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Author(s)	Haruki, Yusuke; Ogawa, Kenji
Citation	European journal of neuroscience, 53(8), 2669-2680 https://doi.org/10.1111/ejn.15157
Issue Date	2021-02-23
Doc URL	https://hdl.handle.net/2115/84203
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Type	journal article
File Information	haruki&ogawa_author_manuscript.pdf



Role of anatomical insular subdivisions in interoception: interoceptive attention and accuracy have dissociable substrates

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Running title: Insular subdivisions in interoception

Keywords: insula; fMRI; interoception; heartbeat counting task

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Word counts: 5611 words

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5 **Funding statement**

This study received funding from JSPS KAKENHI (Grant/Award Numbers: 18H01098, 19H05493, 19H00634).

Conflict of interest

10 The authors declare no potential conflict of interest.

Author contributions

YH designed the experiments, collected the data, performed the analysis, and wrote the manuscript. KO contributed to experimental design and analysis, and also edited the
15 manuscript.

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Abstract

Prior neuroimaging studies have supported the idea that the human insular cortex plays an important role in processing and representing internal bodily states, also termed “interoception.” According to recent theoretical studies, interoception includes several aspects such as attention and accuracy. However, there is no consensus on the laterality and location of the insula to support each aspect of interoception. Thus, we aimed to identify the anatomical insular subdivisions involved in interoceptive attention and accuracy; we examined 28 healthy volunteers who completed the behavioral heartbeat counting task and interoceptive attention paradigm using functional magnetic resonance imaging. First, interoceptive attention induced significant activation in the bilateral frontal operculum, precentral gyrus, middle insula, middle cingulate cortex, and supplementary motor area. Then, we compared the activation in anatomically predefined insular subdivisions during interoceptive attention. The highest activation of the middle short gyrus was noted within the insular cortex, followed by the anterior short gyrus and posterior short gyrus, while no significant hemispheric differences were observed. Finally, the interoceptive accuracy index, measured using the heartbeat counting task, strongly correlated with the activity of the right dorsal anterior insula/frontal operculum. These findings suggest that interoceptive attention is associated with the bilateral dorsal mid-anterior insula, which supports the processing and representation of bodily signals. In contrast, the more dorsal anterior portion of the right insula plays a key role in obtaining accurate interoception.

Keywords: insula; fMRI; interoception; heartbeat counting task

Introduction

The information arising from within our body can contribute to various cognitive functions; for example, an increased heart rate might be indicative of mind-body stress and an empty stomach can motivate an individual to eat. The term “interoception” encompasses a broad
5 range of concepts regarding internal state, including the senses and processes associated with the nervous system and the interpretation of signals originating from within the body (Azzalini et al., 2019; Critchley and Garfinkel, 2017; Critchley and Harrison, 2013).

Interoception is a comprehensive and multi-dimensional concept; thus, studies on interoception should describe which specific aspect of interoception is being discussed.

10 Recent studies have attempted to find some distinct aspects of interoception by proposing various dimensions across conscious interoception, such as attention (the process of focusing on one’s internal bodily environment), accuracy (the ability to correctly perceive changes arising from within the body), and sensibility (the subjective tendency to feel one’s body states) (Ceunen et al., 2013; Garfinkel et al., 2015; Murphy et al., 2019). Typically,
15 interoceptive accuracy is measured using a behavioral task, such as the heartbeat counting task, and sensibility is assessed via a questionnaire regarding interoception. Accuracy and sensibility can be considered as distinct concepts because both vary greatly between individuals and seldom correlate with each other (Garfinkel et al., 2015; Garfinkel and Critchley, 2013). In contrast, attention seems to be a general aspect; therefore, the
20 interoceptive attention paradigm is often employed as a task that records brain activity pertaining to interoception (Pollatos and Schandry, 2004; Wiebking et al., 2010); however, unlike accuracy and sensibility, an objective evaluation of interoceptive attention is

difficult. Since each aspect of interoception is measured in different ways and has different properties, it is important to distinguish the aspects from each other when discussing interoception to avoid misunderstandings.

The autonomic nervous system relays bodily signals to the central nervous system; for
5 interoception, the insular cortex is involved at the cortical level due to its importance in processing and representing such afferent signals. Bodily information is relayed through subcortical regions, such as the brainstem, hypothalamus, and thalamus, through the lamina I spinothalamic and vagus/glossopharyngeal cranial pathways and are projected principally to the posterior insula and primary somatosensory area (Craig, 2002; Craig, 2003;
10 Oppenheimer and Cechetto, 2016). It has been proposed that bodily information in the posterior insula is transmitted forward along the rostrocaudal axis, integrated with other sensory inputs in the middle insula, and finally re-represented in the anterior insula to be consciously available (Craig, 2009; Frot et al., 2014).

These models assume that each subdivision of the insular cortex has a unique role.
15 According to a large-scale meta-analysis on the functions of the insular cortex (Kurth et al., 2010), the subdivisions of the insula were activated by different task domains, such as the activation of the dorsal anterior region by the cognitive domain (such as attention, memory, and speech), the ventral anterior region by the social-emotional domain (such as emotion and empathy), and the dorsal middle posterior region by the sensorimotor domain (such as
20 somatosensory and motor functions). In addition to the differences in anatomical location, a neural asymmetry in the insula has been suggested, wherein the positive emotions are associated with activation in the left anterior and mid-insula, while negative emotions

activate the bilateral anterior and mid-insula (Duerden et al., 2013; Strigo and Craig, 2016). These functional specializations may be related to differences in their structural connections with the other regions. While the posterior insula is connected to the parietal region, including the postcentral gyrus, the dorsal anterior insula is connected to the frontal operculum, and the ventral anterior insula to the limbic regions (Cerliani et al., 2012; Cloutman et al., 2012). The insular cortex seems to have a wide variety of functions between the hemispheres and along the rostrocaudal and ventrodorsal axes. Careful consideration on the structure-function variety of the insula would be needed in the literature regarding interoception, which posits that the insula is the core region.

