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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

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https://doi.org/10.1016/j.neuroimage.2017.10.004 Received 29 June 2017; Accepted 2 October 2017 Available online 3 October 2017 1053-8119/© 2017 Elsevier Inc. All rights reserved. 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-

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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) = 2290 Hz/px; volumes = 1200. 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 \approx 0.694 Hz), whereas the lower boundary was determined by the length of data (1/(1200 * $0.72 \text{ s}) \approx 0.001 \text{ Hz}$). 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, -4)-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 task-positive network or positive correlation with seeds in the DMN, they were labeled as 1; while voxels have significant negative 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 and that between 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 network and DMN. The conjunction analysis shows that seeds in the taskpositive network tend to be positively connected to the rdAI (Fig. 1, yellow part) whereas those in the DMN tend to be positively connected with the rvAI (Fig. 1, cyan part). The negative connections are opposite to the positive connections. The dorsal-ventral segmentation can be seen in frequency bands of slow 6, 5, 4, and 3, indicating the band-limited segmentation of rAI. The dorsal-ventral segmentation is independent of global signal regression, as shown by almost the same distribution of rdAI and rvAI with data without global signal regression (see Fig. S1).

Effects of seed, frequency, and their interactions

The ANOVA shows that the seed effect spreads over almost the whole brain with interlaced distribution, except for part of the primary visual and sensorimotor cortices (Fig. 2), indicating that the FCPs of rdAI and rvAI cover almost the whole brain in the interphase way. The frequency effect is mainly located in the sensory region (the visual, auditory, olfactory, and somatosensory cortices) as well as the limbic system (Fig. 2), indicating that communications between the rAI and external- and internal-worlds are influenced by frequency. The interaction of seed by frequency is primarily located in the AI, DMN, fronto-parietal network and limbic system (Fig. 2), including both externally- and internallyoriented systems.

Complementary FCPs of rdAI and rvAI

We examined the resting-state whole brain functional connectivity associate with rdAI and rvAI, respectively. Similar to previous findings (Chang et al., 2013; Deen et al., 2011; Nomi et al., 2016; Touroutoglou et al., 2012), the rdAI is positively related to the dorsal and ventral attention networks and sensorimotor network (SMN), while the rvAI is positively linked to the DMN and limbic system (Fig. 3). By contrast, the rdAI is negatively connected to the DMN, while the rvAI is negatively associated with the dorsal and ventral visual streams as well as the SMN. The complementary pattern appears at frequency bands from slow 6 to slow 3. In other words, the positive connection of the rdAI is to an externally-oriented system involving in cognitive and motor control, whereas that of the rvAI is to an internally-oriented system involving in interoceptive, emotion, and self-related processes. Conversely, the negative connection of the rdAI is to an internally self-related system whereas that of the rvAI is to an externally visual-motor system. The complementary connective pattern of rdAI and rvAI is independent of global signal regression (see Fig. S2).

The correlation between the rdAI and rvAI predicts the anticorrelated systems associated with the rdAI. Significant negative correlations are found between the rdAI-rvAI relationship and the anti-correlated systems associated with the rdAI at slow 6 and slow 5 (Fig. 4). There are no significant correlations between the rdAI-rvAI relationship and other systems (-0.182 < r < 0.152, p > 0.101). In other words, the effective modulation of rdAI to the anti-correlated systems dependents on the anti-correlation between the rdAI and rvAI in a frequency dependent way.

Discussion

In this study, we demonstrated that the rAI could be divided into two functional parts which are frequency dependent. Specifically, their functional connections are focused on from the slow 6 to slow 3 frequency bands. The dorsal and ventral parts of rAI are not simply connected to the cognitive- and emotional-related systems, or to the externally- and internally-oriented systems. Instead, the rvAI is specially connected to the limbic internal system whereas the rdAI and rvAI are linked to output- and input-related external systems, respectively. These findings may improve our understanding of the low frequency spectral fingerprints of cognition and the two coordinated systems in our brain.

