心臓と胃の内受容感覚に関わる主観的経験と その個人差による脳内ネットワークの変調: fMRI 研究

Awareness of cardiac/gastric interoception and its individual differences modulate the neural dynamics

晴木 祐助[1, 2, *], 鈴木 啓介[1], 小川 健二[1]
Yusuke Haruki, Keisuke Suzuki, and Kenji Ogawa
[1]北海道大学, [2]日本学術振興会
Hokkaido University, Japan Society for the Promotion of Science
[*]haruki@let.hokudai.ac.jp

Abstract

Senses that arise from within the body are referred to as interoception. Empirical studies on interoception have primarily utilized cardiac sensation (senses related to one's heartbeat) because of its easiness of measuring non-invasively. With this practice, however, it is unclear whether interoception is a unimodal sensory phenomenon. Here, we show that the different types of phenomenal interoception evoke a particular pattern of neural activities. Specifically, attention on cardiac and gastric (related to the stomach) interoception activated different brain regions and altered the functional connectivity in these regions. Furthermore, individual differences in cardiac/gastric sensitivity were associated with intrinsic functional connectivity of the insular cortex. Submodalities of interoception would be distinctive in their neural dynamics as well as phenomenal experience.

Keywords — interoception, fMRI, functional connectivity

1. Introduction

Interoception refers to senses that arise from within the body. For example, hunger, heartbeat sensations, dizziness, urination, fever, and many other phenomenal experiences are subject to interoception. Empirical studies on interoception, however, have been unable to incorporate such diversity due to the difficulty of measuring and manipulating bodily signals.

Awareness of cardiac signals has been extensively used to investigate the characteristics of interoception. Behavioral tasks on heartbeat perception (e.g., counting own heartbeat) have revealed a large individual difference in cardiac interoception (or its sensitivity) [1]. Although those tasks have been widely used and well-validated, cardiac sensitivity does not necessarily correspond to bodily awareness in broader sense. Subjective sensibility to interoception measured via questionnaire and cardiac sensitivity usually do not correlate with each other [1]. Another study has shown that a meditation practitioner does not have sensitive cardiac interoception [2].

One seminal opinion regarding the neural substrates of interoception suggests that the insular cortex, particularly the right anterior insula, plays critical role in generating phenomenal interoception [3]. This idea has been supported by fMRI studies using cardiac interoception [4, 5]. However, given the variety of phenomenal interoception, we consider that the opinion could be suspicious without a direct comparison of brain activity between cardiac and other types of interoception. Several fMRI studies have already used gastric (senses related to stomach sensation) and urinary (related to bladder) interoception to capture the neural basis of interoception [6, 7], but none of them compared the neural activation by the types of interoception.

Here, we directly compared neural activation during cardiac and gastric interoception to test whether the different types of phenomenal interoception evoke particular pattern of brain activation. In addition to differences in activation, we also focused on temporal dynamics (functional connectivity) between the brain regions during cardiac/gastric interoception. Furthermore, we assessed individual differences in cardiac and gastric sensitivity and tried to associate it with the intrinsic, task-free functional connectivity in the insular cortex. Through a series of analyses, we showed that the brain dynamics underlying cardiac and gastric interoception largely differ, highlighting the importance of submodalities of interoception.

2. Materials and Methods

2.1. fMRI experiments

A total of 30 healthy volunteers (12 women, 21.61 ± 2.45 years old) participated in the experiment on two occasions, at least a week apart. On day 1, we asked participants to experience fMRI scanning to obtain brain activation during rest and performing tasks. Participants first underwent a fiveminute resting-state fMRI scan in which they looked at a fixation crossbar with their eyes open and did not think anything in particular.

Subsequently, we asked participants to perform an interoceptive attention task in the scanner [6, 7], which was modified for our purposes. The task had three conditions: HEART (related to cardiac), STOMACH (related to gastric), and VISUAL (control). In each condition, participants tried to perceive sensations from the instructed source (i.e., heart, stomach, and slight color change of words) by directing their attention. There were five trials for each condition per run, with five runs repetition (a total of 125 scans per condition).