Although empirical works suggest that the right anterior insula is central to interoception, there is little information regarding the multidimensionality of interoception and the laterality and variations of the insula. Many neuroimaging studies have emphasized the general involvement of the right anterior insula in interoception, revealing that a single aspect of interoception, such as the subjective intensity rating of interoceptive sensation and the interoceptive accuracy (IAc) index, was related to the activity of the right anterior insula (Caseras et al., 2013; Craig et al., 2000; Critchley et al., 2004; Von Leupoldt et al., 2008; Pollatos et al., 2007). These studies may support the view of sympathetic bodily representation that occurs exclusively in the right anterior insula, but others implicitly challenge this notion. That is, studies employing the interoceptive attention paradigm have often reported the activation of the bilateral middle insula (Avery et al., 2014; Failla et al., 2020; Haase et al., 2016; Stern et al., 2017; Wiebking et al., 2010). A meta-analysis on interoceptive attention (especially heart attention) found that the cluster was consistently

activated in the bilateral (but somewhat right-lateralized) dorsal middle insula (Schulz, 2016). Although right insula dominance in relation to autonomic input asymmetry has been suggested (Craig, 2008; Zaki et al., 2012), to the best of our knowledge, no study has specifically examined the extent of laterality in interoception.

5 Indeed, the neural activity in the insula is associated with an origin of conscious interoception; however, some incongruencies are present about its detailed localization. We believe that these inconsistencies could be because prior studies did not thoroughly investigate both the structure-function variety of the insular cortex and the distinct interoceptive modalities. In particular, we suspected that the patterns in which the insular
10 cortex is involved in terms of interoceptive attention and accuracy are different, as implied by Schulz (2016). Therefore, we performed two experiments on the same day: the behavioral heartbeat counting task to measure an individual's IAc index and a functional magnetic resonance imaging (fMRI) scanning during interoceptive attention. We then thoroughly examined the differences in activities among the subdivisions of the insula
15 during interoceptive attention to assess the extent of laterality and localization in the insula. Additionally, we identified the exact region of the insula that is related to the differences in individual IAc scores. Two to four functional divisions of the insula have been confirmed in prior large-scale meta-analyses (Cauda et al., 2012; Chang et al., 2013; Deen et al., 2011; Kurth et al., 2010), but these studies did not effectively divide the dorsal region, which
20 might be associated with interoception, into its four distinct anatomical gyri (Faillenot et al., 2017; Morel et al., 2013; Türe et al., 1999). Thus, we used the anatomical divisions of the insula as regions of interest (ROI) while assuming that a distinct anatomical gyrus may

be uniquely associated with interoceptive attention. Based on previous results, we hypothesized that the right middle insula would show the highest activation during interoceptive attention (Schulz, 2016; Simmons et al., 2013; Zaki et al., 2012), and that it would be associated with IAc scores (Caseras et al., 2013; Critchley et al., 2004; Pollatos et al., 2007), which might be distant from the activation peak coordinate associated with interoceptive attention.

Materials and methods

Participants

We recruited 29 healthy, right-handed volunteers to participate in this study. One participant was excluded from the analysis because the scanning suddenly stopped due to defects during the experimental run, yielding incomplete data. Thus, the final analysis included 28 participants (12 women; age, 19-28 years). Written informed consent was obtained from all the participants. The handedness of each participant was assessed using a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971) in Japanese (Hatta and Nakatsuka, 1975). The study was conducted in accordance with the Declaration of Helsinki. The ethics committee of Hokkaido University approved the experimental protocol.

Heartbeat counting task

A heartbeat counting task, outside the fMRI scanner, was used to assess each participant's interoceptive accuracy (Schandry, 1981); this task was performed on the day of the fMRI experiment. After obtaining signed consent forms, a pulse oximeter (IWS920, Tokyo

Devices; Tokyo, Japan) was placed on the participants' left ring finger while they sat on a chair. To avoid feeling a pulse, they were instructed to place their arms on the desk and not to lean back in their chair. Before the task started, the apparatus was set in an appropriate position so that the participant reported no sense of their bloodstream exteroceptively (e.g.,
5 via their finger on the pulse oximeter, wrists on the desk, or buttocks on the chair). The experimenter verbally instructed the participants to "count each heartbeat you feel in your body especially around the heart, from the time you hear the cue sound to when you hear the same sound again, and then tell me how many heartbeats you felt." The experimenter also told the participants, "do not estimate the number of heartbeats; if you feel nothing,
10 please tell me so." This was done to ensure that participants only counted sensations felt inside their body and did not estimate the number of heartbeats, as this would affect the IAc (Desmedt et al., 2018; Ring and Brener, 2018). Subsequently, the participants were given 2 min of rest to control their levels of arousal, which was followed by the task trial. The participants performed three task trials with different time windows (25 s, 35 s, 45 s) after a
15 short training trial (10 s). The order of the time windows was randomized for each participant before the trial began. The IAc index was individually calculated using the following formula (Pollatos et al., 2008; Tsakiris et al., 2011):

$$\text{IAc index} = \frac{1}{3} \sum_{i=1}^3 \left(1 - \frac{|\text{recorded heartbeats} - \text{reported heartbeats}|}{\text{recorded heartbeats}} \right)$$

According to this calculation, the IAc could range from 0 to 1. Scores closer to 1 indicated
20 small differences between the subjectively counted heartbeats and objectively measured heartbeats.