The externally- and internally-oriented systems associated with the rAI

The role of rAI has not been fully understood. Initially, the cognitionemotion dichotomy has been used to describe the functional separation of the dorsal and ventral anterior cingulate cortex and insula (Bush et al., 2000; Chang et al., 2013). In line with this, Touroutoglou et al. (2012). suggested two SNs in the human brain based on the FC of rAI. They found that the dorsal and ventral SNs are related to attentional and affective functions, respectively. However, the cognition-emotion dichotomy of rdAI and rvAI has become increasingly challenged in recent years (Lindquist et al., 2012; Pessoa, 2008; Uddin et al., 2014). On the contrary, the internal-external dichotomy has garnered more support (Menon and Uddin, 2010; Nomi et al., 2016; Zabelina and Andrews-Hanna, 2016). This perspective agrees with most findings about the role of rAI (Uddin, 2015; Uddin et al., 2014). Accordingly, we hypothesized that the task-positive network and DMN should be connected to the rdAI and rvAI, respectively.

In fact, the results show two somewhat different externally- and internally-oriented systems associated with the rAI. Specifically, the rdAI is positively associated with the goal-directed system and negatively related to the DMN. This result is merited because the rdAI is activated in almost all task domains accompanied by the deactivation of the DMN (Binder, 2012; Kurth et al., 2010). Similar to the evidence that the rdAI coordinates the task-positive network and DMN (Chen et al., 2013; Wen



Fig. 1. The functional parcellation of the right anterior insula. Based on seeds in the task-positive network and default mode network, the functional connectivity patterns are separated in the dorsal and ventral parts of the right anterior insula. The functional parcellation is remarkable in lower frequency range from slow 6 to slow 3.



Fig. 2. The effects of seed and frequency and their interaction. The functional connectivity patterns of the right dorsal and ventral anterior insula are interlaced in widespread regions (left). The frequency effect is primarily located in the sensory, motor, and limbic systems (middle). The seed by frequency interaction is mainly lies in the anterior insula, default mode network, fronto-parietal network, and limbic system (right). The results are corrected with FWE method (p < 0.05).



Fig. 3. Functional connectivity patterns of the rdAI and rvAI in frequency bands from slow 6 to slow 3. The rdAI is positively connected to the goal-directed system and negatively connected to the default mode network. The rvAI is positively linked to the default mode network and limbic system and negatively linked to the sensory system. The results are corrected with FWE method (p < 0.05). rdAI: right dorsal anterior insula; rvAI: right ventral anterior insula.



Fig. 4. The relationship between rdAI and rvAI could predict the coordinated ability of the rdAI in slow 6 and slow 5 frequency bands. The more negative the correlation between the rdAI and rvAI, the larger difference between the rdAI based anti-correlated systems.

et al., 2012), we suggest that the rvAI devotes itself to internal processing while inhibiting the input of external information. This role is supported by plenty of Von Economo neurons in the vAI which have a central role in

interoception, emotional experience and social awareness (Craig, 2009). Based on these evidence, we expand the external-internal dichotomy to a more detailed model and show it in Fig. 5. In this model, the rdAI is



Fig. 5. The model of coordinated roles of the rdAI and rvAI. The rdAI and rvAI modulate the externally- and internally-oriented systems, respectively. Being different from the previous model, we show the two systems in details that the externally-oriented systems associated with the rdAI and rvAI are relevant to output and input information, respectively. Furthermore, the rvAI is particularly related to the limbic system.

engaged in the externally-oriented system. It coordinates the task-positive and task-negative networks to produce adaptive behavior (Sridharan et al., 2008; Wen et al., 2012). More importantly, we find the internally-oriented role of the rvAI. The rvAI may be engaged in internal self-referential processing (e.g., the somato-self associated with the limbic system and the social-self associated with the DMN) while restraining the distraction of external information. These roles are identical to the function of vAI in homeostasis and the function of Von Economo neurons in self-awareness (Cauda et al., 2013; Namkung et al., 2017).

Furthermore, the positive correlation between the rdAI and rvAI could disturb the modulation of the rdAI to the anti-correlation between the task-positive network and DMN, suggesting that the anti-correlated systems are not solely determined by the rdAI. The relationship between the rdAI and rvAI is of importance for the coordinating function of rdAI, indicating the balance between functional integration and functional separation.

