI, DTI and resting state fMRI (rsfMRI) datasets, growing interest has been attracted in assessing the structural and/or functional connectivities within cortical networks in brain diseases and healthy controls (e.g., He, et al., 2007; Liu et al., 2008; Johnston et al., 2008; Supekar et al., 2008; Seeley et al., 2009; Dickerson and Sperling, 2009; Suvak and Barret, 2011; Wee et al., 2011; Li et al., 2012a; Li et al., 2012b; Zhang et al., 2012b). However, a fundamental issue is how to localize network nodes, or functionally meaningful cortical regions of interest (ROIs), in these multimodal neuroimaging datasets for structural/functional connectivity assessments (Friston et al., 2003; Goebel et al., 2003; Sporns et al., 2005; Biswal et al., 2010; Van Dijk et

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al., 2010; Hagmann et al., 2010; Li et al., 2010; Liu, 2011; Zhu et al., 2012a; Zhu et al., 2012b).

The previous methods can be roughly grouped into three categories based on the neuroimaging modality that ROIs are defined on. The first school of methods relied on defining cortical ROIs on T1-weighted MRI *images*, e.g., based on anatomical atlases, and then structural/functional connectivities were assessed based on T1-weighted MRI derived ROIs (e.g., Sporns et al., 2005; Dickerson and Sperling, 2009; Wee et al., 2011). The second category of methods defined ROIs on DTI images, on which structural/functional connectivities were then examined (e.g., Zhu et al., 2012b; Li et al., 2012a; Li et al., 2012b). The third group of methods defined ROIs on rsfMRI data directly, such as the independent component analysis (ICA) (e.g., Calhoun et al., 2001; Beckmann et al., 2005) and regional homogeneity (ReHo) method (Zang et al., 2004; Liu et al., 2008), based on which functional connectivities can then be assessed. Though the above three categories of ROI definition methods have been successfully applied in different application scenarios, the functional meanings of those ROIs and their structural correspondences across individuals and populations still remain to be examined and elucidated.

Comparatively, task-based fMRI, e.g., via block-based paradigms, has been widely recognized and used as a benchmark approach to identifying functionally meaningful cortical ROIs (e.g., Haynes et al., 2007; Logothetis, 2008; Friston, 2009). Thus, task-based fMRI data is deemed to provide sound ROI/network node location for assessing structural and/or functional connectivities (Zhu et al., 2012a; Zhu et al., 2012b; Zhang et al., 2012). Unfortunately, in many real-world applications, particularly in clinical scenarios, there may be no task-based fMRI data available. For example, it might be very challenging to acquire high-quality task-based fMRI data for elderly or children participants (e.g., Jack et al., 2010; Epstein et al., 2007). Additionally, the human brain is composed of many functional networks such as working memory, vision, auditory, language, motor, attention, and emotion systems (Zhu et al., 2012b). Extensive acquisition of multiple task-based fMRI datasets for the purpose of obtaining all of those functional networks is time-consuming and cost-prohibitive. Therefore, it is impractical to employ task-based fMRI on large datasets or datasets from other sources and populations, to localize large-scale functional networks and ROIs for structural/functional connectivity assessments (e.g., Liu, 2011; Zhang et al., 2012). Notably, brain networks derived from resting state fMRI data are limited to resting state networks (RSNs) (Damoiseaux et al., 2006; van den Heuvel et al., 2008), which are quite different from those derived from task-based fMRI data such as the five functional networks of working memory, fear, emotion, empathy, and semantic decision making (Zhu et al., 2012b) used in this paper. Currently, it remains unclear whether or not it is possible to infer task-based functional networks from resting state fMRI data. In addition, in some application situations such as the ADNI-2 project (Jack et al., 2010), resting state fMRI data and DTI data are not concurrently available for the same group of subject. Thus, it is important to predict functional ROIs based on structural data such as T1-weighted MRI and/or DTI images.

Typically, DTI and/or T1-weighted MRI scans take only several minutes and are widely available. Therefore, it is very desirable to predict task-based fMRI derived ROIs via DTI and/or T1-weighted MRI data, if it is possible to construct a quantitative mapping between those ROIs and their structural/connectional attributes derived from T1-weighted MRI and/or DTI data. In general, the close relationships between structural profiles and brain functions have been widely reported in the literature (e.g., Passingham et al., 2002; Honey et al., 2009) and our own recent studies (Li et al., 2010; Zhu et al., 2012a; Zhu et al., 2012b; Li et al., 2012a; Li et al., 2012b). Practically, our prior studies in Zhang et al., 2012 have shown that functional cortical ROIs identified by working memory task-based fMRI can be

accurately predicted by DTI-derived fiber connection patterns. Furthermore, our recent multimodal task-based fMRI and T1-weighted MRI studies have demonstrated that consistent morphological structure features such as cortical folding patterns can fairly accurately predict some functional cortical ROIs (Chen et al., 2011). Therefore, both theoretic and empiric studies have already demonstrated the feasibility of predicting functional cortical ROIs via structural neuroimaging data such as DTI and/or T1-weighted MRI images.

Although these prior studies have already shed light on an alternative approach to localizing functionally meaningful ROIs based on DTI (e.g., Zhang et al., 2012) or T1-weighted MRI (e.g., Chen et al., 2011) data, there are very few studies (as far as we know) that have investigated whether DTI derived connectional features and T1-weighted MRI derived anatomical features can be integrated to improve the performance of predicting functional cortical ROIs. Furthermore, the functional ROI prediction capabilities of DTI-based features and T1-weighted MRI-based features have not been quantitatively assessed and compared on large-scale functional brain networks yet (to the best of our knowledge). In recognition of these needs, this paper presents a novel joint modeling approach that simultaneously considers DTI-derived connectional features and T1-weighted MRI-derived anatomical features for functional cortical ROI prediction. Our premise is that T1-weighted MRI and DTI data provide complementary information such as morphological and connectional features for the prediction of functional localizations of ROIs.

Generally, the prediction framework is designed for the cortical ROIs in a functional network via a typical machine learning paradigm and the flowchart of our framework is shown in Fig.1. In the training stage (purple box), concurrent task-based fMRI, DTI and T1-weighted MRI datasets are available for learning the predictive models of functional cortical ROIs. First, group-wise activated peaks from task-based fMRI data are detected and used as benchmark ROIs. Then, connectional and anatomical features from those benchmarks and their neighbors are extracted from DTI and T1-weighted MRI data, respectively. Finally, two models are learnt for the ROIs based on the structural information via the generalized multiple kernel learning (GMKL) (Varma et al., 2009) method. In the prediction stage (green box), however, only DTI and/or T1-weighted MRI datasets are available for functional ROI prediction. The above-mentioned two learnt models are applied on DTI/T1-weighted MRI data of the testing subject. The GMKL models take the advantages of two feature spaces by fusing them and scoring each ROI's candidates to distinguish possible ROI locations from less possible ones. That is, the more positive, the more likely one candidate will be ROI. The PCA model is used as a constraint to ensure that the distribution pattern of a group of selected ROI candidates does not deviate too far away from the pattern of training subjects. The prediction procedure is formulated and solved as an energy minimization problem, in which the GMKL models and the coordinate PCA model are iteratively matched on the candidate ROI locations to obtain two scores, which are defined as the external and internal energy terms, respectively.

The proposed functional ROI prediction framework has been evaluated via cross-validation (black dashed box in Fig.1), in which the functional ROIs derived from task-based fMRI on the testing subjects are used as the benchmark to evaluate the prediction errors. Further validations of the methods are conducted by comparison of the prediction errors with those obtained via state-of-the-art image registration methods on independent dataset. The reproducibility and generalization capability of the methods are also examined, and promising results have been achieved.

The rest of the paper is organized as follows. Datasets used in the paper and the preprocessing steps are detailed in section 2.1. The anatomical and the connectional features,

as well as the GMKL training model and coordinate PCA model, are explained in section 2.2. The ROI prediction procedure is detailed in section 2.3. In the results section, effectiveness of features is explored in section 3.1. Parameters in training and prediction stages are discussed in section 3.2. The cross-validation, comparison with image registration methods on independent datasets, reproducibility experiment, and extension of the methods in application scenarios are presented in sections 3.3-3.6, respectively. Finally, the limitations and possible improvements of the methods in the future are discussed in section 4.