MRI data acquisition

All scans were performed on a Siemens (Erlangen, Germany) 3-T Prisma scanner with a 20-channel head coil at Hokkaido University. Using T2*-weighted echo-planar imaging (EPI), 237 scans were acquired per session, with a gradient echo EPI sequence. The first
5 three scans acquired within each session were discarded to allow for T1 equilibration. The scanning parameters used were as follows: repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle (FA), 90°; field of view (FOV), 192 × 192 mm; matrix, 94 × 94; 32 axial slices; and slice thickness, 3.500 mm, with a 0.875-mm gap. Thus, the voxel size was 2.042 × 2.042 × 4.375 mm. T1-weighted anatomical imaging with an MP-RAGE sequence was
10 performed using the following parameters: TR, 2300 ms; TE, 2.32 ms; FA, 8°; FOV, 256 × 256 mm; matrix, 256 × 256; 192 axial slices; and slice thickness, 1 mm without a gap.

fMRI procedure

The general procedure was based on several previous studies (Kuehn et al., 2015; Simmons
15 et al., 2013; Wiebking et al., 2010; Wiebking et al., 2015), which were modified for our interests. One session consisted of two condition trials: a heart attention condition (interoception) and a control tone condition (exteroception). Each heart and tone condition trial was performed nine times in one session. Each condition trial was composed of a heart/tone attention task block, a concentration rating block (4 s), and a rest block (8 s). In
20 an attention task block, the duration was 12 s, 14 s, or 16 s, with each task presented three times for a total of nine times. Heart and tone trials were alternated throughout the whole session for a total of 18 times. The presentation order within each trial was randomized

before the session began, in which there could be an appearance of identical durations on consecutive task trials (Figure 1). The total experiment consisted of four sessions, with both the heart and tone condition trials performed 36 times in total. Participants were equipped with MRI-compatible headphones and watched the screen via a mirror inside the scanner.

5 After each session, the participants were given a break of approximately 2 min.

Before the first session began, the volume of the tone sound used as a target was individually adjusted in accordance with previous studies (Kuehn et al., 2015). While a dummy EPI scan was running, the experimenter gradually decreased the volume of the tone sound, while the participants gave feedback so that the tone sound was just perceivable.

10 This was done to ensure that the task difficulty level was comparable between the heart attention and tone attention tasks. These adjusted low-volume tone sounds were presented during both the heart attention and tone attention blocks. The duration of the sounds was 200 ms, and the intervals corresponded to each participant's mean beat-to-beat interval that was recorded during the prior heartbeat counting task, while being jittered by 200 ms, to
15 control for habituation effects (Wiebking et al., 2010).

In the heart attention task, the participants were instructed to silently count each heartbeat by focusing on their heart and feeling their heartbeat-related sensations.

Estimating the number of heartbeats was prohibited as with the heartbeat counting task, which was performed outside the MR scanner. Very low-volume tone sounds were
20 delivered through the headphones. The participants were instructed to ignore them and to focus only on their heart to prevent estimation of the number of their heartbeats from the frequency of the tones, although they were not informed of what the sound intervals meant.

A previous study found that tone sounds analogous to heart rate did not facilitate heartbeat detection under explicit instructions (Zaki et al., 2012).

In the subsequent concentration rating tasks, the participants self-reported about how well they felt they had concentrated in the previous blocks, using a scale from one (poor) to four (good) by pressing buttons with their right hand. This was done to ensure participants' attention in the prior task trials (Avery et al., 2014; Simmons et al., 2013). They did not have to report the number of counted heartbeats, and no feedback about the correctness of their response was provided.

In the rest block, a fixation crossbar was presented in the center of the screen, no sound stimulation was played, and the participants were told to watch the bar. Preparing for the next task block was prohibited.

In the tone attention task, the participants counted each tone by concentrating on the sounds presented via a headphone. They reported on their concentration following the same procedure similar to that in the heart attention trial. Because the experimental situations were equal between the two task conditions (e.g., the scanning noise and low-volume tone sounds), the only difference noted was where the participants would focus their attention (heart: on their heartbeats, tone: on the tone sounds). This allowed us to estimate the focal brain activity for interoceptive and exteroceptive attention by subtracting the effects of confounders included in both attention tasks.

Preprocessing of the fMRI data

Image preprocessing was performed using SPM12 software (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). All functional images were initially realigned to adjust for motion-related artifacts. Volume-based realignment was performed by co-registering images using rigid-body transformation to minimize the squared differences between volumes. The realigned images were then spatially normalized using the Montreal Neurological Institute (MNI) template based on the affine and non-linear registration of co-registered T1-weighted anatomical images (normalization procedure of SPM). They were resampled into 3-mm-cube voxels with sinc interpolation. Images were spatially smoothed using a Gaussian kernel of $6 \times 6 \times 6$ mm full-width at half-maximum. Low-frequency noise was removed using a high-pass filter with a cut-off period of 128 s, and serial correlations among scans were estimated using an autoregressive model implemented in SPM12.

Statistical analysis of fMRI data

A first-level general linear model (GLM) analysis was performed to estimate the brain activity related to bodily and auditory attention. Both the heart and tone blocks per session were modeled as separate boxcar regressors that were convolved with a canonical hemodynamic response function, and both the rest and concentration rating blocks were used as the baseline. For each participant, four contrast images were created: heart vs. baseline, tone vs. baseline, heart vs. tone, and tone vs. heart.

Subsequently, we implemented three types of group analyses. First, we performed a random-effects analysis using one-sample *t*-tests. Whole-brain activity in the first-level

contrast images of heart vs. tone and tone vs. heart was independently analyzed to confirm the selective activation for each heart and tone attention. The voxel-level threshold was set to a p -value of $< .05$ and corrected for false discovery rate (FDR). Clusters corrected for FDR ($p < .05$; corresponded to more than 15 voxels) were reported as activated areas.