All scans were performed on a Siemens 3-Tesla Prisma scanner (Erlangen, Germany) with a 64-channel head coil at Hokkaido University. The scanning parameters for functional data were as follows: repetition time, 2,000 ms; field of view, 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.

2.2. Behavioral experiments

On day 2, we asked participants to complete a heartbeat counting task [1, 8] and water load test [9] out of the MRI scanner to assess individual differences in cardiac and gastric sensitivity behaviorally. The heartbeat counting task required participants to silently count the number of their heartbeats in a certain period by focusing on the internal bodily sensation. Estimating the number and taking pulse outside the body was prohibited. We evaluated individual sensitivity of cardiac interoception by comparing the counted number to the actual number of heartbeats. The calculation yielded a score ranging from 0 to 1, with 1 indicating the highest sensitivity.

In the water load test, participants were asked to drink room temperature, non-carbonated water ad libitum using a straw and to stop drinking when they first felt the sign of subjective fullness. A total of 1.5 liters of water was filled in a five-liter capacity container whose contents were invisible from the outside; thus, participants did not know the water volume they consumed. The difference between the total volume and consumed volume was used as an estimation of individual sensitivity of gastric interoception.

2.3. fMRI data analysis

All image processing was performed using SPM12 (Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). The standard procedure of preprocessing (realignment, normalization to Montreal Numerological Institute (MNI) space, and smoothing with 6 mm cube Gaussian kernel) was performed before statistical inference. A high-pass filter was applied with a cutoff of 128 s, and serial correlations among scans were estimated using an autoregressive model to exclude signal noise.

Individual level generalized linear model included each task trial block as separate box-car regressors that were convolved with the canonical hemodynamic response function. To reduce motion-related artifacts, six motion parameters were included as nuisance regressors.

We then performed three group analyses: random effects analysis to directly compare brain activation, psychophysiological interaction analysis to compare the changes in functional connectivity, and correlation analysis for the resting-state fMRI data. First, we performed one sample t-test on random effects using the contrast images of the HEART and STOMACH conditions. By doing so, we identified brain regions selectively activated for cardiac and gastric interoception across the whole brain. These detailed results and further discussion are now available as a preprint [10].

Subsequently, we defined the region of interest (ROI) for the second analysis based on the results of the first analysis. A 4 mm sphere ROI centering on the peak activated coordinates in the first analysis for each condition was created for the most activated four clusters. This resulted in four individual ROIs: the left orbitofrontal (center coordinate: x, y, z) = (-42, 26, -16), left primary visual (-12, -73, -13), right anterior insula (33, 17, 2), and the left primary motor area (-48, -7, 29). Thereafter, we tested whether the attentional focus on the heart/stomach modulates the functional connectivity. We performed a psychophysiological interaction analysis that models the task type (cardiac and gastric), the time course of ROI activity, and the interaction between them. This analysis can estimate task-dependent changes in functional connectivity between the ROI and the other brain regions. The effect of cardiac and gastric interoception on the functional connectivity was computed for each ROI for each participant. Finally, as a group level analysis, we performed one sample t-tests on these individual level results.

The third analysis was independent of the first and second ones. Here, we identified the brain regions that exhibited an enhanced intrinsic (task-free) functional connectivity with the structural subdivisions of the insular cortex in people with high cardiac/gastric sensitivity. We adopted the ROIs from the Hammersmith atlas [11]: the right middle short gyrus for the anterior insula and the anterior long gyrus for the posterior insula. The selection was based on previous findings that the middle short gyrus was the most activated when people focused on their heartbeats [12] and that the anterior long gyrus corresponds to the primary interoceptive cortex that is first projected with visceral signals at the cortical level [13]. Individual correlation maps were generated by extracting the time series signal in each ROI (i.e., the right anterior and posterior insula) and calculating correlation coefficients with the signals of each voxel throughout the whole brain. We also modeled the individual cardiac and gastric sensitivity that was measured via the behavioral experiments as group level covariates of interest. We tested the group level effects of cardiac/gastric sensitivity on the intrinsic functional connectivity by performing one sample t-tests.