2. Materials and Methods

2.1. Data Acquisition and Preprocessing

Dataset 1—Eleven healthy young adults voluntarily participated in this study under IRB approvals. Each participant performed in-house verified block-based tasks including semantic decision making, emotion, fear, and empathy tasks while fMRI data was acquired (Zhu et al., 2012b). DTI and T1-weighted MRI scans were also obtained for each participant. Briefly, T1-weighted MRI, *task-based* fMRI and DTI scans were acquired on a 3T GE Signa scanner at the University of Georgia (UGA) Bioimaging Research Center (BIRC). The functional scans were acquired using a T2*-weighted single shot echo planar imaging (EPI) sequence and were aligned to the AC-PC line; *Other parameters include:* TE=25ms, TR=1500 ms, 90° RF pulse, 30 interleaved slices, acquisition matrix=64×64, spacing=0 mm, slice thickness=4 mm, FOV=220×220 mm, and ASSET factor=2. Diffusion-weighted single shot EPI images were acquired using the isotropic spatial resolution 2mm×2mm×2mm; parameters were TR=15.1s, TE=min-full, b-value=1000 with 30 DWI gradient directions and 3 B0-volumes acquired, matrix size=128×128, 60 slices. T1-weighted MRI images were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol; *Parameters include:* TE=min full, TR=7.5 ms, flip angle=20°, 150 axial slices, slice thickness=1.2 mm, and FOV=256 ×256 mm.

Dataset 2—Seventeen healthy adults participated in a modified version of the operational span (OSPAN) working memory task (3 blocks: OSPAN, Arithmetic and Baseline) during fMRI scans (Faraco et al., 2011) in a GE 3T Signa MRI system at the UGA BIRC under IRB approvals. The functional scans were acquired using a T2*-weighted single shot echo planar imaging (EPI) sequence and were aligned to the AC-PC line. Imaging parameters were the same as those used in Dataset 1. T1-weighted MRI images were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol with the same parameters used in Dataset 1.

Dataset 3—Repeated DTI/T1-weighted MRI scans of seven subjects were obtained from the ADNI-2 project (<http://adni.loni.ucla.edu/>). Imaging protocols and details are referred to the literature report (Jack et al., 2010).

In this work, we acquire and use three different multimodal T1-weighted MRI/DTI/task-based fMRI datasets for the evaluation and validation of the proposed methods, as summarized in Table 1. The working memory network in **Dataset 2** is used in section 3.1 to examine the effectiveness of two types of features and in section 3.4 to compare the prediction performance with image registration methods. **Dataset 2** is also used in section 3.6 to extend the proposed method for DICCOCOL (dense individualized and common connectivity-based cortical landmarks) (Zhu et al., 2012b) prediction. The semantic decision network in **Dataset 1** is used in section 3.2 to validate the choice of positive sample labeling rule introduced in section 2.2.2. The empathy network in **Dataset 1** is used in section 3.2 to verify that the framework is robust against different choices of template. All of the five

networks in **Dataset 1** and **Dataset 2** are used in section 2.2.3 to demonstrate the consistency of the distribution of ROI locations within each network across subjects and in section 3.3 for cross-validation. **Dataset 3** is used in section 3.5 to evaluate the reproducibility of the proposed method.

Preprocessing—Pre-processing steps of DTI data consist of brain skull removal, motion correction, and eddy current correction. The latter two steps are used to increase signal-to-noise ratio. Fiber tracking is performed via the MedINRIA (<http://www-sop.inria.fr/asclepios/software/MedINRIA/>). Brain tissue segmentation is performed on the DTI data via the approaches in Liu et al., 2007. Based on the brain tissue map, the gray matter (GM)/white matter (WM) cortical surface reconstruction is performed (Liu et al., 2008). As for the task-based fMRI data analysis, standard pre-processing steps and the activated foci detection are conducted via FSL FEAT. For detailed information about the task design and activated ROI detection, please refer to Zhu et al., 2012b and Faraco et al., 2011. Briefly, for each task, two-level activation detection with a mixed-effect model is performed on subjects using FSL FEAT. With a threshold of $z\text{-value} > 2.3$, and $p = 0.05$, cluster centers of activation are selected as group-wise ROIs. These ROIs are then transformed back into the individual space of each subject via the approaches in Zhu et al., 2012b. Five most consistently activated ROIs are detected from the empathy task, eight ROIs from the semantic decision making task, fifteen ROIs from the emotion task, and twelve ROIs from the fear task in **Dataset 1**. In addition, eight most consistent activation ROIs are detected from the working memory task in **Dataset 2**. Detailed information about the locations of those functional ROIs in the MNI_152 template space is reported in supplemental Table 1. Notably, the cortical surface reconstructed from DTI data is defined as the standard space within subject by default. Therefore, we use the FSL FNIRT to co-register DTI and T1-weighted MRI data and use FSL FLIRT to co-register DTI and fMRI data for each subject. Our rationale is that fMRI and DTI are both EPI (echo planar imaging) sequences and the geometric distortion from these two modalities tends to be similar (Li et al., 2010b). Therefore, the misalignment will be much less between fMRI and DTI images than the one between fMRI and T1-weighted MRI data, as demonstrated in Li, et al., 2010b. As to the co-registration between DTI and T1-weighted MRI, we adopt a nonlinear registration method (FSL FNIRT) to reduce the alignment error. As for the inter-subjects alignment, one of the training subjects is randomly selected as the template, and other training subjects and testing subjects in the prediction stage are linearly warped onto it via FSL FLIRT. The following training and prediction procedures will be conducted in this selected template space by default. It is worth noting that the contribution of linear registration to our prediction framework is limited to ensure that all subjects roughly have the global similarities, so that the PCA constraint and initial ROI location determination in the prediction stage can work properly. Our proposed framework can be deemed as a novel method that fine-tunes the predicted ROI locations.

2.2 Model Training

In section 2.2.1, we will first introduce two descriptive structural features that are extracted from DTI and T1-weighted MRI data. Then in section 2.2.2, we will introduce how to train the predictive models of functional ROIs from the regression point of view (GMKL). In section 2.2.3, we will adopt a coordinate PCA constraint that models the consistent ROIs location distribution patterns within each functional network, which complements the predictive models of ROIs. Essentially, both of the GMKL model and the PCA model are developed by considering group-wise information across training subjects. The difference between them is that the GMKL model describes functional ROI individually, while the PCA model considers all ROIs within a functional network.

2.2.1 Anatomical and Connectional Profiles—We adopt the 3D SIFT (scale-invariant feature transform) feature (Scovanner et al., 2007) for T1-weighted MRI image and the trace-map feature (Zhu et al., 2011a) for DTI image as the descriptive anatomical and connectional profiles of functional ROIs.

The 3D SIFT feature is originally extracted from T1-weighted MRI volume image. It is implemented on a tessellation-based orientation histogram, which is able to robustly describe 3D local morphological tissue structures within the neighborhood of a functional ROI. More specifically, the 3D SIFT feature is obtained on the voxel of interest (functionally activated voxels in this paper) by computing the 3D gradient orientations of the voxels within an $m \times m \times m$ neighborhood. Then, a histogram to which the gradient orientations are assigned is used as the 3D SIFT descriptor. Therefore, the 3D SIFT feature represents the local structure information, and importantly, it is invariant to image scale and rotation and robust to noise. As for the connectional profiles, we use the recently designed trace-map (Zhu et al., 2011a; Zhu et al., 2012b) as a descriptor of fiber connectivity patterns. Specifically, the trace-map is obtained on a surface vertex of interest by firstly extracting the fibers penetrating its neighborhood surface area. Then, the orientations of the extracted fiber bundles are mapped onto a unit sphere (Zhu et al., 2012b) and a histogram of the orientations is used as the trace-map descriptor to represent the distribution of the fiber trajectories. The major advantage of the trace-map feature is that it can effectively and quantitatively describe the global shape patterns of fiber bundles, thus representing the structural connectivity patterns (Zhu et al., 2011a; Zhu et al., 2012b). In this paper, we extract the 3D SIFT feature on the $11 \times 11 \times 11$ neighborhood of the original T1-weighted MRI volume image, and extract the trace-map feature on a 3-ring neighborhood area (the same size as the one in Zhu et al., 2011a; Zhu et al., 2012b) on the cortical surface. The neighborhood size of 3D SIFT feature is 11 because the radius of the cubic is approximately 5 mm, which coincides with the size (3-ring neighborhood) used to extract the trace-map.