5 Secondly, we conducted another group analysis to explore the insular activity related to interoceptive attention in more detail. We adopted the anatomical image of the insular subdivisions published in Hammersmith brain atlases (Brain Development, www.brain-development.org) as the ROI. These images were constructed as a 3D probabilistic atlas using *in vivo* T1 MR images, including anatomical structures commonly noted in the

10 human insula: the anterior short gyrus (ASG; the most dorsal anterior portion of the insula, left: 6212 mm³; right: 6096 mm³), middle short gyrus (MSG; the dorsal mid-anterior portion; left: 4127 mm³; right: 4629 mm³), posterior short gyrus (PSG; the dorsal mid-posterior portion, left: 5531 mm³; right: 5223 mm³), anterior inferior cortex (AIC; the ventral anterior portion, left: 7599 mm³; right: 7625 mm³), anterior long gyrus (ALG; the

15 dorsal posterior portion, left: 6817 mm³; right: 6568 mm³), and posterior long gyrus (PLG; the ventral posterior portion, left: 6785 mm³; right: 6612 mm³) (Faillenot et al., 2017). These six ROIs were adopted separately from both hemispheres; a total of 12 ROIs were used to compare the activation among the insular cortex. Thereafter, the effects of both the heart and tone conditions were individually estimated as a beta weight among the insular

20 subdivisions based on the first-level results. A repeated-measures analysis of variance (ANOVA) was performed on these beta values with hemisphere (left/right) and location (ASG, MSG, PSG, AIC, ALG, PLG) as the within-factors. Additionally, we assumed that

some confounding effects, such as counting numbers, could be introduced in the heart attention condition. To remove such effects, we computed the difference between the tone attention and heart attention conditions for each ROI individually. Thereafter, a repeated-measures ANOVA was performed on these differences, with hemisphere and location as the within-factors.

In the third group analysis, we conducted a correlation analysis between the hemodynamic response and the individual ability to perceive the internal state, or the IAc index. The second-level contrast image of the heart vs. baseline was created, which modeled the individual IAc index as a covariate of interest. This was then masked using the bilateral insular cortex image parcellated in the Anatomical Automatic Labeling (AAL) brain atlas, which was because the correlation between IAc and the insula activity have been reported in prior studies (Critchley et al., 2004; Pollatos et al., 2007; Tan et al., 2018). A one-sample *t*-test under the insula mask was performed to identify the exact region whose activity correlated with IAc. The threshold was set to a *p*-value of < .005 (uncorrected). Also, we checked whether the activation of insula subdivisions obtained in our ROI analysis was correlated with IAc. Pearson's correlation coefficient between individual IAc and beta values of the 12 ROIs during heart attention was calculated.

Results

Heartbeat counting task

The mean IAc score for all participants was 0.59 (*SD* = 0.24). No significant sex-specific difference was found ($t(25.04) = -0.10, p = .92$), and the IAc scores did not show a

significant correlation with age or heart rate during the counting task ($r = -.30, p = .12; r = -.27, p = .15$, respectively).

fMRI

5 Whole-brain analysis revealed that, compared with the brain regions activated with the tone attention task, the heart attention task induced significant activation of several brain regions, including the bilateral frontal operculum, middle insula, precentral gyrus, middle cingulate cortex, and supplementary motor area (Table 1; Figure 2). None of the significantly activated regions during the tone attention task were comparable to those
10 activated during the heart attention task, with the current threshold.

Repeated-measures ANOVA on the beta estimate values across the insular subdivisions suggested functional differences across the insular cortex (Figure 3). The main effect of location was significant in the heart attention task ($F(5, 135) = 29.35, p < .001, \eta_p^2 = .52$), but the main effect of hemisphere and the interaction between them was not statistically
15 significant ($F(1, 27) = 0.00, p = .99, \eta_p^2 < .001; F(5, 135) = 1.57, p = .17, \eta_p^2 = .06$), suggesting no lateralization of interoceptive attention. Multiple comparison using Shaffer's modified sequentially rejective Bonferroni procedure on the differences among the insular subdivisions revealed the strongest activation in the MSG (adjusted p -values $< .005$); the results also indicated that the ASG and PSG showed higher activation than the AIC, ALG,
20 and PLG regions (adjusted p -values $< .002$; adjusted p -values $< .001$, respectively). In the tone attention condition, the main effect of location and the interaction between the location and hemisphere was significant ($F(5, 135) = 4.09, p = .002, \eta_p^2 = .13; F(5, 135) = 2.51, p$

= .032, $\eta_p^2 = .09$), but the main effect of hemisphere showed no statistical significance ($F(1, 27) = 0.03, p = .88, \eta_p^2 = .001$). A simple effect analysis showed significant difference between the activity of the left ALG ($M = 0.02, SD = 0.13$) and the right ALG ($M = -0.01, SD = 0.15$) ($F(1, 27) = 11.87, p = .002, \eta_p^2 = .31$). A multiple comparison of the
5 locations activated during the tone attention task indicated that the ASG was more strongly activated than the AIC (adjusted $p = .001$).

As a supplementary analysis, we subtracted the beta values acquired during the tone attention tasks in the 12 insula ROIs from those acquired during the heart attention tasks. Repeated-measures ANOVA with these values indicated a significant main effect of
10 location ($F(5, 135) = 9.40, p < .001, \eta_p^2 = .26$), but no significant main effect of hemispheres and the interaction between them ($F(1, 27) = 0.00, p = .95, \eta_p^2 < .001$; $F(5, 135) = 1.02, p = .41, \eta_p^2 = .03$, respectively). Since only the effect of location was significant, we checked whether the values of each location were higher than zero by repeating the one-sample t -tests. As a result, at a threshold of $p < .05$ (Bonferroni-
15 corrected), the ASG, MSG, and PSG regions were significantly activated during the heart attention task, even after subtracting the activations during the tone attention task; however, the AIC, ALG, PLG regions were not activated (ASG: $t(55) = 3.36$, uncorrected $p = .001$, Cohen's $d = 0.63$; MSG: $t(55) = 5.33, p < .001, d = 1.01$; PSG: $t(55) = 4.49, p < .001, d = 0.85$; AIC: $t(55) = 2.51, p = .02, d = 0.47$; ALG: $t(55) = 1.55, p = .12, d = 0.30$; PLG: $t(55)$
20 $= 2.57, p = .01, d = 0.49$).

