OXFORD

Cerebral Cortex, 2023, **33**, 1739–1751
https://doi.org/10.1093/cercor/bhac169
Advance access publication date 3 May 2022
Original Article

How distinct functional insular subdivisions mediate interacting neurocognitive systems

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Recent neurocognitive models propose that the insula serves as a hub of interoceptive awareness system, modulating 2 interplaying neurocognitive systems: The posterior insula (PI) receives and integrates various interoceptive signals; these signals are then transmitted to the anterior insula for processing higher-order representations into awareness, where the dorsal anterior insula (dAI) modulates the prefrontal self-control system and the ventral anterior insula (vAI) modulates the amygdala (AMG)-striatal reward-seeking circuit. We sought to test this view using a multimodal approach. We first used a resting-state functional magnetic resonance imaging (fMRI) approach with a sample of 120 undergraduate students. Then, we unpacked the neuro-cognitive association between insular connectivity and cognitive performance during an Iowa gambling fMRI task. Lastly, an independent Open Southwest University Longitudinal Imaging Multimodal dataset was used to validate the results. Findings suggested that the dAI was predominantly connected to the prefrontal regions; the vAI was primarily connected to the AMG–ventral–striatum system; and the PI was mainly connected to the visceral-sensorimotor system. Moreover, cognitive scores were positively correlated with FC between dAI and the self-control process of ventrolateral prefrontal cortex and were negatively correlated with FC between vAI and the reward-seeking process of orbitofrontal cortex and subgenual anterior cingulate cortex. The findings highlight the roles of our theorized subinsular functionality in the overall operation of the neural cognitive systems.

Key words: insula; functional connectivity; somatic marker hypothesis; Iowa gambling task; subregions.

Introduction

The insular cortex (the insula) has been shown to be relevant for and activated in various cognitive tasks. Its role is often explained with a neural cognitive somatic marker model, suggesting that the insula (i) mediates the reception of interoceptive and body states signals, which are translated into what may be experienced as a subjective feeling, emotional experience, and self-awareness of urge (Damasio, 1994, 1999; Craig 2002, 2010; Craig and Craig 2009) and (ii) biases individuals' behaviors by sensitizing and/or weakening regions involved in reward-seeking and self-control (Droutman, Read, et al. 2015). A growing body of evidence suggests that through the abovementioned functional roles, insular activity can influence attention (Eckert et al. 2009; Menon and Uddin 2010; Nelson et al. 2010), decision-making (Kuhnen and Knutson 2005; Weller et al. 2009; Xue et al. 2010; Clark et al. 2014; Sellitto et al. 2016; Poppa and Bechara 2018), addiction (Naqvi et al. 2007; Naqvi and Bechara 2009; Clark et al. 2014; Venniro et al. 2017), goal-directed cognition (Brass and Haggard 2010; Hoffstaedter et al. 2012), and switching between networks (Sridharan et al. 2008; Menon and Uddin 2010; Manuello et al. 2018; Varjačić et al. 2018).

Such effects are assumed to accrue through the ability of the insula to modulate the excitability and potentiation of interplaying neurocognitive systems (Droutman, Read, et al. 2015). First, the neurocognitive system that mediates reward-seeking, is largely amygdala (AMG)–striatum (STM)-dependent. It typically mediates fast, automatic, unconscious, and habitual behaviors. Second, the neurocognitive system that mediates self-control, is primarily prefrontal cortex-dependent. It mediates deliberation, planning, predicting future outcomes of selected behaviors, and exerting inhibitory control (Verdejo-García and Bechara 2009). Specifically, the insula acts as a "gate" that responds to homeostatic perturbations and generates interoceptive signals (Noël et al. 2013; Naqvi et al. 2014). These signals can exaggerate reward-seeking activity in social–emotion-related limbic systems while weakening activity in prefrontal systems concerned with inhibitory and self-control. It can also modulate prefrontal activity in the other direction, to consume more resources, when

Received: January 29, 2022. **Revised:** April 9, 2022. **Accepted:** April 10, 2022

attention is needed (Wood and Bechara 2014). Thus, the insula can influence cognitive processes that engage the abovementioned neurocognitive systems, namely in situations that involve risk and reward.

Despite these important insights, there is a notable gap in the literature. Specifically, there is growing evidence that the insula, as a relatively large substrate, has subregions (e.g. dorsal anterior, ventral anterior, and posterior) with different functional responsibilities (Deen et al. 2011; Chang et al. 2012; Uddin et al. 2014; Droutman, Read, et al. 2015; Turel et al. 2018). Prior research has primarily focused on the insula as a whole when examining how it influences the reward-seeking and self-control brain systems (He et al. 2019). However, it remains unclear how specific insular subregions might be involved in exerting influences on different neural circuits and ultimately on individuals' behaviors. This paper aims to address this gap and unpack such links using a multimodal approach. Specifically, it seeks to theorize on and illustrate a nuanced view of the subinsular functional anatomy vis-a-vis the lens of the neural cognitive model of somatic marker hypothesis. While recent research started examining this view, we aim at further unpacking it by tying the anatomical subdivision to functional processes that underlie cognition and behaviors, and we aim to do so from both neural and behavioral standpoints. This will provide us a more nuanced understanding not only the insula and its subdivisions but also their functional roles in human cognition and behaviors.

Our recent work proposed that various efferent interoceptive signals generated from physiological states first reach the posterior portion of insula that processes and integrates them into what we call "somatic markers" or representations of body states. The mechanism by which these somatic markers (or body states) can exert influence (or biases) on individuals' behaviors is via transmission to the anterior portion of insula, where the dorsal anterior part of insula is linked to "central executive control"-related networks, while the ventral anterior portion (vAI) of the insula is linked to social–emotion-related limbic networks (Craig 2002, 2010; Droutman, Bechara, et al. 2015; Droutman, Read, et al. 2015; Poppa and Bechara 2018).

Notably, recent brain anatomy works on insular parcellations (see Supplementary Table S1) identified multiple ways to subdivide the insula from 2 regions to 6. Nevertheless, the tripartite division (Deen et al. 2011; Chang et al. 2012; Kelly et al. 2012; Uddin et al. 2014; Nomi et al. 2016) is the most relevant to and aligned with the neural cognitive model of somatic marker hypothesis described above. Thus, we follow it and extend its examination from pure anatomical to also account for the neurocognitive and behavioral manifestations the insular subdivisions (specifically, posterior, dorsal anterior, and ventral anterior) mediate.

The unique roles of specific insular subdivisions received some support, and hence, our view is based on integrating these disperse pieces of evidence. Specifically, the dorsal anterior insula (dAI) is involved in higher cognitive processing and executive control in tasks, such as response inhibition and performance monitoring (Ullsperger et al. 2010). The ventral anterior insula (vAI) is involved in social–emotional processing (Chang et al. 2011) and autonomic function (Dambacher et al. 2014). Lastly, the posterior insula (PI) is involved with sensorimotor processing (Craig 2002; Kurth et al. 2010), pain (Wiech et al. 2014), and language processing (Oh et al. 2014). These findings suggest that specific subregions of insula are instrumental in integrating disparate functional systems involved in processing affect, visceral-sensory-motor, and higher-order cognition. Thus, the interaction of these insular subregions with relevant brain systems requires further studying. The tripartite parcellation of the insula and prior evidence are consistent with the perspective that the insula is a "hub" in the somatic marker model and that it can affect impulsions, reflections, and behavioral responses to stimuli (Noël et al. 2013).