Notably, as we use the cortical surface as the standard space within subject, we map the 3D SIFT feature extracted from the volume image onto the cortical surface vertices. First, we use the co-registration transform field between DTI and T1-weighted MRI to warp the vertex on the surface (DTI space) back into the T1-weighted MRI space, and second, the nearest volume voxel is searched for the vertex. The 3D SIFT feature of the voxel is assigned to the vertex. As for the trace-map feature, it is originally derived from each vertex on the cortical surface (Zhu et al., 2011a; Zhu et al., 2012b). After this step, each vertex on the cortical surface including the functional ROI vertices has two features, which can be extracted from the vertex of the cortical surface in both of the training and prediction stages.

2.2.2 GMKL Models—Based on the two descriptive features in section 2.2.1, our next objective is to design ROI prediction methodologies for each functional ROI. In this section, we will introduce how to train a GMKL model to distinguish an ROI from its neighbors in the two feature spaces. Because training and prediction stages are performed on surface, neighbors of an ROI vertex are defined as vertices within a k-ring area. Figs. 2(b1)-(b3) illustrate 1-ring neighbor vertices (green vertices) of activated ROI vertices (red vertices). The methodologies should meet the following two requirements. First, the model can leverage the discrimination power of the features. Second, the predictive model can effectively fuse the rich information from two structural profiles to facilitate the ROI prediction.

The core of GMKL is based on SVM and is used to meet the first requirement. That is to convert the functional ROI prediction into a regression problem. Three training subjects and three activated ROIs are used as illustrations in Fig.2. Taking ROI #1 in Fig.2 as an example, we define the three ROI #1 vertices (red) in the three training subjects and their

neighbours (green) as training sample denoted by i . In Figs.2 (c1)-(c3), we illustrate the three training sample datasets for the three ROIs in the joint feature space. We denote feature of i by $\vec{x}_i$. Then we label the training samples as positive if they are activated ROIs, while negative if they are not, and denote the label of i by y_i . Referring to the traditional form of the regression function:

$$f(\vec{x}) = w^t \phi_d(\vec{x}) + b \quad (1a)$$

where $\phi_d(\vec{x})$ can be considered as the joint feature space parameterized by d in this paper. Our objective is to distinguish positive samples from negative ones by optimizing parameters w and b based on the training data $\{(\vec{x}_i, y_i)\}$. The blue dashed circle in Figs.2 (c1)-(c3) represent the three trained GMKL models denoted by $G_i = \{w, b, d\}_i$. In the following texts, the anatomical 3D SIFT feature is denoted by $\vec{x}^a$ and the connectional trace-map feature is represented by $\vec{x}^c$.

Here, we apply Eq. 1a on our problem from the regression perspective of view rather than classification. The reason is that more than 1-ring neighbouring vertices are included as the training samples in real application (6-ring in this paper). If our problem is solved as a classification, negative samples (neighbours) will greatly outnumber positive samples (activated ROIs) and the classification results will be biased. Instead, by using regression scheme, we intuitively assume that the further the neighbour vertices are from the ROI vertices, the dissimilar they will be to the ROI vertices with regard to the two features (this will be explored in section 3.1), and therefore the more negative value y_i they will be labelled as. Hence, GMKL models draw no hard boundaries between positive samples and negative ones, like what is illustrated by the blue dashed circles in Figs. 2(c1)-(c3). Accordingly, the labelling rule for y_i is detailed in Table 2, supposing vertices within k -ring neighbourhood are included. For instance, the vertices on the 2nd ring will be labelled by $-1/(k-1)$.

The next objective is to fuse the two features, that is, the 3D SIFT and trace-map features. Generally, the GMKL not only optimizes the parameters w and b in Eq. (1a) via its SVM core, but also the parameters d as well. This provides us an effective way to fuse different feature spaces at the kernel level. Therefore, Eq. (1a) has an alternative classic dual representation:

$$f(\vec{x}) = \sum \alpha_i y_i \langle \phi_d(\vec{x}_i), \phi_d(\vec{x}) \rangle + b \quad (1b)$$

where $\langle \cdot, \cdot \rangle$ is dot product inside which the input data $\{(\vec{x}_i, y_i)\}$ only appear. A function that returns the value of the dot product is defined as a kernel (denoted by $k_d(\vec{x}_i, \vec{y}_i)$ in the GMKL) and can be parameterized by d . Based on this definition, we can tune the kernel as a linear combination of two sub-kernels as:

$$k_d(\vec{x}_i, \vec{x}_j) = \exp \left(- \left(d_a \phi_a^t(\vec{x}_i) A_a \phi_a(\vec{x}_j) + d_c \phi_c^t(\vec{x}_i) A_c \phi_c(\vec{x}_j) \right) \right) \quad (2)$$

where $\phi_a(\vec{x}) = \vec{x}^a$ and $\phi_c(\vec{x}) = \vec{x}^c$ denote anatomical and connectional feature spaces, $A = \{A_a, A_c\}$ complete the feature selection for either $\phi_a(\vec{x})$ or $\phi_c(\vec{x})$, and $d = \{d_a, d_c\}$ can be considered as the weights for linearly combining the two feature spaces. The parameter d , together with w and b , are all automatically optimized via GMKL if we input $\{(\vec{x}_i, y_i)\}$, i.e., the features and labels. For more details on GMKL, please refer to the Supplemental Materials and Varma et al., 2009.

As for the feature selection encoded in $A = \{A_a, A_c\}$, we adopt the Neighbourhood Components Analysis (NCA) (Goldberger et al., 2004) to learn the matrix $A = Q^t Q$ in order to linearly embed features of the labelled samples into lower dimensions. Importantly, other than PCA that deals with unlabelled data equally, the Q in NCA is the linear transformation of the original feature space that maximizes a stochastic variant of the labelled data, such that the distances between samples with different labels (positive or negative in this paper) will be maximized, while the ones with the same label minimized after the features are transformed by Q . Then, $\phi_a^t(\vec{x}_i) A_a \phi_a(\vec{x}_j)$ and $\phi_c^t(\vec{x}_i) A_c \phi_c(\vec{x}_j)$ in Eq. (2) can be rewritten in a feature transformation form as:

$$\phi_a^t(\vec{x}_i) A_a \phi_a(\vec{x}_j) = (Q_a \phi_a(\vec{x}_i))^t (Q_a \phi_a(\vec{x}_j)) = k_a(\vec{x}_i, \vec{x}_j) \quad (3)$$

$$\phi_c^t(\vec{x}_i) A_c \phi_c(\vec{x}_j) = (Q_c \phi_c(\vec{x}_i))^t (Q_c \phi_c(\vec{x}_j)) = k_c(\vec{x}_i, \vec{x}_j) \quad (4)$$

The general kernel function can therefore be rewritten in a compact format as:

$$k_d(\vec{x}_i, \vec{x}_j) = \exp(-(d_a k_a(\vec{x}_i, \vec{x}_j) - d_c k_c(\vec{x}_i, \vec{x}_j))) \quad (5)$$

in which the concept of fusing the two feature spaces on *the* kernel level is clearer.

2.2.3 Coordinate PCA Models of ROI Locations—Other than the GMKL model that deals with functional ROIs individually, the coordinate PCA model is designed for all of the ROIs within a functional network. The feasibility of applying coordinate PCA model to encode the distribution of functional ROI locations depends on the consistency of their distributions across subjects. In this work, the functional ROIs detected from the same task-based fMRI data are considered to be within the same functional network, and the coordinate PCA model is employed on each network separately. Mathematically, supposing there are n ROIs within a functional network of m training subjects, we extend the coordinates of the n ROIs of the j^{th} subject to a coordinate vector and use $d_j = [x_1, y_1, z_1, \dots, x_n, y_n, z_n]$ to denote it. Then, we obtain the PCA transform on the coordinate matrix $P = [d_1^T, \dots, d_m^T]$ by taking subjects as the features to be selected, and compute the ratios of the largest eigenvalue of the matrix to the eigenvalue sum (denoted by r), as reported in Table 3. The high values of the five functional networks (above 0.99) demonstrate the consistency of the functional ROIs location distributions across subjects, suggesting the feasibility of using the coordinate PCA models.

In summary, the trained predictive ROI model consists of two components: 1) the GMKL model for each ROI. Supposing there are n ROIs within a functional network, we use $G_i = \{a, b, d, Q_a, Q_c\}_i$ to denote the GMKL model for the i^{th} ROI, where w, b, d, Q_a and Q_c are the parameters of GMKL; 2) the coordinate PCA constraint denoted by the coordinate matrix $P = [d_1^T, \dots, d_m^T]$ for ROIs within the network. These two components will be used as the external and internal energy terms, respectively, in the prediction stage. Finally, in addition to the two major components, we also compute the average coordinates of each ROI across the training subjects that are linearly warped in the template space, and use them to generate the initial ROI locations and candidates in the prediction stage.