Subsequently, we modeled each participant's IAc index as a covariate of interest into a second-level GLM analysis to investigate the relationship between the IAc and the

observed activation. This analysis revealed a positive correlation between the right dorsal anterior insula/frontal operculum ($x = 33, y = 21, z = 14, 162 \text{ mm}^3$) activity and the IAc (Figure 4). However, we could not find a significant correlation between IAc index and beta values of the 12 anatomical ROIs ($|rs| < .12$, details are exhibited in Supplementary material).

Discussion

Using a well-documented heartbeat counting task and an fMRI paradigm related to interoception, this study aimed to clarify the sensitive brain activation pattern, especially in the insular cortex, with regard to the two dimensions of interoception: attention and accuracy. First, compared with the tone attention task, the heart attention task activated the bilateral frontal operculum, middle insula, precentral gyrus, middle cingulate cortex, and supplemental motor area. Previous studies have reported that these areas are activated during interoceptive attention (Avery et al., 2014; Pollatos et al., 2007; Stern et al., 2017; Tan et al., 2018). By comparing the activation among the insular subdivisions during the heart attention task, we found, for the first time, that the MSG showed the highest activation, followed by the ASG and PSG. Moreover, the current study found no lateralized activation across the insula in the heart attention task, although some previous studies have argued in favor of right insular dominance in overall interoception (Craig, 2009; Critchley and Harrison, 2013). Finally, we found a strong association between an individual's ability to correctly perceive heartbeats (IAc index) and right dorsal anterior insula/frontal operculum activity during the heart attention task. This is in line with previous knowledge

that individual interoceptive accuracy scores correlate almost exclusively with the right anterior insula activity during an interoceptive attention task (Caseras et al., 2013; Critchley et al., 2004; Pollatos et al., 2007).

The differences in activation across the anatomical locations of the insular cortex
5 observed in this study confirm and extend the findings of previous studies. During the heart attention task, the ASG, MSG, and PSG were more activated than the other ventral and posterior portions of the insula (AIC, ALG, and PLG). This indicates the involvement of the dorsal middle-anterior insula in interoceptive attention (Araujo et al., 2015; Kurth et al., 2010; Terasawa et al., 2013), suggesting that these insular regions are strongly associated
10 with processing and representing the internal state of one's own body. In addition, we identified for the first time that among the anatomical locations of the brain, the MSG shows the highest activation during the heart attention task. Human insular subdivisions have variable structural connections with other cortical areas, such that the ASG and MSG have a connection with the frontal area, and the AGL and PLG, with the primary
15 somatosensory area (Cerliani et al., 2012; Cloutman et al., 2012). Therefore, it is plausible that our heart attention task did not activate the long gyri (posterior portions of the insula) because any explicit interoceptive sensation, such as palpitation or pain, was absent during the experiment.

Previous studies have revealed that electrical stimulation of the MSG and PSG evoked a
20 number of bodily responses, including somatosensory, visceral, and pain sensations (Afif et al., 2010; Yu et al., 2018). The current activation of the MSG and PSG may therefore be considered as a reflection of the bodily representation. In particular, the representation

associated with heartbeats could be in the PSG because another study reported that stimulation of the PSG often induced bradycardic effects (Chouchou et al., 2019). Although the ASG stimulations elicited few bodily responses in these studies, the current heart attention paradigm significantly activated the bilateral ASG region even after subtracting the confounding effects like counting numbers and the presented tone sounds. A previous meta-analysis has shown that the ASG is involved in cognitive processes such as working memory (Kurth et al., 2010) in addition to its structural connection with the frontal area. Hence, the current ASG activity may reflect a more cognitive aspect of interoceptive attention, such as searching for heart-related sensations and focusing attention on the internal milieu.

These findings can be incorporated into the results of psychiatric research on interoception. For example, Avery et al. (2014) reported that during interoceptive attention, patients with major depressive disorder exhibited lower activity in the bilateral dorsal mid-insula (especially the mid-posterior, comparable to the PSG) than healthy subjects. They also found that left mid-insula activity was negatively correlated with depression severity and the degree of somatization in the depressed group. Another study has shown that the dorsal anterior insula (corresponding to the ASG, MSG, and PSG) exhibited lower activation in depressed patients than in healthy controls and depression-remitted populations (Wiebking et al., 2015). Taken together, depressed individuals may have an attenuation in bodily representation in the MSG and PSG. In addition, aberrant somatosensation could be represented in the left PSG of people with depression.

This study also highlighted important insights into the laterality of the insula. There was no significant difference in insular activity between the hemispheres regarding interoceptive attention, even after subtracting the effects from possible confounders, which does not support our hypothesis. Previous fMRI studies have suggested right insular dominance in interoception (Simmons et al., 2013; Zaki et al., 2012), which supports the forebrain asymmetry of sympathetic/parasympathetic processing (Craig, 2005; Craig, 2009). Other studies have reported that the bilateral insula is involved in interoceptive attention tasks; however, none of these studies directly compared the activation between the right and left insula (Failla et al., 2020; Haase et al., 2016; Wiebking et al., 2010).

Regarding the asymmetry in autonomic input to the insula, the results of the current study imply that a representation of body states is established by the cooperation of sympathetic activities on the right middle-anterior insula and by parasympathetic activities on the left. This may be supported by the fact that there is a bidirectional information exchange between the left and right insula, especially in the middle and anterior portions (Lacuey et al., 2016).

The activity in the most dorsal region in the right anterior insula was positively correlated with the IAc index measured by the heartbeat counting task. This is in line with many studies that employed a behavioral task to measure individuals' abilities to perceive their own heartbeats (Caseras et al., 2013; Critchley et al., 2004; Kuehn et al., 2015; Pollatos et al., 2007; Tan et al., 2018). This lateralization regarding interoceptive accuracy was once interpreted as right anterior insula dominance for the representation of bodily arousal and the conscious experience of interoception overall (Critchley and Harrison,

2013; Gray and Critchley, 2007). However, this explanation might be inadequate because recent studies have revealed that the anterior insula can be divided into two distinct functional regions: the ventral portion involved in the affective process and the dorsal portion in the cognitive process (Cauda et al., 2011; Cauda et al., 2012; Deen et al., 2011).