Here, we aim to test this perspective, linking brain anatomy, connectivity, and behavioral aspects. We specifically seek to quantitatively describe the characteristics and differences in functional connectivity of each insular subregions with specific key brain regions involved in cognitive processes based on the somatic marker neural cognitive model. To this end, we examine whether each insular subdivision's connectivity and implied functionality is consistent with that of the 3 neurocognitive systems: prefrontal self-control system, AMG–STM reward-seeking system, and visceral-sensorimotor system. To do so, we first mapped the expected functional connectivity patterns of the 3 abovementioned insular subregions based on the somatic marker perspective. We next performed regions of interest (ROI) analysis to quantitatively identify the differences among and the specificity of the functional connectivity networks (FCN) of each insular subregion. Then, we further verified the neurocognitive link between the acquired insular connectivity and behavioral performances using the Iowa gambling functional magnetic resonance imaging (fMRI) task. Ultimately, an independent, large dataset was applied to increase the robustness of findings (see Fig. 1). The results supported the somatic marker view of the insular subdivisions and highlight the unique roles of these subdivisions in receiving, processing, and transmitting interoceptive signals.

Materials and methods

Participants

Neuroimaging data from 120 healthy right-handed undergraduate students (sample 1: 60 males/60 females; male: 19.4 ± 1.1 years old; female: 19.1 ± 0.95 years old) were located as part of a large-scale gene-brain-behavior project (part of the Chongqing sample from Lv et al. 2019). Additional 37 undergraduate students (sample 2: 21.65 ± 1.92 years old) were recruited to complete an

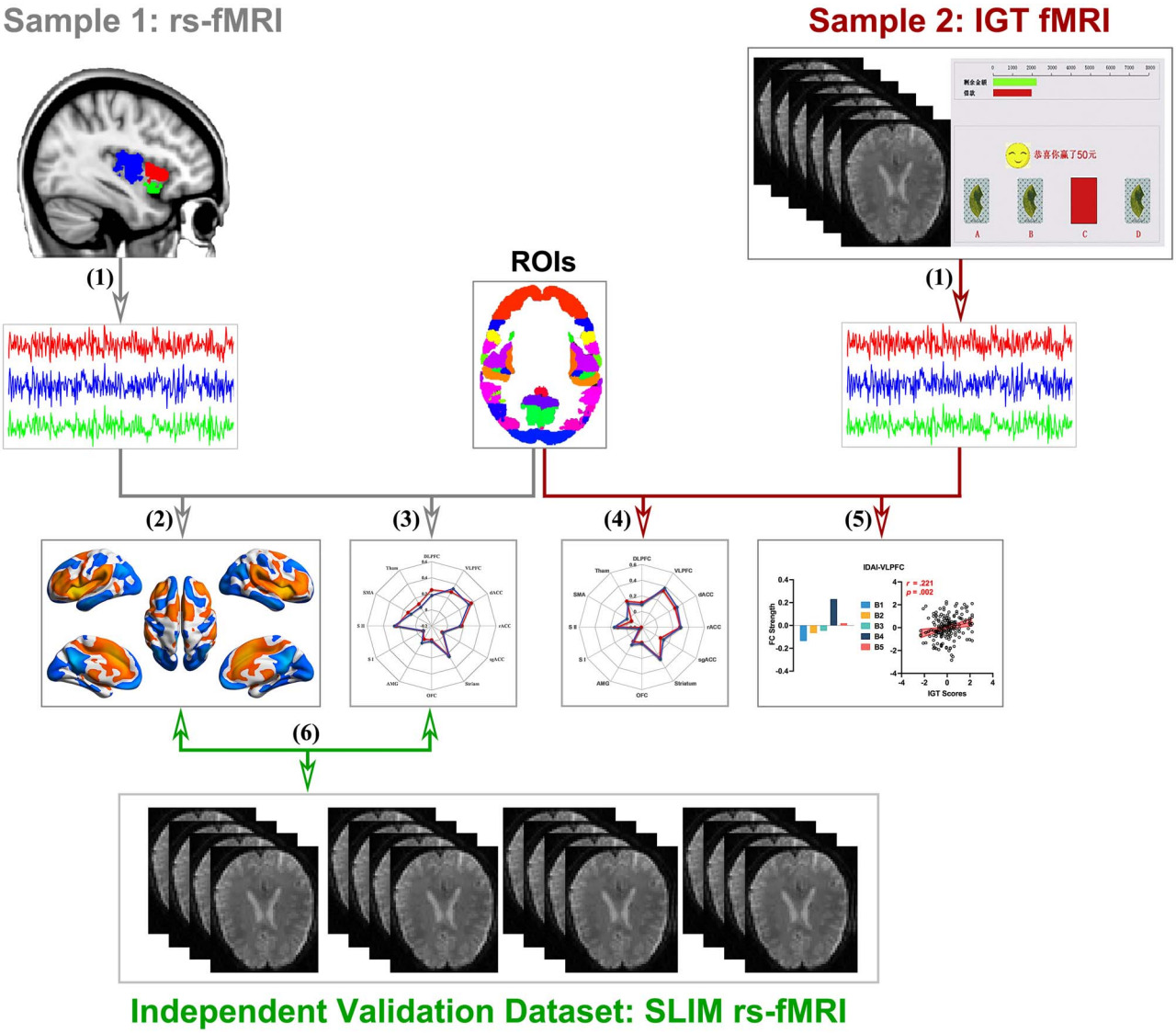

Fig. 1. Insular functional connectivity profiles processing workflow. First, resting-state fMRI data of 120 participants (sample 1) was applied to map the expected functional connectivity profiles of the three insular subregions based on the somatic marker perspective: (1) time courses of insular subdivisions were extracted to perform (2) seed-based functional connectivity; (3) ROI analysis was performed to quantitatively identify the differences among and the specificity of the FCN of each insular subregion. Second, we further verified (4) the acquired functional connectivity profiles using the Iowa gambling fMRI task (sample 2) as well as (5) the neuro-cognitive link between acquired insular connectivity and behavioral performances in the Iowa gambling fMRI task. Ultimately, (6) an independent, large SLIM dataset was applied to increase the robustness of findings.

Iowa gambling fMRI task (see Supplementary Fig. S1 and details in the supplements). Exclusion criteria included: daily consumption of alcohol, or drug abuse; current health issues; neurological or psychiatric disorders; and contra-indications for magnetic resonance imaging (MRI) scanning. Participants were compensated for their time and effort after study completion. All participants provided written informed consent prior to commencing the study, which was approved by the Southwest University Institutional Review Board.