2.3 ROI Prediction

In the prediction stage, the T1-weighted MRI and DTI data of one testing subject in consideration will be used to predict all of the ROIs within a functional network. As illustrated in Fig. 3(b), the purpose of the prediction is to select one from multiple candidates

of one ROI to form a combination of ROI candidates (3 candidates for 3 ROIs highlighted by a triangle in Fig.3 (b)). In this way, the combination can best match the ROI coordinates distribution pattern, and the selected candidates can be the most possible ROIs with positive scores obtained via GMKLs. Generally, prediction can be formulated and solved as an energy minimization problem as:

$$E = (1 - \lambda) E_{\text{int}} + \lambda E_{\text{ext}} \quad (6)$$

where E_{int} (the internal energy term) denotes how much a combination of ROI candidates' coordinate distribution pattern of the network matches the learnt PCA model constraint

$P = [d_1^T, \dots, d_m^T]$ and E_{ext} (the external term) denotes how positive the candidate ROIs can be after they are scored by the GMKL regression model $G_i = \{a, b, d, Q_a, Q_c\}_i$ in the joint anatomical and connectional feature spaces. The prediction procedure is specifically detailed as follows.

1. Initialization—We initialize the search spaces of the n ROIs on the testing subject by firstly finding the nearest vertices, that is, the initialized candidates (the larger yellow vertices in Fig.3(a)), to the average coordinates of all training ROIs (the red vertices in Figs. 2(b1)-(b3)) in the template space. Then, we include all vertices within the k -ring neighborhoods of the initialized candidate and regard them as the candidate ROIs (all yellow

vertices in Fig.3(a)). We denote c_i^j as the j^{th} candidate of ROI i ($c_i^j \in C_i$ where C_i is the k -ring neighborhood). We extract the 3D SIFT and trace-map features for all candidate ROIs, denoted as $\vec{x}_c$. Then, the energy minimization is equivalent to searching for a combination

of candidates $((c_1^{j_1}, c_2^{j_2}, \dots, c_n^{j_n}) \in C_1 \times C_2 \dots C_n)$, which generates the minimal energy E . Here, the superscript j_i is used to indicate that the choice of candidate from C_i of ROI i is

independent from each other. Altogether, there will be $L = \prod_{i=1}^n \|C_i\|$ possible combinations, where $\|C_i\|$ denotes the vertex number in the k -ring neighbourhood C_i of ROI i .

2. Internal energy—As discussed in section 2.2.3, the coordinate PCA constraint encodes the location distribution patterns of all of the n ROIs within a functional network. Thus, in order to construct the internal energy term, we extract the coordinate vector

$\tilde{d}_l = [x_1, y_1, z_1, \dots, x_n, y_n, z_n]_l$ from the l^{th} candidate combination $(c_1^{j_1}, c_2^{j_2}, \dots, c_n^{j_n})_l$ and append it to $P = [d_1^T, \dots, d_m^T]$ in order to obtain $\tilde{P}_l = [d_1^T, \dots, d_m^T, \tilde{d}_l^T]$. It is straightforward that if $\tilde{d}_l$ follows the patterns encoded in P , then, the ratio $\tilde{r}_l$ from $\tilde{P}_l$ will be no less than r from P via PCA. We illustrate three combinations highlighted by colour triangles in Fig. 3(b). The location distribution pattern of the combination highlighted by blue colour appears to be more consistent than the other with those on three training subjects in Figs. 2(a1)-(a3), and the $\tilde{r}$ value is consequently higher. To minimize the internal energy, it is defined as:

$$E_{\text{int}} = \frac{r - \tilde{r}_l}{r} \quad (7)$$

3. External energy—For the candidate $c_i^{j_i}$ for ROI i in combination $(c_1^{j_1}, c_2^{j_2}, \dots, c_n^{j_n})_l$, we transform its anatomical and connectional features via the learnt NCA transformation Q_a and Q_c in the GMKL model $G_i = \{a, b, d, Q_a, Q_c\}_i$, respectively, i.e., $Q_a \phi_a(\vec{x}_{c_i})$ and $Q_c \phi_c(\vec{x}_{c_i})$. Then, we apply the learnt regression part of the model $G_i = \{a, b, d\}_i$ to score the

candidate c_i^{ji} . We use $S_i^{ji} \in [-1, 1]$ to denote the score for candidate c_i^{ji} . According to the labelling rule detailed in Table 2, the more positive score S_i^{ji} is, the more possible the candidate c_i^{ji} will be an ROI vertex. This procedure is also illustrated in Fig. 3(b). Candidates for three ROIs (yellow vertices) are respectively scored by the three GMKL models (the blue dashed circles) in the joint feature space (the white boxes). The three models are the same as those in the training stage (Figs. 2(c1)-(c3)). We consider the n ROIs at the same time and define the external energy as:

$$E_{ext} = 1 - \frac{1}{n} \sum_{i=1}^n S_i^{ji} \quad (8)$$

If we take the combination highlighted by blue colour triangle in Fig. 3(b) for an example and assume the three ROI vertices' PCA ratio r of the three training subjects in Fig. 2 is 0.95, then the internal energy and the external energy will be:

$$\begin{cases} E_{int} = \frac{0.95-0.9}{0.95} \\ E_{ext} = \left(1 - \frac{1}{3}(-0.2 - 0.2 - 0.4)\right) \end{cases} \quad (9)$$

4. Minimization of energy function— E_{int} and E_{ext} have been normalized to $[0, 1]$ before they are linearly combined. Ideally, the optimal combination can be obtained via a global search. However, the $L = \prod_{i=1}^n \|C_i\|$ possible combinations make it time-consuming. Thus, we conduct an iterative local search to seek the minimum. The algorithm is detailed in Appendix I.

3. Results

In order to evaluate the performance of the functional ROI prediction framework, separate *task-based* fMRI-derived activated ROIs from testing subjects are used as the benchmark in the prediction stage. The prediction error is defined as the Euclidean distance between the predicted ROIs and their benchmark counterparts. In this section, first, we will discuss the effectiveness of two types of features. Second, we will explore the influence of the parameters on the ROI prediction performance. Third, we will evaluate the ROI prediction results on the five functional networks in **Dataset 1** and **Dataset 2** via leave-one-out cross-validation. Fourth, as an application example, we separate **Dataset 2** into a training dataset and an independent testing dataset, and compare the prediction results with those obtained via image registration methods by *repeated random-sampling validation*. Fifth, as a reproducibility study, we apply the model trained on healthy subjects in **Dataset 1** and **Dataset 2** on MCI subjects in **Dataset 3**, in which there are two longitudinal DTI and T1-weighted MRI scans. Finally, as a generalization study, we use the ROI prediction framework to train and predict our recently developed Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCOLs) (Zhu et al. 2012b).

3.1 Effectiveness of Features

To demonstrate the effectiveness of the 3D SIFT and trace-map features, we examine their discrimination ability and consistency properties both visually and quantitatively. Discrimination ability indicates the relationship between activated ROI vertices and their neighboring vertices and consistency properties indicate the relationship among corresponding activated ROI vertices across subjects. For instance, we extract the two types of features from ROI #3 vertices in the working memory network on eight training subjects

in **Dataset 2**, and show them in the first rows in Fig. 4(a) and Fig. 4(b). The trace-map (Fig. 4(b)) is visualized in the format of unit sphere onto which the orientations of fiber bundles are mapped (Zhu et al., 2011a). Since it is difficult to visualize 3D SIFT for visual comparison, we simply show the feature in the format of histogram. The consistencies of these two features from ROI #3 across subjects can be visually observed within the first row. For comparison, we also show the features from some vertices on the 1-ring neighborhood vertices (the second rows in Fig. 4(a) and Fig. 4(b)) and some vertices on the 6-ring neighborhood (the third rows in Fig. 4(a) and Fig. 4(b)). The feature consistency within the second rows and the similarity of them to the first rows (ROI vertices) are substantially better than those of the third rows by visual examination.