3. Results

3.1. Behavioral result

The mean score of cardiac sensitivity measured by the heartbeat counting task was 0.43 ± 0.25 while the average volume left in the bottle in the water load test was 1179 ± 189.54 ml. Pearson's correlation coefficient between the two did not reject the null hypothesis that the coefficient was zero ($r = 0.24$, $t_{28} = 1.31$, $p = .20$).

3.2. fMRI result

We report all the results surviving peak level threshold $p < .001$ (uncorrected) and cluster level threshold $15 < k$. Firstly, we found that cardiac interoception enhanced the neural activation in the right anterior insula compared to gastric interoception. In contrast, the activated regions in the gastric contrasted to cardiac interoception encompassed the larger brain areas, including the visual area, sensorimotor region, hippocampus, superior frontal and orbitofrontal cortex (Figure 1).

The functionally defined ROI seeds showed altered functional connectivity with other brain regions depending on the task type (focusing on cardiac or gastric interoception) (Figure 2). Interestingly, the functional seed regions more activated in gastric interoception showed decreased, rather than increased, functional connectivity with other regions during gastric interoception compared to cardiac interoception. More specifically, the left primary visual seed showed decreased functional connectivity with the right occipitotemporal, left temporoparietal, and right frontal regions. The functional connectivity between the left orbitofrontal seed and right frontal/temporal regions also decreased in gastric interoception. The left primary motor seed had decreased connectivity with the medial occipital regions. In the same line, the right anterior insula seed that was more activated during cardiac interoception exhibited decreased functional connectivity with the right primary visual area related to gastric interoception. Only the left primary visual seed showed enhanced functional connectivity with the contralateral primary visual area in gastric interoception.

We also found that individual differences in cardiac and gastric sensitivity were differently associated with the intrinsic (task-free) functional connectivity in the insula (Figure 3). In people with higher cardiac sensitivity, the right primary interoceptive cortex (posterior insula) showed a stronger intrinsic functional connectivity with the bilateral frontal operculum, temporoparietal junction, left frontal pole, and left inferior frontal gyrus but decreased connectivity with the bilateral dorsolateral prefrontal cortex and superior parietal lobule. Such people also had the increased intrinsic connectivity of the right anterior insula with the bilateral ventromedial prefrontal cortex and right temporoparietal junction but decreased with the right middle insula. Conversely, higher gastric sensitivity contributed to stronger intrinsic connectivity of the right dorsal posterior insula with the bilateral putamen and left thalamus. The right anterior insula was more connected with the bilateral temporoparietal junction in people with higher gastric sensitivity.

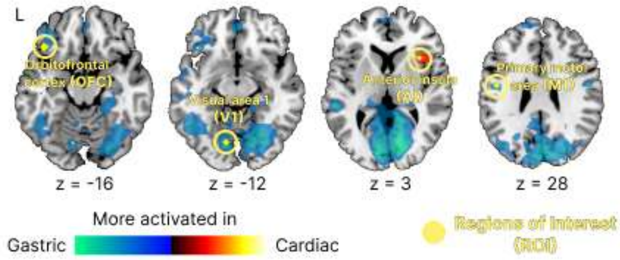

Figure 1. Selectively activated brain regions for cardiac and gastric interoception. z denotes the axial slice in MNI space. ROIs in yellow were used in the psychophysiological

interaction analysis. L: left hemisphere

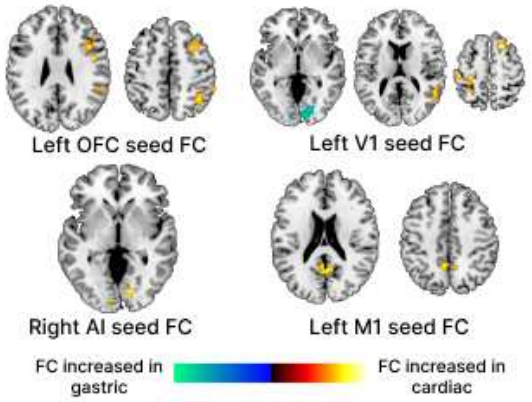

Figure 2. Results of the psychophysiological interaction analysis. Colored regions showed altered functional connectivity in the seed regions defined in Figure 1. depending on the attentional focus (cardiac, hot; gastric, cold). AI, anterior insula; FC, functional connectivity; M1, primary motor area; OFC, orbitofrontal cortex; V1, primary visual area