MRI procedure and data acquisition

Participants (in both samples 1 and 2) were instructed to lay in the scanner and relax with their eyes closed. They were informed to keep the body still during the MRI scanning. Foam pads were used to minimize head motion. A total of 242 resting-state functional MRI images for each participant were acquired in a 3T Siemens MAGNETOM Tim/Trio scanner (Siemens Medical, Erlangen, Germany) in the Southwest University Brain Imaging Center. Functional scanning used a z-shim gradient-echoplanar imaging (EPI) sequence with prospective acquisition correction (PACE). This specific sequence aimed at reducing signal loss in the prefrontal and orbitofrontal areas. The PACE option helped reducing the impact of head motion during data acquisition. The parameters were: time repetition (TR) = 2,000 ms; time echo (TE) = 30 ms; flip angle = 90°; field of view (FOV) = 220 mm; acquisition matrix = 64 × 64, slice thickness = 3 mm, 33 slices. The slices were tilted about 30° clockwise along the AC-PC plane to obtain better signals in the orbitofrontal cortex (OFC). High-resolution structural images were obtained

using an magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2,600 ms; time to inversion [TI] = 900 ms; TE = 3.02 ms; flip angle = 8°; 176 sagittal slices; 256 × 256 matrix size with spatial resolution as $1 \times 1 \times 1$ mm^3).

Image preprocessing

Following image processing was executed using a set of shell and MATLAB scripts that are available on github. These scripts also generate HTML quality-control reports. The specific version of these scripts used in this research can be found at https://github.com/hashilzhao/InsulaSubregionalConnectivities.

Image preprocessing (including samples 1 and 2) was carried out using FSL (fMRIB Software Library) version 5.0.9 (Oxford, United Kingdom, www.fmrib.ox.ac.uk/fsl). The first 3 volumes before the task were automatically discarded by the scanner to allow for T1 equilibrium. Preprocessing included: non–brain tissue elimination using BET (Smith 2002); removal of head motion artifact using MCFLIRT (Jenkinson et al. 2002); filtering using a nonlinear high-pass filter (100 s); spatially smoothing using a 5-mm full-width-half-maximum Gaussian kernel; and grand-mean intensity normalization. Next, a GLM model accounted for 8 confounders, including 6 motion parameters, white matter signal, cerebrospinal fluid signal, and their associated derivatives. The residuals obtained from the above analysis was used for extracting seeds for the functional connectivity analysis.

Seed-based resting-state functional connectivity analysis

The residuals in sample 1 from preprocessing above were used to extract seed-based correlations. These residuals were filtered through a low-pass filter (<0.1 Hz) and were then standardized by subtracting the mean, dividing by the standard deviation, and then scaled by adding 100. Six insular subdivisions (3 on the left and 3 on the right) were defined by Chang et al. (2012). They were manually drawn using Harvard–Oxford cortical atlases combined with the Montreal Neurological Institute (MNI) space template (see Fig. 2a). Subsequently these insular subdivisions were transformed from the standard MNI space into each subject's individual blood oxygen level–dependent (BOLD) space using the transform matrix generated by 3-step registration (the EPI images were first registered to the high-resolution MPRAGE structural images and then into standard MNI space using the linear registration tool FLIRT. Registration from MPRAGE structural images to standard space was further refined using the nonlinear registration tool FNIRT). Partial correlations between mean BOLD signals of these subdivisions and all other voxels in the brain in resting state were calculated through FSL toolbox, FEAT 6.00. In addition, a higher-level analysis examined the differences among insular subdivisions (e.g. dAI vs. vAI) within each subject using a fixed effects model with paired sample *t*-test, the estimates of which were subsequently subjected to group analyses.

The whole-brain functional connectivity of each insular subdivision and the differences among them were tested for sample 1 ($n = 120$) using 1-sample *t*-tests. The group maps resulting from these group analyses were tested with random-effect model using ordinary least squares simple mixed effect with automatic outlier detection (Woolrich 2008). Voxels were labeled as significant with a height threshold of $z > 3.1$ and a cluster probability of $P < 0.05$, family-wise-error corrected for multiple comparisons using Gaussian Random Field Theory. The Harvard–Oxford Cortical and Subcortical atlases and MNI atlases provided with the FSL software were used to identify the anatomical characteristics of all functional connectivity regions and the differences among the 3 theoretically suggested subdivisions (dorsal anterior insula, dAI; ventral anterior insula, vAI; and posterior insula, PI).

ROI analysis

To further quantitatively describe and better nuance the characteristics and differences in functional connectivity between each insular subregion and specific key brain regions in neural cognitive process, we performed an ROI analysis. The selection criteria of ROIs were primarily according to the hypothesis rooted in the neural cognitive model of somatic marker hypothesis (Naqvi and Bechara 2009). Choices were also informed by our whole-brain analysis results, which supplemented the theory-driven choices of key cognitive regions identified by NeuroSynth meta-analysis (Yarkoni et al. 2011). These have led to identifying 23 ROI for which masks were defined according to FSL available atlases combined with the MNI template. These ROIs includes: social–emotional processing of the bilateral AMG, OFC, and subgenual anterior cingulate cortex (sgACC) and rostral anterior cingulate cortex (rACC), and STM; executive control processing of the bilateral dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (DLPFC), and ventrolateral prefrontal cortex (VLPFC); and sensorimotor processing of bilateral primary and secondary somatosensory cortexes (SI and SII), supplementary motor area (SMA), and thalamus (THAM) (see Fig. 2b). The AMG, STM, THAM, and OFC were selected from the Harvard-Oxford Cortical and Subcortical Atlas. SI and SII were selected from the Juelich Histological Atlas. The dACC, rACC, and sgACC were defined following the division proposed by Vogt et al. (2005). The DLPFC was defined as BA8, 9, and 9/46 located in the superior and middle frontal gyrus; and the VLPFC was defined as BA44, 45, and lateral part of area 47/12 of the inferior frontal gyrus (Wiech et al. 2014).

At the individual level, for each subject, functional connectivity between insular subdivisions and other ROIs was calculated using Pearson correlation. Specifically, the residuals from the preprocessing above were registered to the MNI152 standard space using FLIRT with the registration transformations derived before.

