IV. 1 Functional Module of the Brain Correlates the Trait Anxiety by Colonic Distention


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Introduction

Psychological factors may play an important role in visceral perception. A close relationship between emotional state and gastrointestinal function is reported in patients with functional gastrointestinal disorders, including irritable bowel syndrome (IBS)\(^1\). There is increasing experimental evidence to suggest an interaction between emotional context, cognition and sensory processing\(^2,3\). The cerebral evoked potential to gastrointestinal stimulation has been shown to be modulated by attentional processes\(^4\), it may reflect such higher level processing of painful stimuli\(^5\).

Psychological stress response induces gastrointestinal symptoms such as abdominal pain, diarrhea or constipation in humans\(^6\). These phenomena are explained by stress-induced colonic motility\(^7\) and visceral perception abhorred by the stress\(^8\). IBS is a functional gastrointestinal disorder characterized with chronic abdominal pain and abdominal bowel habituation. Functional relation between central nervous system and gastrointestinal tract begins to be clarified and brain-gut interactions are considered to be major pathophysiology of IBS\(^9,10\).

Personality property is closely related to stress response. The processing of the information about perception from the gastrointestinal tract to the brain may be related to personality traits\(^11\). However, brain regions of personality traits as well as anxiety trait that relate to stress response is uncertain. We are imaging that the multiple control sites are interconnected so that stress responses can be organized, at varied degrees of complexity, some involving the recruitment of just a few brain sites, others requiring a concerted large-scale operation, but often involving both cortical and subcortical sites.
To vilify the following hypotheses, we examined the brain images and personality trait during colonic distention in humans.

**Method**

**Subjects**

Fifteen volunteers participated in this study. Their were all male, right-handed, and aged 22.2 (mean SE). All subjects were free from gastrointestinal symptoms or signs. Each underwent a basic evaluation to exclude organic disease including a history and physical examination and colonoscopy. All subjects gave informed consent as approved by the Ethics Committee in Tohoku University School of Medicine.

**Distention Protocol**

On the day before examination, the subjects took the low residue diet. At 21:00 before the examination, they ingested 17g (13.6%) of magnesium citrate, 75mg of sodium picosulfate, and 24mg of sennoside A & B to cleanse the colon. Subjects were tested in the fasted state at 8:15. Colonoscope was inserted to the splenic flexure and splinting device was inserted along the scope. After the removal of the scope, a thin plastic bag (Svenstics Medical, Stockholm) of maximal volume (700ml, 10cm diameter when fully inflated) was advanced into the descending colon. The location of the bag was confirmed with X-ray fluoroscopy. The splinting device was removed and the bag was taped in place. Subjects were laid in bed at 9:15 for the rest.

The colonic distention stimuli were provided with computerized barostat equipment (maximal inflation rate, 38ml/s [Medtronics Synectics, Shoreview, MN]). The sham stimulation with 0 mmHg was given at first. The colon was then stimulated with the bag pressure of 40 mmHg for 80 seconds.

**Psychological measurement**

Before the stimulation, subjects were required the answer to questioner in the State Trait Anxiety Inventory (STAI)\(^1\)\(^2\).

**PET scanning**

Plaster head support was set for each subject to minimize head movements during the PET imaging. By using 68Ge/68Ga radiation source, transmission scan for the \(\gamma\)-ray
absorptive correction was done before positron emission tomography (PET) scanning. The PET scan room was made to be under the gloom. The subjects closed their eyes with waking.

$[^{15}\text{O}]$ labeled water which was synthesized by the cyclotron was injected from the right arm vein with the beginning of colonic distention. At 10 seconds after the beginning of $[^{15}\text{O}]$ labeled water injection and colonic distention, both radioactivity and peak pressure of the bag reach plateau. The PET scanning then started and continued for 70 seconds. We measured regional cerebral blood flow (rCBF) during 4 scans (70 seconds each) using a PET scanner in three-dimension sampling mode (HEADTOME V SET-2400W, Shimadzu, Japan).

**Analysis**

The PET image analyzed for brain image analysis software (Statistical Parametric Mapping; SPM99, The Wellcome Department of Cognitive Neurology, London) according to the method of Friston et al$^{14}$. All slices (63 sheet) including the brain images were extracted. The PET images were realigned, spatially normalized and transformed into an approximate Talairach-Tournoux stereotactic space$^{13}$, 3D Gaussian filtered (FWHM = 13 mm), and proportionally scaled to account for global confounders. The size of each voxel was set at $2 \times 2 \times 2$mm.

