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Subregions of the human superior frontal gyrus and their connections

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ABSTRACT

The superior frontal gyrus (SFG) is located at the superior part of the prefrontal cortex and is involved in a variety of functions, suggesting the existence of functional subregions. However, parcellation schemes of the human SFG and the connection patterns of each subregion remain unclear. We firstly parcellated the human SFG into the anteromedial (SFGam), dorsolateral (SFGdl), and posterior (SFGp) subregions based on diffusion tensor tractography. The SFGam was anatomically connected with the anterior and mid-cingulate cortices, which are critical nodes of the cognitive control network and the default mode network (DMN). The SFGdl was connected with the middle and inferior frontal gyri, which are involved in the cognitive execution network. The SFGp was connected with the precentral gyrus, caudate, thalamus, and frontal operculum, which are nodes of the motor control network. Resting-state functional connectivity analysis further revealed that the SFGam was mainly correlated with the cognitive control network and the DMN; the SFGdl was correlated with the cognitive execution network and the DMN; and the SFGp was correlated with the sensorimotor-related brain regions. The SFGam and SFGdl were further parcellated into three and two subclusters that are well corresponding to Brodmann areas. These findings suggest that the human SFG consists of multiple dissociable subregions that have distinct connection patterns and that these subregions are involved in different functional networks and serve different functions. These results may improve our understanding on the functional complexity of the SFG and provide us an approach to investigate the SFG at the subregional level.

Introduction

The superior frontal gyrus (SFG) is located at the superior part of the prefrontal cortex and is considered to be composed of several cytoarchitecturally different subregions including the Brodmann areas of 6, 8, 9, and 32 (Brodmann, 1909; Petrides and Pandya, 1999, 2002). As summarized in Fig. S1, the SFG has been reported to be involved in a variety of cognitive and motor control tasks. Specifically, the posterior part of the SFG including the supplementary motor area (SMA) is mainly activated by motor tasks (Chouinard and Paus, 2010; Martino et al., 2011; Nachev et al., 2008); the lateral part of the SFG is involved in execution within working memory (du Boisgueheneuc et al., 2006; Owen, 2000; Owen et al., 1998; Petrides, 2000) and attention (Corbetta et al., 2008; Fox et al., 2006); and the medial part of the SFG is commonly deactivated during the cognitive-related processing and has been ascribed to be a component of the default mode network (DMN) (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). The above-mentioned evidence suggests the existence of subregions in the human SFG. Furthermore, each SFG subregion is supposed to have its unique connection pattern and to participate in its specific function. However, the SFG has always been described as a single brain area and few studies have focused on the anatomical and functional heterogeneities of the SFG, especially the distinct connection patterns of the SFG subregions.

Most of our knowledge concerning subregions of a structure of interest comes from post-mortem analyses of cyto- or myeloarchitectures (Vogt et al., 1995; Zilles and Amunts, 2009, 2010), which enables us to parcellate the human cortex at a microscopic resolution (Schleicher et al., 1999). However, these methods only consider the internal microstructure of a brain area and not its connections to other brain areas. A connectivity-based parcellation will provide additional information to improve our understanding of the structural and functional specializations of a particular brain area. Diffusion tensor tractography (DTT) can show inter-regional anatomical connectivity in vivo (Johansen-Berg and Rushworth, 2009) and has been extensively used to parcellate heterogeneous brain regions based on their anatomical connection patterns, such as the thalamus (Behrens et al., 2003b), the medial frontal cortex (Johansen-Berg et al., 2004), the cingulate cortex (Beckmann et al., 2009), and the amygdala (Bach et al., 2011). The parcellation

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results were consistent with those from cytoarchitecture and tract tracing studies (Johansen-Berg et al., 2004; Mars et al., 2011).

In contrast with that DTT can exhibit anatomical connection between two brain regions; resting-state functional connectivity (rsFC) can reveal functional correlation between every two regions by evaluating the temporal coherence of the low frequency blood oxygen level dependent (BOLD) signals. The combination of these methods will simultaneously show both the anatomical and functional connection patterns of a brain area, which is essential for understanding its functional specialization. Based on previous cytoarchitectural and functional studies of the SFG in both humans and animals, we hypothesize here that the human SFG includes at least three functionally independent subregions that are involved in different brain functional networks. To test this hypothesis, we applied a DTT-based parcellation scheme to the human SFG using a spectral clustering algorithm and studied the anatomical and functional connection patterns of each SFG subregion from the perspective of functional networks. Then we validated the parcellation result by similar analysis of the bilateral SFGs in another independent data set with different scan parameters. Finally, the anatomical connection pattern of each SFG subregion was investigated by observing fingerprint of each subregion with target regions and the rsFC pattern of each subregion was analyzed by seed-based rsFC analysis.