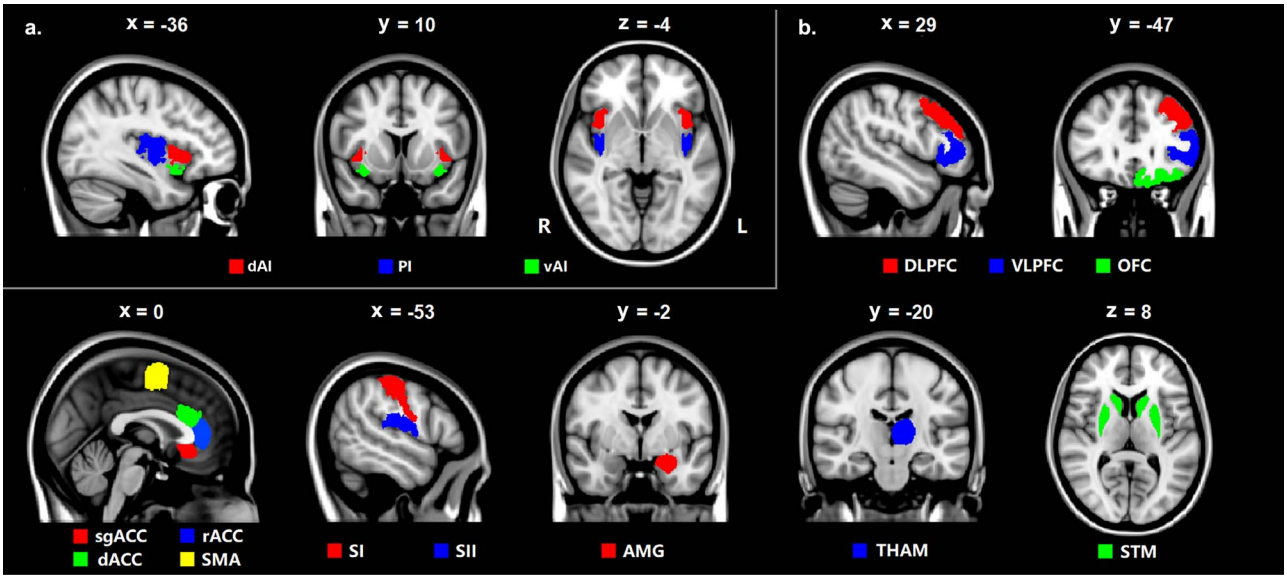

Fig. 2. a) The location of 6 ROIs, 3 on the left and 3 on the right insula: The left and right dorsal anterior insula (red), ventral anterior insula (green), and PI (blue). b) The ROI: DLPFC, VLPFC, OFC, dACC, rACC, sgACC, SMA, SI, SII, AMG, THAM, and STM.

Then, the mean BOLD signal series of insular subdivisions and each ROI were extracted and normalized. Finally, the functional connection between each insular subdivision and the bilateral ROIs was calculated with the normalized mean BOLD signal series. Before the group statical analysis, these functional connection values (correlations) were normalized using Fisher's Z transformation.

At the group level, to quantitatively identify the differences among functional connectivity of ROIs, hemispheres, and insular subdivisions, we performed a 3-way ANOVA with the factors insular subdivisions (dAI, vAI, and PI), hemisphere (left and right), and ROIs (AMG, dACC, rACC, sgACC, DLPFC, VLPFC, OFC, STM, THAM, SI, SII, and SMA). Bonferroni correction was used for correcting for multiple comparisons in the follow-up simple effect tests.

Task-based functional connectivity of insular subdivision during IGT

To verify and unpack the functional connectivity profiles of insular subregions with cognitive network components, we first calculated the functional connectivity of each insular subdivision with the beforementioned key brain regions in an Iowa gambling fMRI task. Then, to test whether the functional connectivity between insular subregions and bilateral target regions is related to the corresponding behavioral performance during Iowa gambling task, Pearson correlations were calculated between the relative connectivity strength and behavioral performances of each block during the Iowa gambling task. All outcomes were corrected for multiple comparisons using false discovery rate (FDR) (Benjamini and Hechtlinger 2014).

Independent validation using open Southwest University Longitudinal Imaging Multimodal dataset

To establish generalizability of the FCN with insular subregions, we used the Southwest University Longitudinal Imaging Multimodal (SLIM) dataset. Given the coherence of MRI data, we selected all SLIM dataset participants who had complete T1-weighted images and resting-state functional images (collected at a second time point). This resulted in a sample of $n = 226$ participants.

The functional scans were collected at the Southwest University Center for Brain Imaging using a 3.0-T Siemens Trio MRI scanner (Siemens Medical). During the resting-state MRI scanning, participants were instructed to lie down, close their eyes, and rest without thinking about a specific thing but to refrain from falling asleep. The 8-min scan of 242 contiguous whole-brain resting-state functional images was obtained using gradient-EPI sequences with the following parameters: TR = 2,000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm, slices = 32, slices thickness = 3 mm with1 mm gap, and voxel size = 3.4 × 3.4 × 3 mm^3. T1-weighted anatomical images with high resolution were obtained using a 3D MPRAGE sequence with the following parameters: TR = 1,900 ms, TE = 2.52 ms, TI = 900 ms, flip angle = 9°, resolution matrix = 256 × 256, slices = 176, thickness = 1.0 mm, voxel size = 1 × 1 × 1 mm^3.

Results

Seed-based functional connectivity analysis

The results of the connectivity of the examined three bilateral (a total of 6) insular subdivisions with all other voxels in the brain are shown in Fig. 3a, Supplementary Tables S2 and S3, and Supplementary Excel File. The