Furthermore, we use the distance matrix to quantitatively demonstrate the discrimination power and consistency property of these two features (Fig. 5). In either vertical or horizontal direction of the distance matrix, the ROI #3 vertices from training subjects #1 to #8 are in the front (top-left corner). They are followed by the vertices in the further and further neighborhoods (i.e., from 1-ring to 6-ring neighborhood). The ring index color bars are shown beside the matrix. Within the k-ring neighborhoods, the vertices are also ordered from subject #1 to #8. The element of the matrix is computed in the same way as that for computing the kernel (Eq.2), but the two types of features are computed separately:

$$\begin{cases} k_a(\vec{x}_i, \vec{x}_j) = \exp(-\phi_a^t(\vec{x}_i) A_a \phi_a(\vec{x}_j)) \\ k_c(\vec{x}_i, \vec{x}_j) = \exp(-\phi_c^t(\vec{x}_i) A_c \phi_c(\vec{x}_j)) \end{cases} \quad (10)$$

For comparison, matrices generated from the features before and after feature selection via NCA are shown in the left column ((a) and (c)) and the right column ((b) and (d)) of Fig. 5, respectively. For the matrices in the left column, the feature selection matrices A_a and A_c are both identity matrices. The values of matrices are individually normalized into [0, 1] and color-coded by the same distance color bar.

By examining the left column, we can find that the matrices follow the trend of increasing distance from the left-top corner to the right-bottom corner. We highlight three areas in the matrices generated from the original features by the white boxes. The top-left box includes vertices within the 2-ring neighborhoods of functional ROI vertices from all 8 training subjects, while the bottom-right box includes the ones within the vertices on the 6-ring neighborhood. The lower distance values in the top-left box compared to the higher distance values in the bottom-right one in both matrices, demonstrate the feature consistency within the nearby neighborhood across subjects, and that this consistency drops while the vertices go further from the functional ROI vertices. Meanwhile, the bottom-left box includes the feature distances between the vertices on the 6-ring neighborhood and those within 2-ring neighborhoods. By comparison with the top-left box, the distance values in the bottom-left are substantially higher, demonstrating the group-wise discrimination power of these two features which can discriminate ROI vertices from those far away from them. In the matrices in the right column, the kernels used in GMKL follow the same trend. However, the transition from the low value to the high value along the diagonal direction from the top-left to the bottom-right in those matrices is swifter than the ones in the left column. The reason is that we label ROI vertices and their 1-ring neighbors as positive, while the others as negative and we apply NCA on these labeled features. Therefore, this result also demonstrates the effectiveness of NCA which maximizes a stochastic variant of the labelled data, such that the distances between the samples with different labels (positive or negative) will be maximized, while the ones with the same label will be minimized.

Also, we explore if the features extracted from the 3-ring neighborhood/11×11×11 cubes are appropriate to capture sufficient structural information. For trace-map, we extract fiber

bundles from 3-ring, 4-ring, 5-ring, and 6-ring neighboring areas of a vertex to generate the feature. Accordingly, $11 \times 11 \times 11$, $15 \times 15 \times 15$, $19 \times 19 \times 19$ and $23 \times 23 \times 23$ cubes of a voxel are used to generate the 3D SIFT features. Then, similar to Fig. 5, we select one subject and compute the distance matrices based on ROI #3 and all of its neighboring vertices within 6 rings. The matrices for the two types of features are computed separately (Figs. 6(a) and 6(b)). Moreover, within each ring index, taking vertices on the 6-ring for example (Figs. 6(c) and 6(d)), four features with different extraction sizes are separated. Specifically, the top-left white box in Fig. 6(d) is a distance matrix based on $11 \times 11 \times 11$ cube 3D SIFT features extracted from all vertices on the 6-ring neighborhood of ROI #1. The vertices within each of the four blocks on the diagonal are arranged in the same order.

We firstly examine the 6-ring block in Figs. 6(c) and 6(d), where vertices on the 6-ring are far away from each other, so that their features can vary from each other greatly. We define the blocks highlighted by the white boxes as the similarity maps among this group of vertices. We can observe that patterns of the four diagonal blocks are similar to each other, indicating that the four choices of feature extraction sizes do not greatly impact the relationship between the vertices in the feature kernel. This result can also be observed in other ring blocks highlighted by white boxes in Figs. 6(a) and 6(b). In addition, we show the features derived from functional ROI #3 vertex with four different extraction sizes in Figs. 6(e) and 6(f). It can be observed from the first row/column that the distance value is very low, suggesting that the four choices of extraction sizes generated fairly similar features. Based on all the results above, we can conclude that the 3-ring trace-map and the $11 \times 11 \times 11$ -cube 3D SIFT can capture sufficient local structural information compared to other three sizes, and therefore we use them in the following sections of this paper.

3.2 Parameters in Model Training and ROI Prediction

In both of the training and prediction stages, we use the 6-ring region ($k=6$) as the training sample dataset size or candidate dataset size in the prediction stage. The reasons are two-fold. First, as shown in Fig. 4, the similarity of the vertices on the 6-ring with the functional ROI vertices is relatively low. Thus, a larger neighbourhood size is unnecessary. Second, in the prediction stage, considering the distance between the initial location and the benchmark functional ROI, 6-ring is large enough to cover most distances between them. To demonstrate this point, we compute the distance between the benchmark ROI generated from separate fMRI data and its initial guess location. We also compute the distances between the benchmark ROIs and their neighbouring vertices on the 6-ring neighborhood. The distributions of these two distances are presented in Fig. 7. The total numbers of the vertices in these two distributions are normalized to 1, respectively, for comparison. It can be clearly seen that the mean distance between the initial location and the benchmark is approximately 9 mm, which is far less than the distance between two vertices separated by 6-rings on the surface (approximately 12 mm). Therefore, 6-ring neighbourhood is a suitable choice for building a search space, which guarantees that most locations of activated ROIs to be predicted can be reachable.

In the training stage, we label the activated functional ROI vertices and their 1-ring neighbourhood as positive, as shown in Table 2. To justify this choice, we use the semantic decision making network in **Dataset 1** as a test bed and apply different labelling rules and the prediction framework. The leave-one-out strategy is applied on the subjects in the dataset and the average prediction errors are used to measure the performances of different labelling rules. The results are detailed in Table 4. On average, the prediction errors obtained based on labelling vertices within 1-ring and 2-ring as positive samples (shaded rows) are substantially smaller than others, and they are relatively close to each other (6.24 mm and

6.20 mm). Therefore, we use the labelling rule in the second row in Table 4 in all experiments throughout this paper.

In the prediction stage, we use the following parameters: $\tilde{k}$, $\varepsilon = 0$ and $t_{max} = 10$. For most cases, the predicted ROI locations are stable when the iteration number is less than 10. As to the weight λ , we sample 11 values with a constant step within the range of $[0, 1]$ and evaluate the prediction results with the benchmark functional ROIs on the five functional networks via leave-one-out validation. The average prediction errors of each network with different weights are shown in the rows in Fig. 8. The column on the most left side and the column on the most right side show the prediction errors with either E_{int} (PCA model) or E_{ext} (GMKL models) alone, respectively. It can be clearly seen that joint use of two energy terms E_{int} and E_{ext} performs better than either of the term alone. The best performance in different networks can be obtained based on the different weights highlighted by the black boxes. Therefore, we use the λ values in the black boxes for the five functional networks throughout the paper.

In order to evaluate the effect of different choices of the template onto which all of other training and testing subjects are linearly registered, we use five randomly selected training subjects as templates and use the empathy network in **Dataset 1** as a test bed to examine the ROI prediction framework. All the parameters in the five runs are the same. The average prediction errors of the five runs are 6.68 mm, 6.55 mm, 6.89 mm, 7.12 mm and 6.81 mm, respectively. This result suggests that the different choices of template have no significant impact on the ROI prediction performance. In fact, the initial location can be directly affected by using different templates. Essentially, the relatively large search scope (6-ring) discussed previously can ensure that the ROI prediction framework is robust to the template choice.

