Frequency dependent hub role of the dorsal and ventral right anterior insula

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ABSTRACT

The right anterior insula (rAI) plays a crucial role in generating adaptive behavior by orchestrating multiple brain networks. Based on functional separation findings of the insula and spectral fingerprints theory of cognitive functions, we hypothesize that the hub role of the rAI is region and frequency dependent. Using the Human Connectome Project dataset and backtracking approach, we segregate the rAI into dorsal and ventral parts at frequency bands from slow 6 to slow 3, indicating the frequency dependent functional separation of the rAI. Functional connectivity analysis shows that, within lower than 0.198 Hz frequency range, the dorsal and ventral parts of rAI form a complementary system to synchronize with externally and internally-oriented networks. Moreover, the relationship between the dorsal and ventral rAIs predicts the relationship between anti-correlated networks associated with the dorsal rAI at slow 6 and slow 5, suggesting a frequency dependent regulation of the rAI to brain networks. These findings could improve our understanding of the rAI by supporting the region and frequency dependent function of rAI and its essential role in coordinating brain systems relevant to internal and external environments.

Introduction

The human brain operates as a highly organized multi-scale system consisting of multiple structural and functional networks (Bullmore and Sporns, 2009; Chan et al., 2016). The execution of normal brain function requires orchestration among networks such as the balance between task-positive and task-negative networks (Fox et al., 2005). Inter-network cooperation depends on the modulation of particular brain regions which usually serve as functional hubs (Cole et al., 2013; Liu et al., 2015). The right anterior insula (rAI) has been thought to be an important hub in coordinating brain networks to produce adaptive behavior in various cognitive processes (Chen et al., 2013; Sridharan et al., 2008). Specifically, it has been confirmed that the rAI modulates the default mode network (DMN) and cognitive control network in attention-demanding tasks (Sridharan et al., 2008; Wen et al., 2013).

Recent studies have suggested that the rAI could be further divided into dorsal and ventral functional sub-parts (Chang et al., 2013; Deen et al., 2011). The right dorsal AI (rdAI) is a core region of the salience

network (SN) and is connected to cognitive control networks. Typically, it is activated in almost all tasks involving goal-directed cognition (Chang et al., 2013; Nomi et al., 2016). By contrast, the right ventral AI (rvAI) is rich in Von Economo neurons and has been demonstrated to be involved in interoception, emotion, and social awareness via connections with the limbic system (Evrard et al., 2012; Uddin, 2015). Similar to the limbic system, the DMN is primarily involved in internal thoughts, such as self-reference processing, episodic memory, planning and so on (Andrews-Hanna et al., 2010; Mason et al., 2007; Raichle, 2015), indicating that the DMN is more likely to be connected with the rvAI. Therefore, we surmised that the rdAI and rvAI may be prone to connect with externally- and internally-oriented systems, respectively (Menon and Uddin, 2010; Zabelina and Andrews-Hanna, 2016).

Besides the functional separation hypothesis, the spectral fingerprints hypothesis (Maris et al., 2016; Siegel et al., 2012) suggests that disparate cognitive processes are implemented by different brain networks embedded in specific frequency bands. For instance, neural oscillations in beta and gamma bands have been found to play distinctive roles in top-

down and bottom-up information streams (Bastos et al., 2015). The externally-oriented and internally-oriented systems have also been reported to be dominated by delta-theta and alpha-beta bands, respectively (Lakatos et al., 2016). The spectral fingerprints of these two systems in the low frequency blood oxygen level dependent (BOLD) signal fluctuations is undetermined yet, although frequency-specific functions have been widely observed in this frequency range in cognitive processes and clinical cases (Martino et al., 2016; Palva and Palva, 2012; Wang et al., 2016).

In the current study, we investigated whether the hub role of the rAI is region and frequency dependent. Specifically, we used the Human Connectome Project (HCP) 100 unrelated dataset to explore whether the externally- and internally-oriented systems are connected to different parts of the rAI and whether these connections are frequency dependent. In reverse, whether the sub-parts of rAI are connected to other systems other than the conventional externally- and internally-oriented systems and whether these connections are frequency dependent.

Methods

Data acquisition

The resting-state functional magnetic resonance imaging (rfMRI) data of 82 subjects were used in this study. The sample was selected from the HCP 100 unrelated dataset (https://db.humanconnectome.org) with the criteria that respiratory, cardiac, and head movement data are available in all runs (rfMRI_REST1_LR, rfMRI_REST1_RL, rfMRI_REST2_LR, and rfMRI_REST2_RL). REST1 and REST2 were acquired on two different days. The HCP scanning protocol was approved by the local Institutional Review Board at Washington University in St. Louis. Informed consent was obtained from all subjects. All participants were scanned on a customized Siemens 3-T connectome-Skyra scanner. The imaging parameters used to collect the rfMRI data were as follows: TR = 720 ms; TE = 33.1 ms; flip angle = 52°; 2 mm isotropic voxels (FOV = 208 × 180 mm; 72 slices); multiband factor = 8; echo spacing = 0.58 ms; bandwidth (BW) = 2 290 Hz/px; volumes = 1 200. Full details on the HCP dataset could be seen in Van Essen et al.'s article (Van Essen et al., 2013).