5 In addition, the right dorsal anterior insula and frontal operculum are proposed as the core structures for cognitive processing, such as attentional control and salience detection (Dosenbach et al., 2007; Eckert et al., 2009; Menon and Uddin, 2010; Touroutoglou et al., 2012). Thus, the consistent relationship between the activity of the individual IAc and right dorsal anterior insula might be distinct from that of the bilateral middle-anterior insula
10 during general interoceptive attention. This suggests that the right dorsal anterior insula plays a key role in gaining an accurate perception of internal bodily states via top-down attention, such as filtering body signals from noise. Nonetheless, it is also possible that the higher the activity of the right dorsal anterior insula while focusing on heartbeats, the more sympathetic bodily arousal is re-represented there (Gray and Critchley, 2007), facilitating
15 conscious perception of heartbeats. If this were true, the individual IAc index would be associated with the quality of the bodily re-representation rather than with attentional processes. Although conclusion cannot be inferred from the present results alone, it is likely to be true in one of these two cases. Clarification the role of right anterior insula in accurate, not for general interoception is needed to orient the future researches aiming at
20 individual differences in interoception.

Limitations of this study

The current study has several limitations. First, we stated that insular involvement in interoceptive attention and accuracy could be dissociable. However, the task administration for interoceptive attention and accuracy differed because we employed a heart attention task using fMRI; moreover, the heartbeat counting task was performed outside of the MRI scanner. An individual IAc score is known to be temporally stable (Ehlers et al., 1995; Ferentzi et al., 2018), and we tried to make the two heartbeat counting tasks comparable with strict instructions, but it is still possible that there were differences in postures or task environments. Second, we introduced tone stimuli during both heartbeat and tone attention tasks to make both conditions more comparable for the subtraction analysis. Whereas the presentation of auditory stimuli during interoceptive attention task was commonly used in the previous studies (Critchley et al., 2004; Kuehn et al., 2015), this could, however, cause multisensory integration even when the participants attended to interoception. Although the volume of tone was adjusted so small that participants had to pay much attention to perceive, subliminal auditory stimuli might affect the pattern of brain activation elicited by their attention to the heart. Thus, our interoceptive attention paradigm might be somewhat different from the pure attention to interoception and might cause the absence of significant activity in the posterior insula. Third, in our ROI analysis, we used structural subdivisions of the insula that were constructed using probabilistic mapping, which can have several overlaps with each other by nature. This would cause an increase in the activation similarity between two adjacent ROIs. Therefore, it may be inappropriate to declare that the MSG of the insula was the most involved in interoceptive attention, although the current analysis obtained clearly significant results.

Conclusion

In conclusion, our findings elaborate and extend previous knowledge regarding the relationship between interoception and the insular cortex. Recent studies have uncovered multiple aspects of interoception, and critically, the current study revealed the different involvement of the subdivisions of the insula in interoceptive attention and accuracy.

Interoceptive attention was found to induce activation of the bilateral mid-anterior insula.

In contrast, interoceptive accuracy—the correct perception of any change in the body—was positively correlated with the activity of the dorsal margin of the right anterior insula,

which is considered as the center of attentional control. Identifying the distinct relationship between each aspect of interoception and the subdivisions of the insular cortex would facilitate the understanding of the nature of interoception and the function of the insula in further detail.

Acknowledgments

This work was supported by JSPS KAKENHI (grant numbers 18H01098, 19H05493, 19H00634; provided to KO).

Abbreviations

AAL, anatomical automatic labeling; AIC, anterior inferior cortex; ALG; anterior long gyrus; ANOVA, analysis of variance; ASG, anterior short gyrus; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; GLM, general linear model; IAc,

interoceptive accuracy; MNI, Montreal Neurological Institute; MSG, middle short gyrus; PLG, posterior long gyrus; PSG, posterior short gyrus; ROI, region of interest.

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Tables

Table 1: Anatomical regions, peak voxel coordinates, and t-values of observed activations.

The peak-level threshold was set to $p < .05$ (FDR-corrected) and the cluster size was also corrected for extent threshold with FDR ($p < .05$).

Anatomic region	Voxels	MNI coordinates			<i>t</i> -value
		x	y	z	
<i>Heart attention > Tone attention</i>					
L Rolandic operculum	120	-54	2	8	7.71
Dorsal mid-insula		-36	2	8	6.23
Precentral gyrus		-57	5	26	5.86
R Rolandic operculum	39	57	2	5	7.60
L Supplementary motor area	46	-9	-1	59	6.84
L Middle cingulate cortex	72	-9	8	35	6.79
R Supplementary motor area		3	5	47	6.31
R Supplementary motor area	15	9	-4	65	6.02
<i>Tone attention > Heart attention</i>					
<i>No voxel has activated</i>					