3.3 Validation of the Framework via Task-based fMRI Data

We use the leave-one-out scheme on the eleven subjects in **Dataset 1** and the eight subjects in **Dataset 2** to validate the proposed framework. We also apply the framework using only one feature space (3D SIFT or trace-map) without the PCA constraint, and the framework using two feature spaces without the coordinate PCA constraint. To demonstrate the result, we use bubbles (radius = 3mm) to highlight the benchmark vertices and the predicted ROI vertices. The prediction ROIs (color bubbles) of the five functional networks obtained from the abovementioned different methods, together with the benchmark ROIs (white bubbles), are shown in the first two rows of Fig. 9. Quantitatively, we compute the average prediction errors obtained from the leave-one-out experiments and show them in Fig. 9(f). On average, the prediction errors of the four methods (the joint model with PCA constraint, the joint model without PCA constraint, the model with T1-weighted MRI feature, and the model with DTI feature) are 6.38 mm, 7.06 mm, 8.06 mm and 8.12 mm, respectively. From both visual inspection and quantitative comparisons, it is evident that the prediction errors of the five functional networks via joint modeling of anatomical and connectional profiles are substantially smaller than those via the model with the features individually. The prediction error decreases by 12.41% or 13.05%, compared with the model using T1-weighted MRI feature or DTI feature alone. The prediction errors via joint modeling with coordinate PCA constraint further decreased by 9.63% compared with those without coordinate PCA constraint (20.84% and 21.43% compared to the model with T1-weighted MRI feature or DTI feature individually). We perform t-test on the prediction errors between three pairs of methods on the five functional networks: joint model with PCA constraint vs. joint model without PCA constraint, joint model with PCA vs. model with T1-weighted MRI feature, and joint model with PCA vs. model with DTI feature. The p-values are reported in Table 5. It is evident that most of them are less than 0.05, suggesting the statistical significance of the

improvement by the joint model with PCA constraint. One exception is the p-value of joint model with PCA constraint vs. joint model without PCA constraint for empathy network, because the optimal weight λ equals to 1 as shown in Fig. 8, indicating that adding the PCA constraint or not makes no difference on the prediction performance. All of the results in Fig. 9 and Table 5 demonstrate that the functional ROI prediction capability can be significantly improved by combining the two modalities of T1-weighted MRI and DTI data and can be further improved by adding the coordinate PCA constraint.

3.4 Comparison with Image Registration Methods

Here, we use eight subjects of **Dataset 2** to train the ROI prediction model and the other nine subjects as an independent testing dataset. The repeated random-sampling validation is performed (repeated time=100) and the average prediction errors and standard deviations of the 8 ROIs across testing subjects are shown in Table 6. For comparisons, we use four linear or nonlinear image registration methods to warp the 8 training subjects to the testing subject space, and map the functional ROIs on the training subjects to the testing subjects accordingly. The finally predicted ROIs are the centroids of the corresponding registered functional ROIs from 8 training subjects in the testing subject space. The DTI space is used as standard space within subjects as introduced in section 2.1 and the FA (fractional anisotropy) image derived from DTI data is used in registration because of two reasons. First, fMRI data does not contain adequate structural information, so it is not fair to compare the registration results based on fMRI data with our method; Second, T1-weighted MRI data is not used because mapping functional ROIs from fMRI to T1-weighted MRI images could introduce greater registration errors than mapping them to DTI data, because the geometric distortions in DTI and fMRI tend to be similar (Li et al., 2010b). The default configurations of the four registration methods are adopted here and only the key parameters are listed as follows. FSL FLIRT (Jenkinson and Smith, 2001): cost function: correlation ratio; interpolation method: trilinear; degrees of freedom: 12. FSL FNIRT (Andersson et al., 2008): Flirt transform is applied first; isotropic warp resolution: 10 mm×10 mm×10 mm; the order of the B-spline functions modeling the warp-fields is 3; multi-resolution sub-sampling parameters: 4×2×1. ANTS (Avants et al., 2008): transformation model: symmetric normalization transformation model; metric: cross-correlation. HAMMER (Shen and Davatzikos, 2002): Image segmentation is applied via FAST first. Iteration number: 50; step ratio: 0.05; neighborhood search size 12×10×8.

The distances between the predicted ROIs and the benchmark ROIs on the testing subjects are computed. On average, the prediction errors via our method, FSL FLIRT, FSL FNIRT, ANTS and HAMMER are 6.04 mm, 7.89 mm, 8.01 mm, 7.49 mm and 7.96 mm, respectively. We further perform t-test on the prediction errors between each registration method and our method, and the p-values are 0.024, 0.016, 0.019 and 0.021, respectively. These results demonstrate that our method is significantly better than the above mentioned image registration methods. However, it should be noted that these compared image registration algorithms were originally designed for anatomical alignments, but not specifically for functional ROI prediction studied here. If these image registration methods could take the advantage of multimodal DTI/MRI data in the future, their performances in functional ROI localization could be substantially better than what was reported in this paper.

Finally, taking one out of the one hundred cross-validation experiments as an example, we show the distribution of the prediction errors of the 72 ROIs (8 working memory ROIs × 9 testing subjects) obtained via the proposed method and the ones via a linear registration method (FSL FLIRT) in Fig.10. Statistically, the average prediction error of our proposed method is 5.97 mm. Notably, there are many ROIs that can be accurately predicted with

errors down to 2 mm - 4 mm (the blue bins in Fig.10). This improvement, compared with linear registration method (red bins in Fig.10), can be considered significant even in fMRI spaces (voxel resolution 3.75 mm $\times$ 3.75 mm $\times$ 4 mm).

3.5 Application on MCI Dataset

We apply our ROI prediction methods on the longitudinal ADNI-2 dataset (**Dataset 3**) under the premise that the anatomical and connectional structures in ADNI-2 mild cognitive impairment (MCI) subjects are not significantly different from healthy controls, and that no significant difference can be found between the two longitudinal scans given that the time interval is around 3 months. In order to measure the distances between the predicted ROIs from two longitudinal scans, we linearly register the FA images of the first scan onto the second one via FSL FLIRT for each subject, because our methods are conducted on DTI-derived cortical surfaces. Before we measure the distances between predicted ROIs of two runs, the linear image registration errors are measured between two cortical surfaces by searching the nearest vertex on the first-run surface for each vertex on the second-run surface and computing the Euclidian distance that defined as the registration error between these two vertices. We map the registration errors onto the surface of the second scans (Supplemental Fig. 1) and the average error is around 1.26 mm. This result confirms that it is feasible to measure the prediction errors between two runs in the same space, i.e., the cortical surface of the second run. As an example, the prediction results of the empathy network from one subject are shown in the bottom row of Fig. 11, and the small distances between predicted ROIs of two longitudinal scans can be observed. Furthermore, we extract the fiber bundles from the predicted ROIs of two scans, and show them with those extracted from three training subjects as templates in Fig. 11. As for the anatomical profile, we show the transverse slices of T1-weighted MRI which pass the predicted ROIs of two scans and those of the three templates. It should be noted that the T1-weighted MRI slices are extracted from the subjects in their original volumetric images because 3D SIFT features are extracted individually in the original space. Numerically, we report the distances between ROIs from two longitudinal scans of the five networks in Table 7. On average, the reproducibility errors between the two scans are 3.73 mm, 3.47 mm, 3.41 mm, 3.81 mm and 3.43 mm in the five networks, respectively. In summary, the high similarity among the predicted ROIs in two scans and the template ones in terms of the fiber bundles and anatomical profiles (Fig. 11), as well as the small distances between the predicted ROIs of two scans (Table 7), all support the reproducibility of our ROI prediction methods.

3.6 Application on DICCCOLs

As another application example, we apply our ROI prediction framework to predict 95 functionally labeled DICCCOLs (Zhu et al., 2012b), which have both consistent connectional profiles across subjects and corresponding functional identifications (Zhu et al. 2012b). The same 10 subjects used to generate the model DICCCOLs in Zhu et al. 2012b in **Dataset 2** are used in this section. By taking DICCCOLs as consistent landmarks across subjects, we substitute the DICCCOLs for the functional ROIs in both of the training and prediction stages. It should be noted that the PCA constraint cannot be directly conducted on the 95 DICCCOLs by taking all them as a network, because it remains unknown if they are within a functional network and the 95 ROIs across many subjects might introduce large ROI location distribution variation that the PCA cannot handle. Instead, because the 95 DICCCOLs consist of 9 functional networks (Zhu et al., 2012b), we apply the model training and prediction framework on each network separately. In Fig. 12, we show the average prediction errors via the leave-one-out cross-validation scheme on the 10 subjects similar to that in section 3.3. Also, we compare the prediction errors among three methods: the joint model with PCA constraint, the model with only anatomical feature, and the model with only connectional feature. On average, the prediction errors are 6.30 mm, 8.40 mm and

8.76 mm for the three methods, and the prediction error of the joint model with PCA constraint decreases by 28.08% and 25.01%, compared to the other two methods. These results further demonstrate the superiority of the proposed method via joint model with PCA constraint.