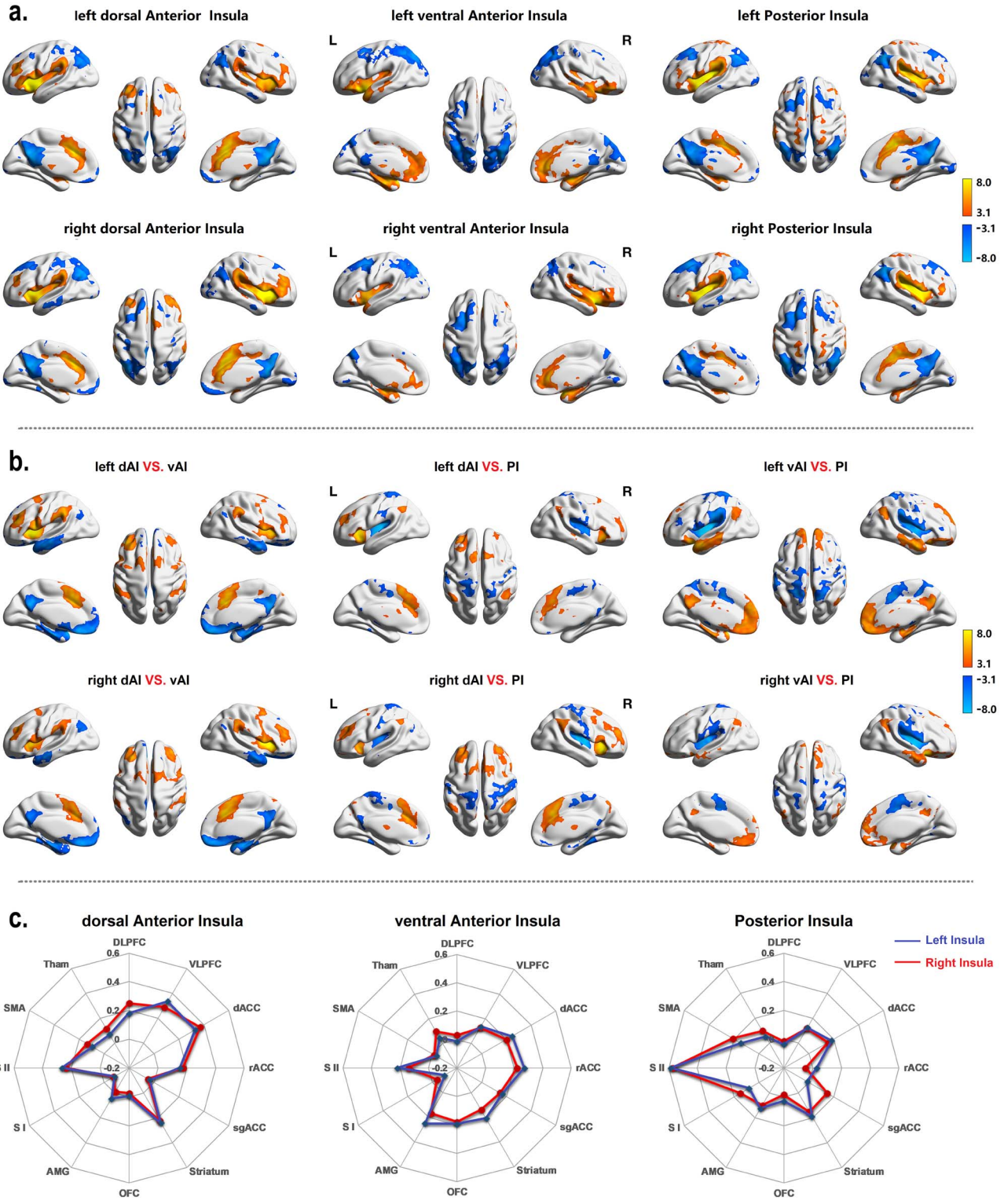

Fig. 3. a) The functioal connectivity pattern with insular subdivisions. ($z > 3.1$, $P < 0.05$). Orange indicates positive functional connectivity with the insular subregion, whereas blue indicates the opposite. b) Comparison between insular subdivisions' functional connectivity. ($z > 3.1$, $P < 0.05$). Orange indicates that functional connectivity with the former insular subregion of "VS." was stronger than with the latter, blue indicates the opposite. c) Differential functional connectivity of insular subdivisions with cognitive network components. The dAI was predominately connected with higher cognition and executive control related brain regions: DLPFC, VLPFC, dorsal STM, and dACC; The vAI was preferentially connected to social-emotional processing and autonomic function-related brain regions: AMG, OFC, ventral STM, rACC and sgACC; The PI was primary connected to brain regions related with sensorimotor: SI, SII, and SMA.

brain activity in the left dAI was significantly positively correlated with bilateral VLPFC, DLPFC, ACC and paracingulate gyrus, STM, supramarginal gyrus (SG), OFC, temporal pole, SI, SII, and SMA activations and were negatively correlated with bilateral precuneus, PCC, lateral occipital cortex (LOC), middle temporal gyrus (MTG), angular gyrus (AG); VLPFC, hippocampus, DLPFC, SI, and SII.

The brain activity in the left vAI was significantly positively correlated with bilateral OFC, ACC, temporal pole; VLPFC, AMG, STM; hippocampus and para-hippocampal gyrus, and THAM activations; and negatively correlated with LOC, precuneus, DLPFC and VLPFC, SPL and AG, SI, and SII activations.

By contrast, the left PI showed strong positive functional connectivity with the bilateral SI, SII and SMA, temporal pole, VLPFC, OFC, ACC and PCC, STM, SMA, and SG and negative functional connectivity with the bilateral LOC, precuneus, PCC and AG, DLPFC, VLPFC, and MTG. Similar patterns were also seen in the right dAI, vAI, and PI FCN.

In addition, we compared the 6 insular subdivisions' FCN. Results are given in Fig. 3b, Supplementary Table S4, and Supplementary Excel File. Compared to the left PI FCN, the left dAI FCN showed stronger FC strength with the DLPFC, VLPFC, ACC, OFC, AG, STM, LOC, and SG and showed weaker FC strength with SI, SII and SMA, precuneus, SPL, PCC, AG, LOC, AMG, and hippocampus. Whereas, the left vAI FCN showed stronger FC strength with the OFC, VLPFC, DLPFC, ACC, PCC, LOC, precuneus, AG, and MTG, it showed weaker FC strength with the SI, SII and SMA, ACC; VLPFC, SG, precuneus, PCC, SPL, LOC, and STM. In addition, the left dAI FCN had stronger FC strength with the DLPFC, VLPFC, ACC, SI, SII, and SMA, SG, SPL, temporal pole, and STM and had weaker FC strength with the OFC, VLPFC, AMG, hippocampus, PCC, precuneus and AG, and temporal pole. The right insular subdivision FCNs produced a similar pattern of differences.

ROI analysis

As Fig. 3c shows, the 3-way repeated-measures ANOVA analysis revealed a significant interaction with high effect-size (>0.50) between ROIs and insular subdivisions ($F_{(12.0,1429.2)} = 320.8$, $P < 0.001$, partial $\eta^2 = 0.729$) and significant interactions but low effect-size (<0.10) between ROIs and hemisphere ($F_{(6.9882.6)} = 10.338$, $P < 0.001$, partial $\eta^2 = 0.080$), between insular subdivisions and hemisphere ($F_{(1.7207.3)} = 5.827$, $P = 0.005$, partial $\eta^2 = 0.047$), and between ROIs, hemisphere and insular subdivisions ($F_{(12.0,1426.9)} = 4.732$, $P < 0.001$, partial $\eta^2 = 0.038$). These results suggested that the 3 insular subdivisions had complete distinct FCN patterns and that the functional connectivity between insular subdivisions and ROIs significantly differs between the left and right hemispheres.

We next performed a follow-up simple effect analysis. The results revealed that (i) dAI had a significantly stronger functional connectivity strength with ROIs, including the VLPFC, DLPFC, dACC, and STM compared to vAI and PI, and that vAI had a significantly stronger functional connectivity strength with ROIs, including AMG and OFC, rACC, and sgACC compared to dAI and PI. In addition, PI had a significantly stronger FC strength with ROIs, including SI, SII and SMA. Moreover, dAI and vAI had a significant stronger FC strength with DLPFC, dACC, and rACC compared to PI. (ii) the ROIs, including DLPFC, VLPFC, dACC, and OFC, had a significantly stronger functional connectivity strength with insular subdivisions in the left hemisphere than in the right hemisphere.

Task-based functional connectivity of insular subdivision

As Fig. 4a–c, Supplementary Fig. S2, and Supplementary Tables S5–S7 show, task-based functional connectivity of insular subregions in the Iowa gambling task had a similar pattern to this observed in the resting-state fMRI. Specifically, results revealed that dAI had a significantly stronger functional connectivity with ROIs, such as the VLPFC, DLPFC, dorsal STM, and dACC, compared to vAI and PI and that vAI had a significantly stronger functional connectivity with ROIs, such as AMG, OFC, ventral STM, and sgACC, compared to dAI and PI. In addition, PI had a significantly stronger FC strength with SI, SII and SMA and weaker FC strength with rACC and VLPFC compared to dAI and vAI.

Next, insular FC-IGT scores correlation analysis revealed that IGT scores were positively related to the assumed executive control related processing manifested in functional connectivity between the left dAI and VLPFC ($r = 0.221$, $P = 0.002$, FDR-adjusted) and that negatively related to the assumed reward-seeking processing manifested in functional connectivity between left vAI and VLPFC ($r = -0.243$; $P < 0.001$, FDR-adjusted), right vAI and OFC ($r = -0.228$; $P = 0.002$, FDR-adjusted) as well as right vAI and sgACC ($r = -0.254$; $P < 0.001$, FDR-adjusted; Fig. 4d).