5 MNI, Montreal Neurological Institute; L, left hemisphere; R, right hemisphere.

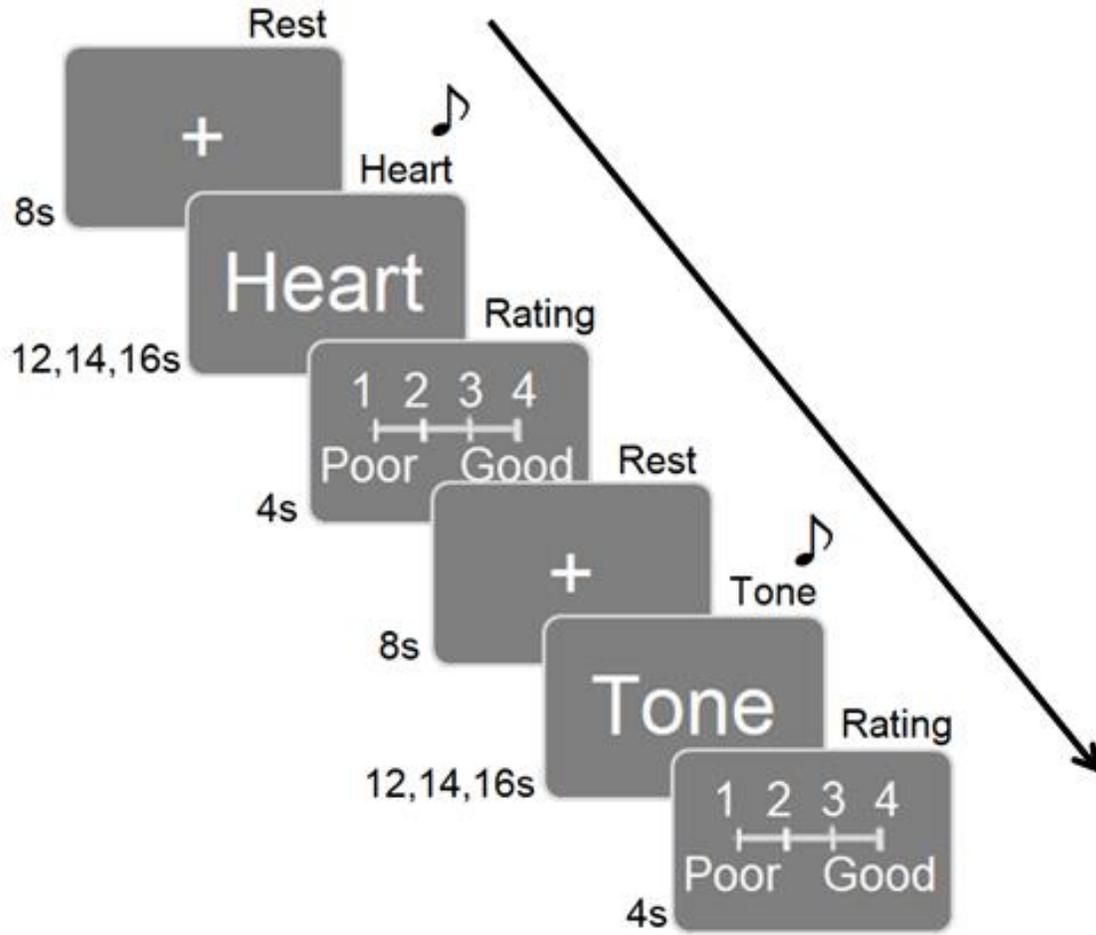


Figure 1. Example of the time course of the fMRI tasks. The heart attention and tone attention condition trials were presented alternatively. The trials consisted of the task block (12 s, 14 s, or 16 s), rating block (4 s), and rest block (8 s). In the task block, participants counted their own heartbeats (heart attention task) or tone sounds (tone attention task) following each visual instruction, respectively. Participants then rated how well they had concentrated in the previous task block using a scale from one (poor) to four (good) by pressing a response button with their right hand. In the following rest block, the fixation cross was displayed. During both task blocks, slight tone sounds were continuously played via headphones.

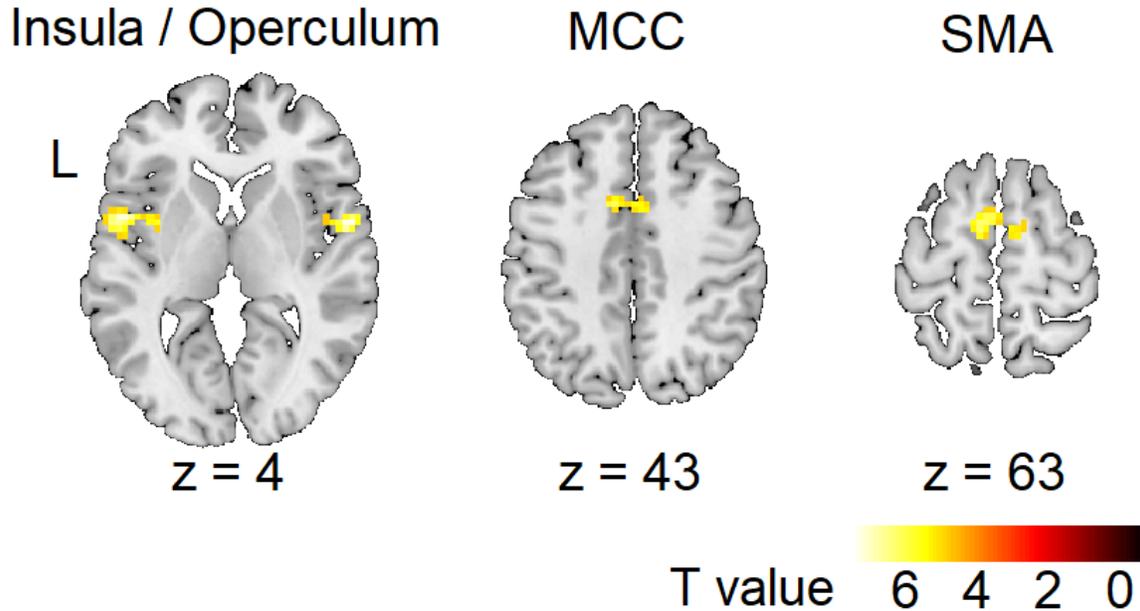


Figure 2. Activated brain regions in the heart attention condition compared to the tone attention condition. Activation was reported with a threshold p-value of $< .05$, corrected for multiple comparisons for the false discovery rate (FDR) with an extent threshold p-value of $< .05$. L, left hemisphere; MCC, middle cingulate cortex; SMA, supplementary motor area. MNI coordinates of the activated foci are reported in Table 1. Figures are displayed in the axial slices with z denoting locations in the MNI coordinates.