Materials and methods

Subjects and MRI data acquisition

Two different data sets were obtained in this study. Data set 1 was obtained from 12 healthy, right-handed subjects (5 males; mean age: 25.5 years, range: 22–28 years), whereas data set 2 was obtained from another cohort of 8 healthy, right-handed subjects (3 males; mean age: 22.3 years, range: 19–24 years). Data set 1 included diffusion tensor imaging (DTI), structural MR imaging, and resting-state functional MRI (fMRI) data, whereas data set 2 only included DTI with different scan parameters and structural MR imaging data. All MR images were acquired using a Signa HDx 3.0 T MR scanner (General Electric, Milwaukee, WI, USA) with an eight-channel phased-array head coil. DTI data were acquired by a single-shot echo planar imaging sequence. The DTI parameters of data set 1 were: repetition time (TR) = 15 s; echo time (TE) = 73 ms; matrix = 128 × 128; field of view (FOV) = 256 × 256 mm^2; in-plane resolution = 2 mm × 2 mm; slice thickness = 2 mm without gap; 69 axial slices; 50 non-collinear diffusion gradients (b = 1000 s/mm^2) and 3 non-diffusion-weighted images (b = 0 s/mm^2). Sagittal 3D T1-weighted images were acquired by a brain volume (BRAVO) sequence (TR/TE = 7.8/3.0 ms; FOV = 256 × 256 mm^2; matrix = 256 × 256; in-plane resolution = 1 mm × 1 mm; slice thickness = 1 mm, no gap; 188 slices). The DTI parameters of data set 2 were the same as for data set 1 except for the following: TR = 10 s; TE = 64.2 ms; slice thickness = 3 mm; 45 axial slices; and 55 diffusion gradients. The structural images of data set 2 were the same as for data set 1 except for the following: TR/TE = 8.0/3.0 ms; and 176 slices. The resting-state fMRI data of data set 1 were obtained using a gradient-echo single-shot echo-planar imaging sequence with the following parameters: TR/TE = 2000/30 ms; slice thickness = 3 mm; 1 mm gap; matrix = 64 × 64; FOV = 240 × 240 mm^2; in-plane resolution = 3.75 mm × 3.75 mm; 38 transverse slices; 180 volumes. During fMRI scans, all subjects were instructed to keep their eyes closed, to stay as motionless as possible, to think of nothing in particular, and not to fall asleep. The study was approved by the Medical Research Ethics Committee of Tianjin Medical University, and all participants provided written informed consent forms.

Tractography-based SFG parcellation

ROI definition

The boundaries of the SFG were defined according to descriptions in a prior study (John et al., 2006). The anterior boundary was the anterior termination of the olfactory sulcus, which separated the SFG from the frontal polar; the posterior boundary was the superior part of the precentral sulcus; the infero-lateral boundary was the superior frontal sulcus; and the infero-medial boundary was the cingulate sulcus. According to this definition, the SFG here consisted of BA 6, 8, 9 and 32. The SFG was firstly extracted from the Harvard–Oxford cortical structural atlas with a threshold of 25% minimum probability. Then we manually delineated the region of interest (ROI) of the SFG in the Montreal Neurological Institute (MNI) space according to the boundary definition by John et al. (2006). After that, the seed ROI was transformed back to the individual native DTI space using the inverse of linear transformation and nonlinear deformations. Finally, the seed ROI of the SFG was checked on the coronal, axial and sagittal planes slice-by-slice in every subject to ensure that the ROI of each subject satisfied with the boundary definition by John et al. (2006).

DTI data preprocessing

The DTI and the T1-weighted images were both preprocessed using tools including FMRIB's Diffusion Toolbox (FSL 4.0; http://www.fmrib.ox.ac.uk/fsl) and statistical parametric mapping (SPM8) package (http://www.fil.ion.ucl.ac.uk/spm). After correction for eddy current and head motion, the skull-stripped T1-weighted images were firstly co-registered to the b = 0 images in native DTI space, and then transformed to the MNI space. Finally, the inverted transformation parameters were used to transform the seed and target masks from MNI space to the native DTI space with nearest-neighbor interpolation.

Probabilistic tractography

Probabilistic tractography was performed using the FSL software package. Probability distributions for fiber directions at each voxel were calculated using multiple fiber extension (Behrens et al., 2007) based on a previously published diffusion modeling approach (Behrens et al., 2003a, 2003b). To compensate for the distance-dependent effect, probability counts were corrected by the length of the pathway. Connectivity distribution is the expected length of the pathway that crosses each voxel times the number of samples that cross it (Tomassini et al., 2007). We then estimated the connection probability between each voxel in the seed region and any other voxel of the brain by calculating the number of traces from the seed voxel to the target voxel (any other voxel in the brain). To reduce false positive connections, we thresholded the path distribution estimates using a connection probability of $p < 0.002$ (10 out of 5000 samples). Finally, the connection profiles were stored at a lower resolution of 5 × 5 × 5 mm^3 (Johansen-Berg et al., 2004). Based on the native connectivity matrix, a cross-correlation matrix was calculated that quantified the similarity between the connectivity profiles of the seed voxels (Johansen-Berg et al., 2004).

Tractography-based parcellation

The cross-correlation matrix was then fed into a spectral clustering algorithm with an edge-weighted centroidal Voronoi tessellation for image segmentation (Wang et al., 2009) for automatic clustering. The goal of clustering the cross-correlation matrix was to group together voxels of the seed region that share similar connection profiles with other voxels of the brain. The number of component clusters was, however, chosen by the experimenter.

Selection of cluster number

In order to avoid an arbitrary choice of the number of clusters, we used a cross-validation method to determine the number of clusters which yielded optimal consistency across subjects and hence the optimal number of clusters. Specifically, we employed a leave-one-out