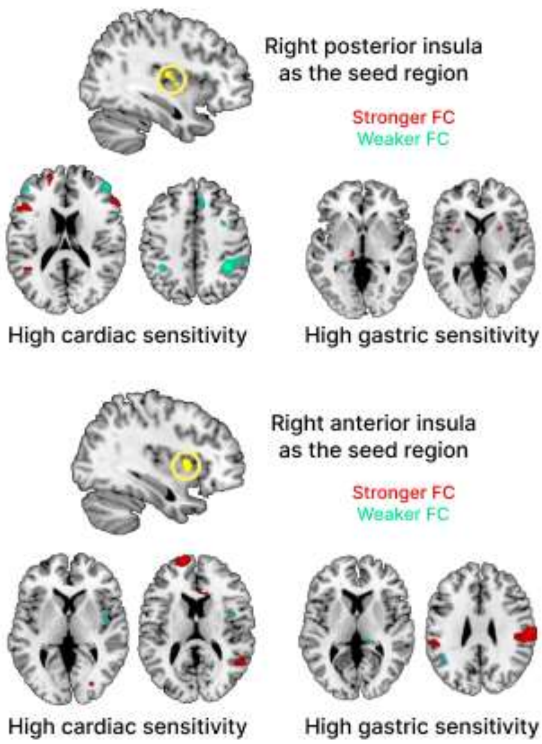

Figure 3. Subdivisions of the insula showing altered intrinsic functional connectivity depending on individual difference in cardiac/gastric sensitivity. FC, functional connectivity

4. Discussion

In this study, we show that focusing on cardiac and gastric interoception activated different brain regions and altered their functional connectivity depending on the task type. Moreover, intrinsic (task-free) functional connectivity in the insular cortex with other brain regions was associated with individual differences in cardiac/gastric sensitivity measured via behavioral tasks. These results reveal that the different types of phenomenal interoception are associated with particular neural dynamics in the human brain, suggesting that interoception is not a unimodal sensory experience even at the neural level.

A previous meta-analysis on fMRI studies using cardiac interoception identified the consistently activated brain regions in the right insula and supplementary motor area [14]. These results strongly supported the dominance of the right insula in interoception [3, 4, 5]. However, the present study showed gastric interoception activated a widespread region across the sensorimotor region and frontal region in gastric interoception, while cardiac interoception enhanced the activation in the right insula. Therefore, the role of the right insula for interoception may be cardiac-specific rather than interoception in general.

Moreover, we found task-modulation effects on functional connectivity in the brain regions that were selectively activated during cardiac/gastric interoception. In general, functional connectivity in these functionally defined seed regions reduced during gastric compared to cardiac interoception. The results show that gastric contrasted to cardiac interoception evoked enhanced activation over distributed brain areas, but they were functionally disconnected from other brain regions.

It is interesting to note that gastric interoception showed enhanced but functionally disconnected activations in the primary visual and sensorimotor area. It appears puzzling that brain activation in the primary sensory cortex differed between conditions because any visual or sensorimotor signals were absent in the present interoception task. This could be explained by differences in the functional roles of each phenomenal interoception [10]. For example, the functional role of gastric interoception has been proposed to modulate feeding and foraging behavior in which agents must properly regulate their sensorimotor ability [15]. In line with this, it could be reasoned that gastric interoception that is likely to occur during food intake may be more relevant to the visual and sensorimotor regions than cardiac interoception.

Furthermore, individual differences in intrinsic functional connectivity in the right anterior and posterior insula were associated with interoceptive sensitivity. Particularly, higher sensitivity in cardiac interoception contributed to the increased connectivity in both the anterior and posterior insula with the frontal and temporal regions. Sensitive cardiac interoception was also characterized by the decreased connectivity in the posterior insula with the superior parietal region and the anterior insula with the ipsilateral middle insula. In contrast, high gastric sensitivity enhanced the intrinsic functional connectivity in the anterior insula with the bilateral temporoparietal junction and in the posterior insula with the putamen. Together, the functional connectivity between the right anterior insula and temporoparietal junction may be necessary for sensitive interoception over modalities. However, cardiac sensitivity may require the (de)coupling of the insula with the regions orienting attention (the superior parietal and frontal regions) compared to gastric interoception. This result would be in line with the proposal that cardiac sensitivity would be enhanced via attentional modulation of sensory gain of the heartbeat-related signals [16].