To clarify the region where the rCBF fluctuates by correlating with trait anxiety in the colonic distention, we examined by using the ‘simple regression analysis’ option in SPM. We set 0.18 % level of significance or less (uncorrected, $Z \geq 3.00$) as the region of significant correlation.

**Results**

**Trait anxiety score of subjects**

Trait anxiety scores of subjects were 44.33 8.65 (mean SD, minima 26 to maxima 58). The normal score range in trait anxiety was 25 to 75. After the colonic distention, all subjects reported their emotion and visceral perception during the distention protocol. They reported increasing the negative emotion such as anxiety and perceived stress, and the visceral perception such as abdominal distention, abdominal pain, and urgency for defecation.
Brain activity correlates the trait anxiety by colonic distention

The simple regression analysis showed positive relation between trait anxiety and rCBF during the colonic distention (uncorrected p = 0.0018, Table 1). They were the left middle frontal gyrus (BA 10, Fig. 1-A), the left orbitofrontal gyrus (BA11, Fig. 1-B), the left prefrontal gyrus (Fig. 1-C), and the right inferior temporal gyrus (BA20, Fig. 1-D). Conversely, there were no regions of significantly negative correlation with the trait anxiety by colonic distention.

Discussion

The most important part of this study is that the prefrontal cortexes were significantly correlated to the trait anxiety by colonic distention in human. Our results suggest that trait anxiety may be related to central processing of visceral perception by colonic distention in humans. The prefrontal cortex participates in linking perception of stimuli to the guidance of behavior\(^{15}\), including the flexible execution of strategies for obtaining rewards and punishments\(^{16}\). Regions in the medial and ventral aspects of the frontal lobe seem especially important in relating information about external sensory stimuli to interoceptive information that represents emotional significance. The prefrontal area checks the given stimulation with experience and memory accumulated and may be the position which finally determines the meaning of stimulation; comfort or discomfort\(^{17,18}\).

Recently, the significant negative correlation between late peak latency of cerebral evoked potential and hypochondriasis in Minnesota Multiphasic Personality Inventory by esophageal electro stimulation was reported\(^{11}\). Previously finding suggested the cognitive pattern associated with some personality variables might promote visceral hypersensitivity via cortical processing.

Our results also suggest that cognitive patterns associated with neurotic variables such as depression and anxiety might promote visceral hyper and/or hyposensitivity via cortical processing.

Acknowledgements

References


Table 1. Covariation of rCBF with STAI (positive correlation).

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (x, y, z)</th>
<th>Z score</th>
<th>p value</th>
<th>Voxels in Cluster</th>
</tr>
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<tbody>
<tr>
<td>Middle Frontal Gyrus</td>
<td>L</td>
<td>10</td>
<td>-34 64 -6</td>
<td>3.37</td>
<td>&lt; 0.001</td>
<td>44</td>
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<tr>
<td>Orbitofrontal Gyrus</td>
<td>L</td>
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<td>-18 52 -22</td>
<td>3.07</td>
<td>0.001</td>
<td>133</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
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<td></td>
<td>-30 4 28</td>
<td>3.10</td>
<td>0.001</td>
<td>77</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>R</td>
<td>20</td>
<td>52 -12 -46</td>
<td>3.07</td>
<td>0.001</td>
<td>35</td>
</tr>
</tbody>
</table>

Coordinate refer to location in stereotaxic space. Table shows at Maxima in the search value defined a priori. Height threshold P = 0.0018, Extent threshold k = 20 Voxels (uncorrected). BA: Brodmann Area.
Fig. 1. Brain regions of positive correlation between rCBF and STAI by the simple regression analysis (p < 0.0018 uncorrected). (A) showed demonstrating voxels in the left middle frontal gyrus, (x y z), (-34 64 -6), (B) the left orbitofrontal gyrus, (x y z), (-18 52 -22), (C) the left precentral gyrus, (x y z), (-30 4 28), and (D) the right inferior temporal gyrus (x y z), (52 -12 -46) that significant correlated to trait anxiety. There were superimposed on the structural MRI scan of a single subject. Bottom showed the linear regression between PET signal across subjects and trait anxiety in STAI. Blue dots were indicated the subject data, and red were linear regression lines. Color bar indicated T-score by the simple regression analysis option in SPM99.