Independent validation of open SLIM dataset

To further extend the robustness and breadth of our insights, we used 2 independent datasets. We first extracted the FC maps of each insular subregion in the sample 1 dataset ($n = 120$) and then in the SLIM dataset ($n = 226$). Next, we defined the overlap of activation between the 2 independent datasets as FC maps of the sample 1 dataset divided by those in the SLIM dataset to obtain the ratio of cluster sizes and intensity. These ratios represented the overlapped regions and strength in the FCN between the 2 independent datasets.

The SLIM dataset showed mostly similar but enhanced pattern in (i) the seed-based functional connectivity and (ii) ROI analysis with each insular subregion (Supplementary Figs. S3 and S4). Specifically, as Fig. 5a shows, our results had 85.1%/82.9%, 70.3%/82.5%, 79.9%/78.6%, 84.6%/78.4%, 63%/78.9%, and 80.5%/80.2% overlap ratios

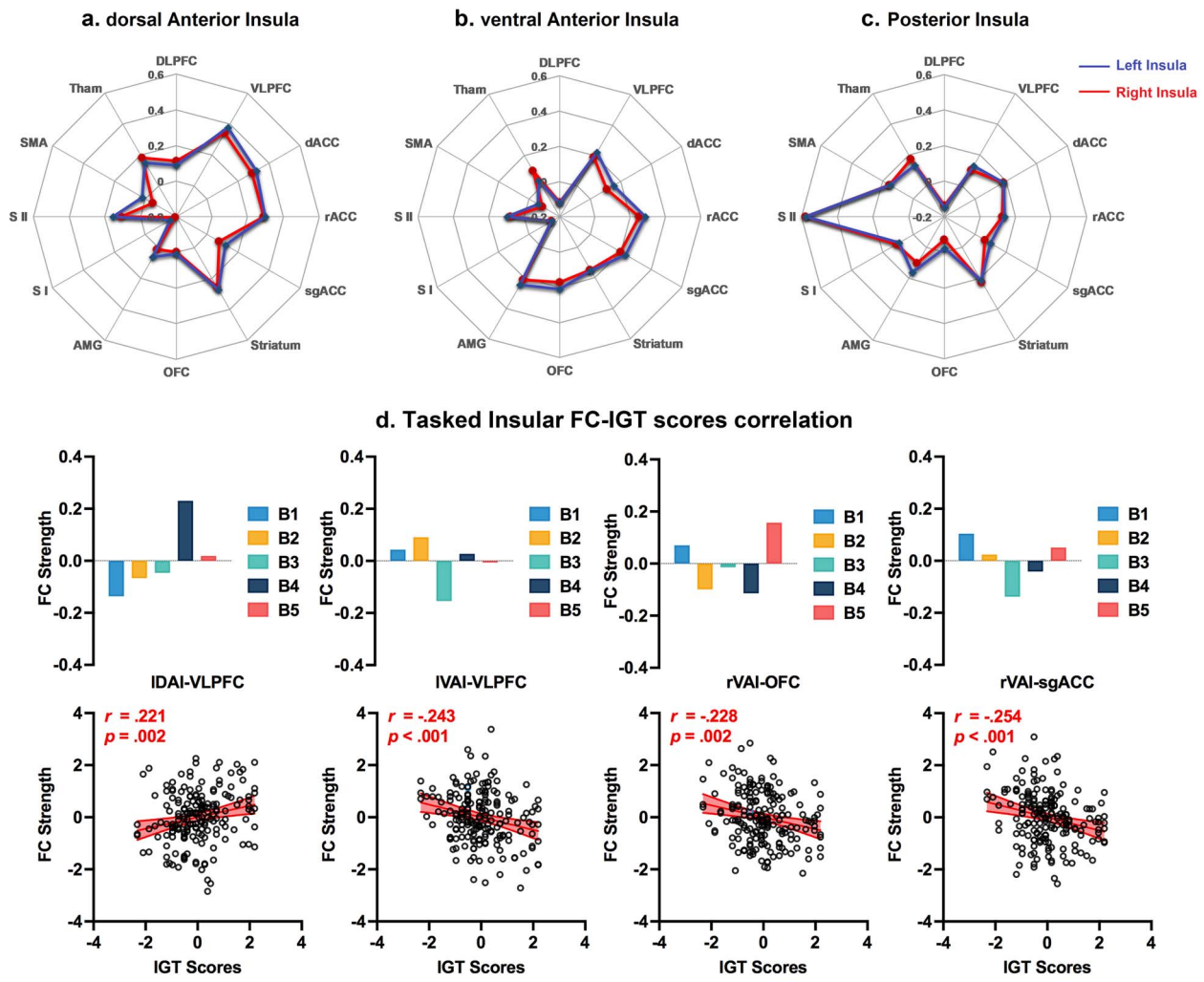

Fig. 4. Task-based functional connectivity pattern of insular subdivisions with cognitive network components during Iowa gambling fMRI task: a) Dorsal anterior insula showed significantly higher connection probability with higher cognition- and executive control-related brain regions: DLPFC, VLPFC, dorsal STM, and dACC. b) Ventral anterior insula was preferentially connected to social–emotional processing and autonomic function-related brain regions: AMG, OFC, ventral STM, rACC, and sgACC. c) PI showed higher connection probability with brain regions related with sensorimotor: SI, SII, and SMA. d) Insular connectivity was correlated with behavioral performances across 5 blocks during the Iowa gambling task. All *P* values in correlation have been corrected by FDR correction. Abbreviations: dAI, dorsal anterior insula; vAI, ventral anterior insula; B1–5, blocks 1–5 during the Iowa gambling fMRI task.

with the regions and strength (respectively) in the positive FCN of left dAI, vAI, PI and right dAI, and vAI and PI in the SLIM dataset. Our results also had the following overlap ratios with the negative FCN of left dAI, vAI, PI and right dAI, and vAI and PI in the SLIM dataset: 80.7%/81%, 58.2%/85.6%, 84%/80.8%, 73.9%/76.3%, 56.6%/89.2%, and 83%/78.8%. Overall, the functional connectivity strength between ROIs and insular subregions in our results is consistent with those in the SLIM dataset (Fig. 5b and Supplementary Fig. S5).