Frequency specific functional systems of the rAI

The frequency effect of the functional systems associated with the rAI could be understood from three facets: (1) the functional connection of the rAI is focused on the very low frequency range from slow 6 to slow 3; (2) the frequency specific local connections within the low frequency range; and (3) the frequency dependent modulation of the rdAI-rvAI relationship to inter-network correlation.

First, the FC of rdAI and rvAI appears only at frequency range from slow 6 to slow 3. The lack of FC at slow 2 and slow 1 may be due to decreased FC strength and increased noise as frequency increases, although we have regressed out head motion parameters, respiration and cardiac noises (Lin et al., 2015; Thompson and Fransson, 2015). Alternatively, some studies have suggested that the higher frequency range really has particular physiological meanings (Lin et al., 2015; Thompson and Fransson, 2015). Compared with BOLD signal fluctuations in the infra-slow frequency range (0.01-0.1 Hz), those in the slow frequency range (0.1–1 Hz) has got much less attention, resulting in inadequate understanding of its psychophysiological meanings which warrants future investigations (Boubela et al., 2013; Gohel and Biswal, 2015; Yuan et al., 2014). The current results add new evidence to the functional significance of low frequency BOLD signal fluctuations, indicating that the BOLD signal fluctuations in higher frequency range deserve further research.

Second, the frequency effect within the low frequency range is primarily located in the sensory, motor, and limbic systems. These regions are primarily involved in exogenous and endogenous information processing. The lack of frequency effect in the association cortex may be due

to differentiated cytoarchitectures or functions of different brain regions (Song et al., 2014). The natural or dominant frequency of the brain is found to be region-specific in higher frequency range (Murray et al., 2014; Rosanova et al., 2009), leaving its frequency characteristics in the lower frequency range (<1 Hz) largely unknown. Recently, the frequency specificity of different brain regions has been constantly reported (Baria et al., 2011; Song et al., 2014; Zuo et al., 2010), indicating that frequency specificity is pervasive even in the very narrow low frequency band (0.01-1 Hz). The results that frequency effect appears in regions involved in information processing rather than in information integration suggest that these two kinds of regions possess different frequency characteristics. In previous studies, we observed responses in the supplementary motor area in a wider frequency range than those in the task control network (Wang et al., 2014, 2015). It, therefore, seems that different brain regions can communicate with other regions in distinctive frequency bands depending on spatial, time, or cognitive factors (Siegel et al., 2012). These factors are warranted in future studies to elucidate mechanisms of frequency-specific organizations of brain networks in the low frequency range.

Third, the relationship between the rdAI and rvAI influences the coordinated capability of the rdAI to the anti-correlated systems in a frequency specific means. Of note, this is the first study to uncover the frequency characteristics of the coordinated role of the subparts of rAI. It seems that the coordinated role the rdAI dependents on the relationship between the rdAI and rvAI in slow 6 and slow 5 frequency bands, whereas in the higher frequency range, the rdAI and rvAI play their roles independently. This result is in line with the perspective that more complex and integrated functions are executed in lower frequency range (Penttonen and Buzsáki, 2003). Although the dominant frequency of each brain function is thought to be established by evolution and experience (Schroeder and Lakatos, 2012), each brain region has been suggested to have specific intrinsic frequency determined by the characteristics of neural system (Li et al., 2015; Murray et al., 2014; Rosanova et al., 2009). We show that the functional segregation and functional integration from the point of frequency dependence, shedding new light on the functional coordination and frequency characteristics of brain systems.

Overall, the frequency specific functional relationships are consistent with recent viewpoint that different brain regions have distinctive intrinsic frequency (Murray et al., 2014) and coherent with other regions in different frequencies to fulfill various psychological activities (Siegel et al., 2012). This underlying hypothesis may provide us a frequency route to decoding complicated brain functions.

Conclusions

In summary, we demonstrated for the first time that the externallyand internally-oriented systems have different connection patterns with the rdAI and rvAI. The frequency specificity is pervasive at the system level. It influences not only the strength of inter-regional FC but also the functional segregation and functional integration.

Author contributions

Y.W., L.Z., and H.C. designed the experiment; Y.W., L.Z., and Q.Z. analyzed the data; Y. F., L.Z., Q.Z., Q.C., W.L., X.D., B.B., and H.C. wrote the paper.

Competing financial interests

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.10.004.

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