Data preprocessing

The data with minimal preprocessing pipeline (Glasser et al., 2013) was used. This pipeline includes artifact removal, motion correction and registration to standard space. Standard preprocessing procedure was further applied to the data according to Finn et al.'s study (Finn et al., 2015) which included removal of the linear trend, removal of linear components related to the six motion parameters and their first derivatives, regression of respiratory and cardiac noises, the mean time courses of white matter and cerebrospinal fluid as well as the global signal, smoothing with a full-width half-maximum (FWHM) of 6 mm. The time series was band-pass filtered with the ideal filter (including six frequency bands: slow 6: 0.001–0.01 Hz, slow 5: 0.01–0.027 Hz, slow 4: 0.027–0.073 Hz, slow 3: 0.073–0.198 Hz, show 2: 0.198–0.5 Hz, and slow 1: 0.5–0.694 Hz). The higher frequency boundary was determined by the Nyquist theorem ((1/0.72 s)/2 ≈ 0.694 Hz), whereas the lower boundary was determined by the length of data (1/(1200 * 0.72 s) ≈ 0.001 Hz). The filtered time series of each run was normalized by subtracting the mean and dividing by the standard deviation. The normalized time courses were linked together, forming a series of 4 800 time points.

The segmentation of the rAI with backtracking approach

To investigate whether the task-positive and task-negative networks are connected to different parts of the rAI, we first computed the functional connectivity (FC) between regions of interest (ROIs) in these two networks and the rAI. The FC analysis within predefined six frequency bands was performed based on ROIs proposed by Fox et al. (2005). Task-positive regions were centered in the intraparietal sulcus (−25, −57, 46), the frontal eye field (25, −13, 50), and the middle temporal region (−45, −69, −2). Task-negative regions were centered in the medial prefrontal cortex (−1, 47, −4), posterior cingulate cortex (−5, −49, 40), and angular gyrus (−45, −67, 36). The radius of each ROI was 6 mm. The target region of FC was determined with the rAI template (Deen et al., 2011). The voxel-wise temporal correlation between each ROI and the target region was computed and transformed to the Fisher's z value in each frequency band. Of note, we regressed out the global signal to improve the specificity of correlations for different ROIs as suggested by Murphy and Fox (2017). Because the global signal regression could induce negative correlation (Murphy and Fox, 2017), we replicated the FC analysis using data without global signal regression to check the influence of this bias.

In order to obtain the functional parcellation of the rAI, conjunction analysis was performed in each frequency band. Following Fox et al.'s study (Fox et al., 2005), the effective region of rAI was determined by one sample t-test ($p < 0.05$, z > 3, cluster size > 17 voxels) at each frequency band. If the voxels in the rAI have significant positive correlation with seeds in the task-positive network or negative correlation with seeds in the DMN, they were labeled as 1; while voxels have significant negative correlation with seeds in the task-positive network or positive correlation with seeds in the DMN were labeled as −1. The voxels without significant correlation with any of the seeds were equals to 0. The labeled voxels were then overlaid, resulting in regions with labels from 0 to ±6. The subparts of rAI were defined as regions with label ≥5 or ≤ −5 (Fox et al., 2005).

The FC pattern of dorsal and ventral parts of the rAI

To investigate the functional connectivity patterns (FCPs) of rdAI and rvAI and their frequency effect, the voxel-wise FC was conducted based on two seeds in the rAI in each frequency band. The region and frequency effects were evaluated with the repeated measures analysis of variance (ANOVA) using SPM12 (www.fil.ion.ucl.ac.uk/spm). The frequency bands and seeds were served as within subject factors. Post hoc analyses were conducted using paired-samples t-tests. All resulting maps were corrected using family-wise error (FWE) method ($p < 0.05$) for multiple comparisons (Worsley et al., 1996).

The relationship between rdAI-rvAI correlation and the role of network reconciliation

We further asked whether the relationship between the rdAI and rvAI influences their role of network reconciliation. To answer this question, we conducted the Pearson's correlation analysis (1) between the rdAI-rvAI relationship and the anti-correlated systems associated with the rdAI, and (2) between the rdAI-rvAI relationship and the anti-correlated systems associated with the rvAI. The relationship between the rdAI and rvAI and that between the anti-correlated systems were assessed with the mean signal in each ROI. The ROIs of anti-correlated systems were determined by regions with positive or negative effects in paired-samples t-tests.

Results

The task-positive network and DMN are connected to different parts of the rAI

Because there is no prior evidence about the distinctive roles of subparts of the rAI in modulating the task-positive network and DMN, we cannot use predefined templates of rdAI and rvAI. Instead, we used the backtracking approach to determine whether the rAI could be separated into two different parts based on the FC with seeds in the task-positive