Discussion

In this study, we sought to provide an integrative anatomical-functional-behavioral perceptive on the tripartite parcellation of the insula through the lens of the somatic marker hypothesis. We specifically aimed at examining whether the division of the insula into 3 functional subregions is consistent with the somatic market hypothesis portrayal of insula functionality. If so, we expected to see unique connectivity patterns of the insular subdivisions which are consistent with the roles of the insula in interoceptive signaling and the modulation of neurocognitive processes (e.g. decision-making). To this end, we first used a resting-state fMRI analysis approach to reveal the functional connectivity patterns of insular subdivisions and hence to illustrate the insula's, more nuanced than known before, mediating role in the neural cognitive model of the somatic marker hypothesis. We mapped the functional connectivity patterns of insular subdivisions and further performed ROI analysis to unpack the differences among them and their FCN. Supporting the link between insular connectivity and behaviors, we show that the acquired functional connectivity of insular subregions was significantly correlated with behavioral performance during

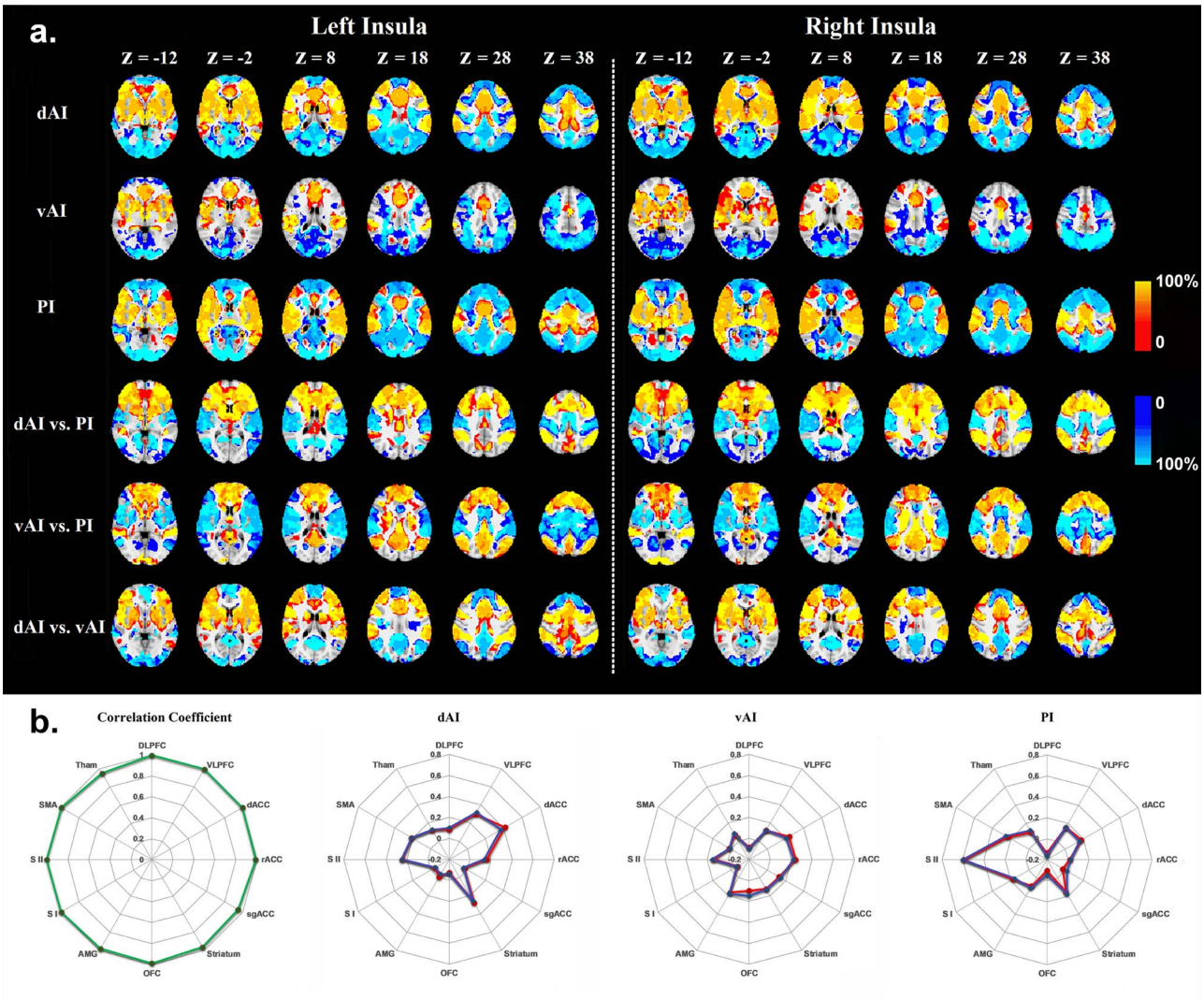

Fig. 5. The overlap between 2 independent datasets in the cognitive networks with insular subdivisions. a) The 2 independent datasets showed a highly similar pattern in the seed-based functional connectivity maps and strength. b) The functional connectivity pattern of ROIs and insular subregions in the Sample 1 dataset (blue) and the SLIM dataset (red) is quite highly overlapped and correlated (green).

the Iowa gambling task (Fig. 3c and Supplementary Fig. S6). Finally, to increased robustness, we validated the acquired functional connectivity patterns of insular subregions using an independent dataset (SLIM).

The abovementioned analyses revealed that the 3 insular subdivisions had distinct functional connectivity patterns and also presented hemispheric differences. Specifically, consistent with the neural cognitive model of the somatic marker hypothesis, dAI was predominantly connected to prefrontal brain regions that mediate self-control (e.g. DLPFC, VLPFC, dACC, and dorsal STM). In addition, vAI was largely connected with regions that mediate reward-seeking (e.g. AMG, OFC and vACC, sgACC, and ventral STM). Lastly, PI exhibited more predominant functional connectivity with regions of the brain's visceral-sensorimotor system (e.g. SI, SII, and SMA).

The dAI and regions that mediate self-control

The brain regions that mediate self-control provide humans with means for controlling impulses. They therefore allow a more flexible pursuit of long-term goals (Noël et al. 2013). They include 2 subsystems: 1 "cool" and 1 "hot" executive function systems (Zelazo and Müller 2002). The "cool" executive function refers to a set of goal-directed, future-orientated cognitive skills, including the inhibition of prepotent impulses, cognitive flexibility, and working memory (Anderson 1998; Miyake et al. 2000). It typically involves dorsolateral prefronto-striatal circuits and the frontoparietal network (Kerr and Zelazo 2004). By contrast, "hot" executive functions are posited to include affective cognitive abilities, such as the ability to delay gratification and affective neurocognitive process (Zelazo and Carlson 2012; Tsermentseli and Poland 2016). It is mainly mediated by paralimbic orbitomedial and

ventromedial frontolimbic structures (Bechara et al. 2005).

Consistent with our hypothesis, we observed that dAI was significantly correlated with bilateral VLPFC, DLPFC, dACC and paracingulate gyrus, dorsal STM, SG, OFC, and temporal pole. The ROI analysis and task-based FC during the Iowa gambling fMRI task further confirmed the significant connectivity between dAI and "cool" executive process of DLPFC, VLPFC, and dACC. This is in line with findings that there is a bidirectional connection between the insula and the abovementioned prefrontal regions (Cloutman et al. 2012). In addition, an activation of dAI was observed during higher cognitive processing. For example, Ramautar et al. (2006) observed greater activation of bilateral insula during failed response inhibition. A meta-analysis revealed that error and negative feedback predominantly activated the anterior insula, especially the right anterior part, indicating the close link between the anterior insula and performance monitoring (Ullsperger et al. 2010). Such finding indicated that the dAI can modulate/influence the process of reflecting through its functional coupling with the key regions involved in both "cool" executive functions (DLPFC and ACC) and "hot" executive functions (VLPFC and VMPFC).