4. Discussion and Conclusion

We present a novel computational framework for functional cortical ROI prediction by jointly modeling the anatomical and connectional profiles. We train the model of ROI location distributions and the joint regression models of anatomical and connectional features derived from functional ROIs. Prediction of functional ROIs on testing subjects is performed by matching the trained models onto the multimodal T1-weighted MRI and DTI data of each individual subject. The prediction problem is formulated as an energy minimization problem, in which ROI location distribution and joint regression model of anatomical and connectional features are defined as the internal and external energy terms, respectively. Extensive experimental results have demonstrated that the prediction accuracy can be significantly improved by fusing anatomical and connectional profiles from the regression perspective and by ROI location distribution constraint. The functional ROI prediction performance significantly outperforms those based on linear or nonlinear image registration algorithms, and the reproducibility and generalization ability of the framework are also promising. Our work has demonstrated that connectional and anatomical models of functional cortical ROIs have remarkable prediction capability, providing further support to the close relationship between brain structure and function, such as the concept of connectional fingerprint in Passingham et al., 2002.

Our interpretation of the fact that the ROI prediction accuracy can be significantly improved by fusing anatomical and connectional profiles from the regression perspective is that both of the anatomical and connectional features offer complementary information that characterizes the functional locations of cortical ROIs. Furthermore, the GMKL takes the advantages of the richness of the two features by automatically adjusting the weights, which takes the tradeoff between the two features in the kernel level. In Supplemental Fig. 2 and Supplemental Table 2, we further explored how the two features spaces can provide complementary information. We used the functional ROI vertex as the benchmark to compute the distance between itself and its other neighboring vertices in 3D SIFT and trace-map feature space separately. The feature distance is defined as the same as those in Fig. 5. For the purposes in this paper, which is functional ROI prediction for both features, only one minimal distance value is expected to appear in the location of the functional ROI vertex for both features, as illustrated in Supplemental Fig. 2(d). This case occurs in 56.5% of all functional ROIs used in this paper, suggesting the reasonable effectiveness of the framework in both training and prediction stages. However, it is possible to have one distinctive feature such that unexpected minimum can be found, e.g., those illustrated in Supplemental Figs. 2(a) and 2(b). Fortunately, for these two cases, the other feature still holds the desired situation. Altogether, these two cases account for approximately 34.7% of all ROIs. Interestingly, after we train GMKL models for the two ROIs in Supplemental Figs. 2(a) and 2(b), parameters $\{d_a, d_c\}$, which are automatically determined, are $\{0.43, 1.50\}$ and $\{1.10, 0.10\}$, respectively. Although the value of $\{d_a, d_c\}$ cannot be compared directly across cases, we can still find that $d_c > d_a$ when it only has varying 3D SIFT features, and $d_a > d_c$ when it only has distinctive trace-map features. This is the reason that we used GMKL to fuse the features in order to take advantages of both feature spaces. Only for a few rare cases (8.7%), in which we have both varying features, GMKL may be trapped in *unexpected* minima and generate biased models. We explored all functional ROIs in this paper following the way in Supplemental Fig. 2 and summarized the ratios of the four situations in Supplemental Table 2. The statistical results demonstrate that it is relatively rare that the two

feature spaces could be in conflict and thus cause the occurrences of local minima. In the future, adding more training subjects might be a possible solution to explore, in order to further reduce the chance of local minima.

Currently, our methods focus on the most consistent ROIs, but other potentially important factors such as descriptive power of features, ROI location variability across subjects and ROI size are not taken into consideration yet. These factors may be the targets of further improvements under this framework. In the near future, first, we plan to investigate and explore whether other anatomical and connectional features extracted from the corresponding functional ROI locations can be more consistent and distinguishable from their neighboring locations. Second, it has been reported that the peak activations detected from fMRI data may be shifted by some factors as detailed in Li et al., 2010, causing the reduced consistency of structural features derived from these locations. Therefore, optimization methods like those proposed in Li et al., 2010 could be used to optimize the consistency of the ROI locations first, and then learning predictive ROI models, *as the second stage*, can be performed. Third, we can possibly substitute more powerful models that will integrate the variability information into the constraint for the current coordinate PCA model that only encodes the consistent information. For instance, the group-wise replicator dynamics approach (Ng et al., 2009) could be an alternative approach to model the variability of the structural connectivity among the ROIs. Fourth, as for the ROI size, a hierarchical scheme could be a possible approach, in which the training methods could be performed on ROIs with multi-scales, e.g., from the lobe scale (rough) to the vertex/voxel level (fine). As a result, the ROI prediction framework would be accomplished by following the rough-to-fine scale order to fine-tune the predicted locations step by step. Fifth, the fusion methodology of the two neuroimaging modalities in this paper is linear (Eq. (2) and Eq. (5)), which could be further improved in order to fully take the advantages of two modalities. For instance, the nonlinear combination of the two modalities could be explored in the future. Finally, the current ROI prediction framework is conducted on the cortical surface, which causes the limitation that it can only be used for cortical ROI prediction. We predict that a similar sub-cortical ROI prediction procedure may be designed directly on volume image/ sub-cortical surface in the future.

Finally, we plan to apply the ROI prediction framework in the future on large-scale networks of multimodal fMRI and DTI/T1-weighted MRI datasets for structural/functional connectivity analysis, e.g., those in Zhu et al., 2012b. We believe these predictive models of functional ROIs can be potentially applicable to many other application scenarios which have only DTI and/or T1-weighted MRI data, but without task-based fMRI data. This capability could substantially contribute to provide network nodes for elucidation of possible altered connectivities in brain diseases such as Alzheimer's disease (Jack et al., 2010) and Schizophrenia (Zhang et al., 2012b).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix I: Algorithm: Iterative Local Search

1. $q \leftarrow 0$
2. Initialize $(c_1, c_2, \dots, c_n)_q$.
3. repeat
4. Define the local search space $\tilde{C}_i^q \subset C_i^q$ to be the $\tilde{k}$ -ring size neighborhood ($\tilde{k} < k$) centered at the initialized location $c_i^q \in (c_1, c_2, \dots, c_n)_q$
5. Globally search for the combination $\min (c_1, c_2, \dots, c_n)^{\min}_q$ with the minimal energy $E[(c_1, c_2, \dots, c_n)^{\min}_q]$ in the search space of $\tilde{C}_1^q \times \tilde{C}_2^q \times \dots \times \tilde{C}_n^q$.
6. **until** converged, i.e., $\sum_{i=1}^n \|c_i^q - c_i^{q-1}\| \leq \varepsilon$ **or** iteration times exceed t_{max} , where $\|c_i^q - c_i^{q-1}\|$ denotes the Euclidean distance between two locations of successive iterations.

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Research Highlights

1. Joint modeling of anatomical and connectional features for ROI prediction.
2. A machine learning framework for developing predictive models of ROIs.
3. High accuracy in predicting large-scale functional network ROIs.
4. High reproducibility in ROI prediction.
5. Wide applications in scenarios without task-based fMRI data.

Figure 1.

The flowchart of our framework: model training and ROI prediction. Purple box: the training stage; green box: the prediction stage; black dashed box: evaluation of the prediction results based on concurrent task-based fMRI data.

Figure 2.

Illustration of the two training models. Three training subjects and three activated ROIs are used in this illustration. (a1-a3): Illustration of coordinate distribution of three activated ROIs across the training subjects. The distribution will be used to train the PCA models of ROI locations; (b1-b3): Illustration of three activated ROIs and their neighbors (only 1-ring neighbors of the ROIs are used in the illustration); (c1-c3): Illustration of GMKL models for the three ROIs. Red vertices/dots denote activated ROIs, while green ones denote their neighbors. More details are referred to the main text.

Figure 3.

Illustration of the prediction stage. One testing subject and three ROIs to be predicted are used in this illustration. (a): Illustration of initializing candidates (yellow vertices) for ROIs on the testing subject; (b): Illustration of applying GMKL models and PCA model onto the testing subject to obtain two types of scores accordingly. More details are referred to the main text.

Figure 4.

(a) 3D SIFT features extracted from ROI #3 vertices across 8 training subjects are shown in the first row (peak). Features extracted from some vertices on the 1-ring neighbors and 6-ring neighbors of the ROI vertices are respectively illustrated in the second row (1-ring) and the third row (6-ring); (b) Illustration of the trace-map features in the same way as (a).

Figure 5.