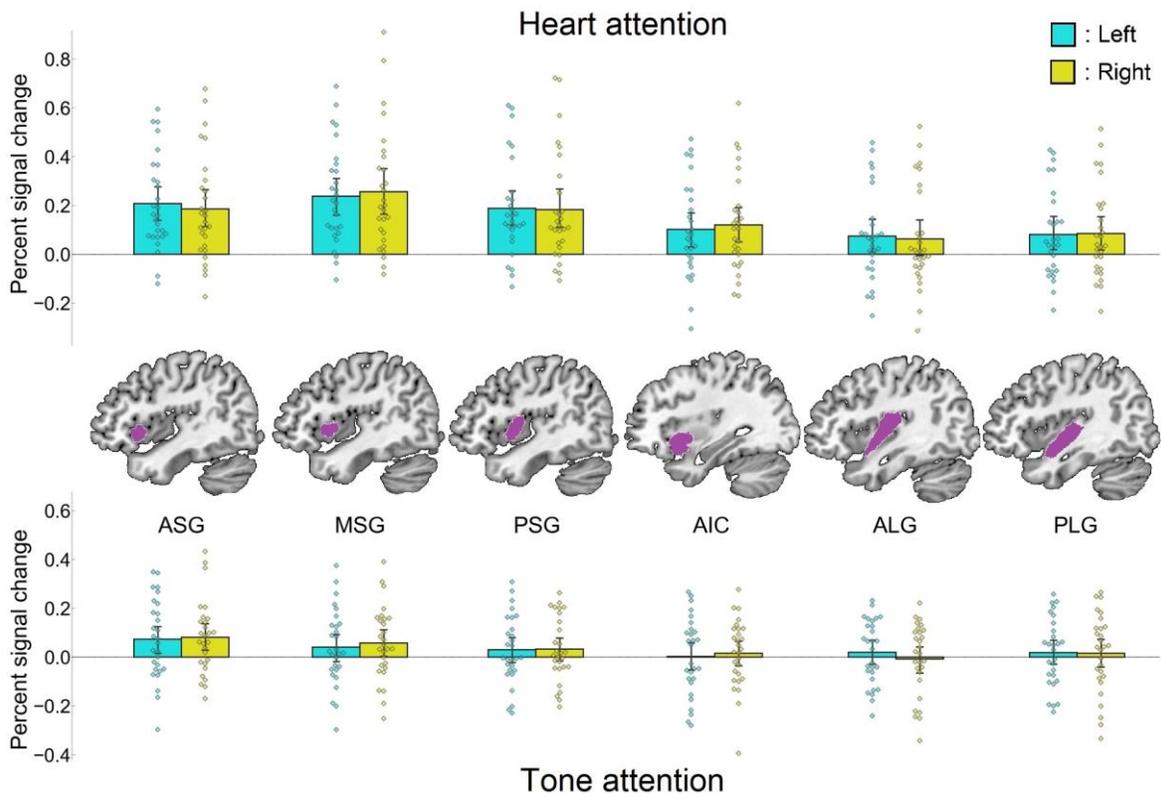


Figure 3. The averaged effects of each task condition among the subdivisions of the insular cortex. The Y values (percent signal change) correspond to the acquired beta values. The upper and lower six columns are associated with the subdivision of the insula shown in the center. Each point that overlaid on the barplots corresponds to the raw data of each participant. Error bars indicate a 95% confidence interval. ASG, anterior short gyrus; MSG, middle short gyrus; PSG, posterior short gyrus; AIC, anterior inferior cortex; ALG, anterior long gyrus; PLG, posterior long gyrus.

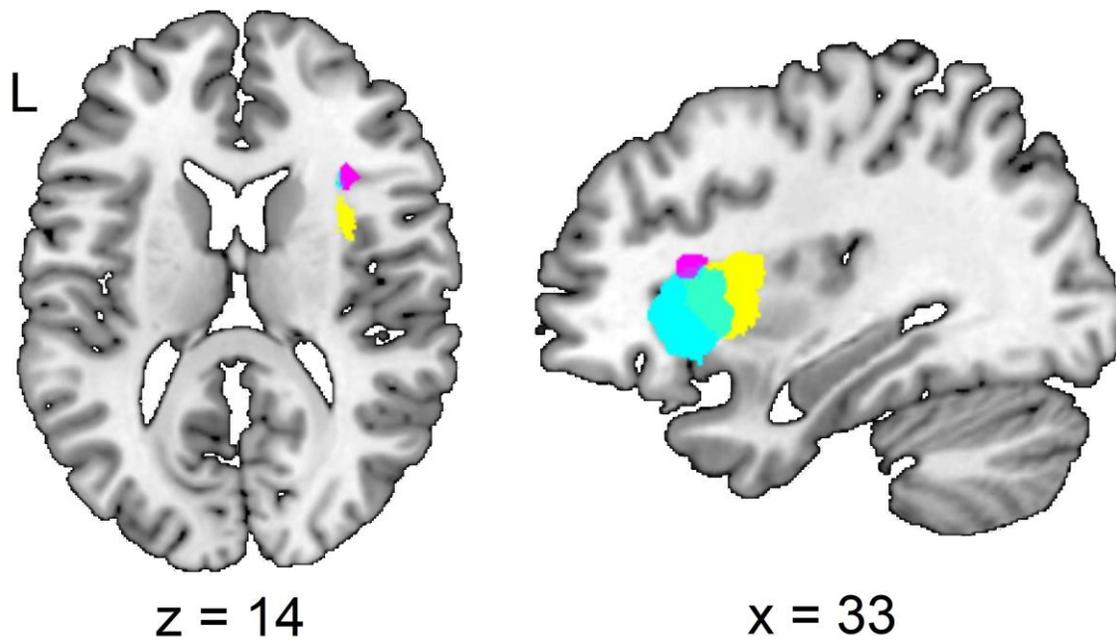


Figure 4. The region exhibiting an activation that correlated with the interoceptive accuracy index. Only the right dorsal anterior insula/frontal operculum (purple cluster, MNI coordinates: $x = 33$, $y = 21$, $z = 14$) was associated with individual interoceptive accuracy.

5 The ASG (cyan) and the MSG (yellow) that were used in our ROI analysis are shown in the overlay as a reference. Figures are displayed as axial slice with z and sagittal slice with x , with the letters denoting locations in the MNI coordinates.