The vAI and regions that mediate reward-seeking

Unlike the regions that mediate self-control, regions that mediate reward-seeking are involved in Pavlovian, fast, and poorly deliberated responses triggered by potent cues (e.g. sex and food). These regions include the basal ganglia and their cortical effective inputs (Belin et al. 2009). This system of regions also includes the AMG–striatal neural circuit, which is a critical structure for the incentive motivational effects of a variety of nonnatural or natural rewards (Wise 2002). Thus, this system of regions is the key to generating "wanting" and approach behaviors.

In the present study, we found that the vAI was significantly correlated with bilateral OFC, AMG, ventral STM, rACC, sgACC, VLPFC, hippocampus, para-hippocampal gyrus, and THAM activations. ROI analysis further verified that vAI had a significantly stronger FC with the AMG, OFC, ventral STM, vACC, and sgACC compared to PI. Moreover, task-based FC of vAI with OFC and sgACC revealed a significant negative correlation with behavioral performance during the Iowa gambling fMRI task. The results were in line with the argument that vAI is involved in social–emotional processing (Sanfey et al. 2003; Singer et al. 2009; Chang et al. 2011) and autonomic function (Dambacher et al. 2014). One explanation is that the vAI translates interoceptive signals generated by PI into what one subjectively experiences as a feeling of desire, anticipation, or urge, which ultimately sensitizes the reward-seeking regions of the brain (Naqvi and Bechara 2009; Verdejo-Garcia et al. 2012; Droutman, Read, et al. 2015). See Naqvi et al. (2014) for review. Similarly, OFC, ventral STM, rACC, and sgACC are involved in implicit motivational value and salience (Rothkirch et al. 2012) and induction of motivational states (Noël et al. 2013). As mentioned above, the AMG–striatal neural circuit is a critical structure for the incentive motivational effects of a variety of nonnatural or natural rewards (Wise 2002). Therefore, we expected that vAI plays a role in modulating the impact of incentive stimuli on motivational states and behavior by modulating the driving reward-seeking system. Our results supported this notion and demonstrated that the vAI is functionally associated with regions that mediate reward-seeking.

The PI and the interoceptive awareness system

The interoceptive awareness system mediates the sensing of the internal state of body (Khalsa and Lapidus 2016). It specifically mediates a set of sensory processes that signal the physiological state of peripheral tissues, including temperature, tissue damage, itch, taste, ingestive oral sensation, and general visceral sensation from the gut and cardiovascular system (Naqvi et al. 2014). These interoceptive signals first reach the PI bilaterally, which is the primary interoceptive cortex where low-level sensory features are processed. Then the information is passed to the anterior insula, where higher-order interoceptive representations reach awareness (Craig 2002, 2010). Therefore, the PI serves as a gate that allows transfer into higher order processing. It converges and integrates various sensory signals and relays these signals into higher order interoceptive representation process.

In line with our hypothesis, the whole brain analysis showed that the PI had strong functional connectivity with the SI, STM, SMA, SG, temporal pole, VLPFC, and cingulate gyrus. The ROI analysis further verified that the PI had a significantly stronger functional connectivity with motor regions, including SI, SII, and SMA. Our results therefore confirmed the notion that the PI is associated with the somatosensory and sensorimotor processing (Craig 2002; Napadow et al. 2009; Kurth et al. 2010). This view is supported by tracer studies in primates, which have demonstrated direct white matter connections between the PI and somatosensory regions (Mesulam and Mufson 1982; Mufson and Mesulam 1982; Augustine 1985). Moreover, the PI is an important site for multimodal convergence, directly receiving afferent gustatory, olfactory, auditory, visual, and somatosensory information (Mesulam and Mufson 1985; Singer et al. 2009). Hence, dysfunction of the PI could lead to visual-somato-sensory imbalance, resulting in various neuropsychiatric disorders (Nagai et al. 2007). Wittmann et al. (2010), suggested that the accumulation of physiological changes in body states registered in the PI may be the basis for our experience of time. Based on our results and previous findings, we proposed that the PI could influence individual's interoception (e.g. time perception, homeostasis, and visual somatosensation) through converging and modulating multimodal sensory

signals relayed from the body and relaying them into specific brain regions (Cameron 2001; Craig 2002).

Taken together, our findings indicate that the subdivisions of the insula have distinct roles in the neural cognitive processes that manifest in connectivity and downstream behaviors. This moves the needle in the field and shows that ignoring this heterogeneity in the insula may be suboptimal and lead to imprecise conclusions. While we already know about the parcellation of the insula, we were missing close ties between such parcellations and function connectivity and behavioral manifestations. While we make first strides to address such voids, we call for future research on processes that are mediated by the insula to take a more nuanced view and examine the specific functional roles and connection of insular subdivisions. We also acknowledge that there can be various ways to subdivide the insula (Deen et al. 2011; Chang et al. 2012; Kelly et al. 2012; Uddin et al. 2014; Nomi et al. 2016). Nevertheless, the tripartite division we used is consistent with the neural cognitive model of somatic marker hypothesis. We hence also call for future research to examine other or the same insular subdivisions vis-a-vis different theoretical lenses.

Limitation and future study

Several limitations of this study that pave the way for future research should be acknowledged. First, we applied a seed-based functional connectivity method. While it is a useful starting point, it fails to account for the direction of information interaction between the insula and specific brain regions. Thus, future studies may extend our results by using additional connectivity methods, like dynamic casual modeling, DTI and fiber tracking analysis, and radioactive tracer method, to uncover the information flow direction. Second, our study relied on resting-state fMRI data. Future studies can combine multiple modal indicators/measures (e.g. behavioral indicators, sMRI, DTI, and EEG) with more advanced analysis methods that can reveal the hierarchical structure of various brain regions (e.g. by using the graph theory) to uncover the insula's mediating role in neural cognitive process.

Conclusion

This study examined the insula's mediating roles in the neural cognitive processes through mapping the functional connectivity patterns of 3 bilateral insular subdivisions and identifying the differences in their connectivity to specific regions involved in various cognitive process. We demonstrated that the 3 different insular subdivisions (dAI, vAI, and PI) had completely distinct functional connectivity patterns and varied by hemispheres. Based on these findings, we conclude that different insular subdivisions have different functional roles that map onto the neurocognitive process: the reward-seeking processes, the self-control processes, and visceral-sensorimotor processes.

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Authors' contributions

HZ and QH designed the study, carried out recruitment of subjects and collection of their neuropsychological and imaging data, and conducted the literature and data analysis; HZ, OT, and QH drafted the manuscript; OT and AB provided critical revisions of the manuscript. All authors approved the final version of the manuscript.

Funding

This work was supported by research grants from the National Natural Science Foundation of China (31972906), Natural Science Foundation of Chongqing (cstc2020jcyj-msxmX0215), Fundamental Research Funds for the Central Universities (SWU2209235), the High-end Foreign Expert Introduction Program (G20190022029), and the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (CNLZD2102).

Conflict of interest statement: None declared.

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