The matrices of the distances between ROI #3 and the vertices within their neighborhoods in the feature spaces, that is, the trace-map space ((a) and (b)) and 3D SIFT space ((c) and (d)) in 8 training subjects. (a) and (c) are obtained based on the original features, while (b) and (d) are based on the features transformed by NCA. The elements of the matrices are color-coded according to the right bottom color bar. The values of matrices are individually normalized into [0, 1]. The left-bottom ring index bar denotes how the columns and rows are organized. Please refer to the main text for the interpretation of the white boxes.

Figure 6.

Similar to Figure 5, this figure shows the matrices of the distances between ROI #3 and the vertices within their neighborhoods in the feature spaces with different features extraction sizes for one training subject. Figures (a) and (c) show the trace-map matrices, while figures (b) and (d) show the 3D SIFT matrices. In figures (a) and (b), the white boxes highlight the sub distance matrices of the vertices on the k-ring neighborhood. (c) and (d) show two zoomed-in boxes in (a) and (b), which highlight the distance matrices of the 6-ring neighbor vertices. The boxes in (c) and (d) highlight the distance matrices generated with the same feature extraction size. (e) and (f) show the distance matrices of the features derived from ROI #3 vertex with four different extraction sizes. The feature extraction size is shown beside the matrices. The values of matrices in (a) and (b) are individually normalized into [0, 1]. More details are referred to the main text.

Figure 7.

The normalized distributions of distances between the benchmark functional ROIs and the initial guess locations (blue bins), and the distances between the benchmark functional ROIs and the vertices on its 6-ring neighbourhood (red bins). The total numbers of the vertices in these two distributions are normalized to 1, respectively. guarantees that most locations of activated ROIs to be predicted can be reachable.

Figure 8.

The average prediction errors with different weights for the five functional networks. The prediction errors for the same network with different λ values are displayed in the same row. The optimized weight with regard to the lowest prediction error for each network is highlighted by the black box.

Figure 9.

Validation results by using task-based fMRI-derived functional ROIs as the benchmark. Benchmark ROIs (the white bubbles) and predicted ROIs (color-coded as the same as (f)) of five functional networks are illustrated by bubbles on one subject selected from **Dataset 1** and **Dataset 2** ((a)-(e)). For visualization purpose, the predicted ROIs obtained via the joint model without PCA model (Joint for short), via anatomical features (T1 for short) and via connectional features (DTI for short) and benchmark ROIs are shown in the first row (a1-e1). The predicted ROIs obtained via the joint model with the coordinate PCA constraint (Joint with Constraint for short) and benchmark ROIs are shown in the second row (a2-e2). Comparison of the average prediction errors (mm) with standard variation of the five networks is illustrated in (f).

Figure 10.

The distributions of the prediction errors obtained via our method and a linear registration method (FSL FLIRT) on independent testing working memory fMRI datasets.

Figure 11.

T1-weighted MRI profiles and fiber bundles extracted from the predicted empathy network ROIs of the two scans of one MCI subject, as well as from three training subjects (T for short). The predicted ROIs in two scans are overlapped and shown in the bottom row after being linearly registered into the same space. Yellow bubbles: ROI vertices on training subjects; purple bubbles: predicted ROI vertices on the first scans of the MCI subject; blue bubbles: predicted ROI vertices on the second scans of the MCI subject. The ROI locations on T1-weighted MRI slices are highlighted by the red crosses.

Figure 12.

Comparisons of prediction errors for 95 functionally-labeled DICC COLs among different methods via leave-one-out cross-validation. DICC COL IDs are shown in the horizontal axis, and the vertical axis represents the average prediction errors (*mm*).

Table 1

Summary of the three different datasets regarding their modalities, functional networks and the sections in which the datasets are used.

Dataset	Types	Networks	Sections
Dataset 1	T1-weighted MRI, DTI, fMRI	Emotion, Empathy, Fear, Semantic decision making	2.2.3, 3.2, 3.3,
Dataset 2	T1-weighted MRI, DTI, fMRI	Working memory	2.2.3, 3.1, 3.3, 3.4, 3.6
Dataset 3	T1-weighted MRI and DTI	None	3.5

Table 2

The rules of training sample labelling.

Neighborhood (Ring)	Peak	1	2	3	4	...	k-1	k
y_i	1.0	0.5	$-1/(k-1)$	$-2/(k-1)$	$-3/(k-1)$	...	$-(k-2)/(k-1)$	-1.0

Table 3

The ratios of the largest eigenvalue to the eigenvalue sum obtained from the coordinate PCA in the five networks.

Network	Emotion	Empathy	Semantic Decision Making	Fear	Working Memory
<i>r</i>	0.9968	0.9983	0.9986	0.9986	0.9981

Table 4

The average prediction errors obtained based on different labelling rules. The borders between positive and negative neighbourhoods are highlighted by the dashed lines.

Average Prediction Errors (mm)	Labeling Rules						
	Peak	1 ring	2 ring	3 ring	4 ring	5 ring	6 ring
6.82	1	-1/6	-2/6	-3/6	-4/6	-5/6	-1
6.24	1	1/2	-1/5	-2/5	-3/5	-4/5	-1
6.20	1	2/3	1/3	-1/4	-2/4	-3/4	-1
7.40	1	3/4	2/4	1/4	-1/3	-2/3	-1
8.04	1	4/5	3/5	2/5	1/5	-1/2	-1

Table 5

The p -values ($\times 10^{-2}$) of t -tests between the prediction errors by different methods. (C short for Joint model with PCA constraint, J short for Joint model without PCA constraint, T short for model using T1 feature alone without PCA constraint, and D short for model using DTI feature along without PCA constraint). It is noted that there is no difference between C vs. J for the empathy network.

Networks	Emotion	Empathy	Semantic Decision Making	Fear	Working Memory
C vs. J	0.14	100	1.31	0.39	2.97
C vs. T	0.057	2.14	0.39	0.24	0.13
C vs. D	0.003	5.33	1.75	0.59	0.83

Table 6

Prediction errors via different methods on independent testing working memory fMRI datasets based on *repeated random-sampling validation* (mean $\pm$ standard deviation).

ROI	FLIRT	FNIRT	ANTS	HAMMER	Our Method
1	8.48 $\pm$ 2.46	7.46 $\pm$ 2.97	8.00 $\pm$ 1.79	7.68 $\pm$ 4.34	5.15 $\pm$ 1.91
2	7.62 $\pm$ 1.67	8.03 $\pm$ 2.58	6.65 $\pm$ 2.17	8.37 $\pm$ 2.96	5.94 $\pm$ 2.08
3	6.28 $\pm$ 2.07	7.01 $\pm$ 2.11	7.38 $\pm$ 2.96	6.74 $\pm$ 2.85	6.27 $\pm$ 2.41
4	7.02 $\pm$ 3.19	8.04 $\pm$ 2.83	7.48 $\pm$ 2.54	6.80 $\pm$ 2.44	5.67 $\pm$ 1.62
5	8.84 $\pm$ 2.35	8.28 $\pm$ 2.40	7.02 $\pm$ 2.12	8.57 $\pm$ 2.62	5.03 $\pm$ 1.89
6	6.62 $\pm$ 2.69	6.76 $\pm$ 2.39	7.91 $\pm$ 2.83	7.56 $\pm$ 3.70	6.49 $\pm$ 2.10
7	9.82 $\pm$ 2.24	10.12 $\pm$ 2.50	8.24 $\pm$ 2.40	10.36 $\pm$ 3.11	8.08 $\pm$ 2.69
8	8.45 $\pm$ 2.65	8.40 $\pm$ 3.05	7.20 $\pm$ 2.92	7.66 $\pm$ 2.07	5.68 $\pm$ 3.13

Table 7

Average reproducibility errors of predicted functional ROIs in five functional networks: 1: emotion, 2: empathy, 3: semantic decision making, 4: fear, and 5: working memory.

ROI Network	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	4.59	4.21	4.18	3.64	3.99	3	2.6	3.97	3.89	3.16	2.6	4.39	3.67	4.3	3.78
2	3.77	3.89	2.34	3.48	3.86	-	-	-	-	-	-	-	-	-	-
3	4.28	3.41	3.01	3.31	3.4	3.78	3.49	2.62	-	-	-	-	-	-	-
4	3.82	4.27	3.68	4.83	4.69	3.97	3.52	2.63	4.06	3.27	2.62	4.4	-	-	-
5	3.32	3.34	3.3	3.73	3.24	3.29	3.08	4.13	-	-	-	-	-	-	-