The present results indicated that the neural dynamics underlying cardiac and gastric interoception differed greatly. Although the previous discussion on interoception has depended primarily on studies using cardiac interoception alone, researchers need to consider that interoception has submodalities and some results in a certain modality do not coincide with others. In future studies, the functional roles of different phenomenal interoception in relation to one's behavior, cognition, and emotion would be of interest.

Acknowledgement

This work was supported by JSPS, KAKENHI Grant Number 20K20423 to K.O. and 22J20351 to Y.H, and by JST, CREST Grant Number JPMJCR21P4 to K.S. and.

References

[1] Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., & Critchley, H. D. (2015). "Knowing your own heart: Distinguishing interoceptive accuracy from interoceptive awareness", *Biological Psychology*, 104, 65–74.

[2] Khalsa, S. S., Rudrauf, D., Hassanpour, M. S., Davidson, R. J., Tranel, D., & Davidson, R. J. (2020). "The practice of meditation is not associated with improved interoceptive awareness of the heartbeat", *Psychophysiology*, 57, e13479.

[3] Craig, A. D. (2009). "How do you feel — now? The anterior insula and human awareness", *Nature Reviews Neuroscience*, 10(1), 59–70.

[4] Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). "Neural systems supporting interoceptive awareness", *Nature Neuroscience*, 7(2), 189–195.

[5] Tan, Y., Wei, D., Zhang, M., Yang, J., Jelinčić, V., & Qiu, J. (2018). "The role of mid-insula in the relationship between cardiac interoceptive attention and anxiety: evidence from an fMRI study", *Scientific Reports*, 8(1), 17280.

[6] Simmons, W. K., Avery, J. A., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). "Keeping the body in mind: Insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness", *Human Brain Mapping*, 34(11), 2944–2958.

[7] Deville, D. C., Kuplicki, R., Stewart, J. L., Paulus, M. P., Khalsa, S. S., Aupperle, R. L., Bodurka, J., Cha, Y. H., Feinstein, J., Savitz, J. B., & Victor, T. A. (2020). "Diminished responses to bodily threat and blunted interoception in suicide attempters", *eLife*, 9, e51593.

[8] Schandry, R. (1981). "Heart Beat Perception and Emotional Experience", *Psychophysiology*, 18(4), 483–488.

[9] Herbert, B. M., Muth, E. R., Pollatos, O., & Herbert, C. (2012). "Interoception across modalities: On the relationship between cardiac awareness and the sensitivity for gastric functions", *PLoS ONE*, 7(5), e36646.

[10] Haruki, Y., & Ogawa, K. (March 11, 2022). "Cardiac and gastric interoception have distinct neural substrates", *bioRxiv*

[11] Faillenot, I., Heckemann, R. A., Frot, M., & Hammers, A. (2017). "Macroanatomy and 3D probabilistic atlas of the human insula", *NeuroImage*, 150, 88–98.

[12] Haruki, Y., & Ogawa, K. (2021). "Role of anatomical insular subdivisions in interoception: Interoceptive attention and accuracy have dissociable substrates", *European Journal of Neuroscience*, 53(8), 2669–2680.

[13] Evrard, H. C. (2019). "The organization of the primate insular cortex", *Frontiers in Neuroanatomy*, 13, 00043.

[14] Schulz, S. M. (2016). "Neural correlates of heart-focused interoception : a functional magnetic resonance imaging meta-analysis", *Philosophical Transactions of the Royal Society B: Biological Sciences*, 371.

[15] Kanoski, S. E., & Grill, H. J. (2017). "Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms", *Biological Psychiatry*, 81(9), 748–756.

[16] Ainley, V., Apps, M. A. J., Fotopoulou, A., & Tsakiris, M. (2016). ""Bodily precision": A predictive coding account of individual differences in interoceptive accuracy", *Philosophical Transactions of the Royal Society B: Biological Sciences*, 371.