VIII. 2. Differential Activation of the Human Brain in Response to Sham Stimulation after Experience of Visceral Stimulation


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Introduction

Anticipation of pain is mechanism to prevent future harm by learning signs of impending pain\(^1\)-\(^4\), allowing avoidance of future painful events. Anticipation of an intense visceral stimuli induces activation of orbitofrontal cortex (OFC), PFC, perigenual ACC, thalamus, lentiform nucleus, and PAG region\(^5\).

The placebo effects on the midbrain which contains endogenous opioids during analgesic anticipation\(^6\). Anticipation reduced ACC activity during the earlier phase of pain and the thalamic and the insula activity during the late phase of pain\(^6\). Previous studies provide that anticipation events on pain through the functional module of the brain.

Hypersensitivity to visceral stimulation is major pathophysiology of Irritable bowel syndrome (IBS)\(^7\)-\(^9,10\). However, the brain area related to initial programming of sensitization provoked by the visceral perception is still unknown. This study clarified that brain activation due to sham colonic distention is different between experienced no stimulation and after experienced intense stimulation.

Methods

Subjects. This study was approved by the Ethics Committee of Tohoku University School of Medicine. All subjects gave written informed consent. Forty-five normal volunteers (12 female, 33 male, 20-26 years old, all right-handed) participated in the first study. All subjects were free from gastrointestinal disorder symptoms or signs.

PET scanning. rCBF in each subject was measured during 4 scans (70 seconds each)
using a PET scanner with $^{15}\text{O}$ labeled water (HEADTOME V SET-2400W, Shimadzu, Japan).

The descending colon was distended with a computerized barostat pump (Medtronic Synectics, Shoreview, MN). To clarify the sensitization process to colonic distention, orders of stimuli was set with six different patterns as follows: group 1: sham - 20 - 40 (n = 8), group 2: sham - 40 - 20 (n = 7), group 3: 20 - sham - 40 (n = 7), group 4: 20 - 40 - sham (n = 8), group 5: 40 - sham - 20 (n = 8), group 6: 40 - 20 - sham (n = 7). No subject was informed of the order or intensity of stimuli.

After each stimulation, the subjects were asked to report the 7 items of visceral perception or emotion. Each sensation was evaluated on an ordinate scale.

Data Analyses

PET images were analyzed using SPM2 on a MATLAB platform. PET images were reconstructed using three dimensional filtered back projection algorithm\textsuperscript{11-13). Ordinate visceral perception and emotion were compared between groups with Mann-Whitney U test.

RESULTS

Visceral perception and emotional changes during sham stimulation in different order

In sham stimulation after 40 mmHg distention, abdominal discomfort (Z = 1.86, p = 0.06 corrected for ties; Mann-Whitney U test) and abdominal distention (Z = 1.56, p = 0.11) were not significantly but tended to be higher than sham stimulation without prior distention (group 4 and 5 vs 1 and 2 in sham, Fig. 1).

$rCBF$ changes during sham stimulation in different order

The main effect of the sham stimulation (0 mmHg) after 40 mmHg distention, determined by comparison with group 4 add 5 and group 1 add 2, denoted activation of the right cingulate gyrus (Brodman area; BA24, Z = 4.16, Fig. 2a), right insula (BA13, Z = 4.08, Fig. 2b), and right middle frontal gyrus (BA10, Z = 3.92, uncorrected for multiple comparisons p < 0.001, Fig. 2c).

Discussion

In this study, sham stimulation after the experience of 40 mmHg visceral stimulation activated right cingulate cortex (BA24), right insula (BA13), and right PFC (BA
10) compared to sham stimulation without experience of actual visceral stimulation. These brain areas are relevant to emotions and visceral perception\textsuperscript{14-17). Anticipation of an intense visceral stimuli induces activation of OFC, PFC, perigenual ACC, temporal cortex, thalamus, lentiform nucleus, and PAG region\textsuperscript{5). This response resembles brain activation by the actual rectal stimulus\textsuperscript{5). The placebo effects on the midbrain which contains endogenous opioids during analgesic anticipation\textsuperscript{6). Prior experience of intense stimuli might be evoked anticipation.

Regions in the medial and ventral areas of the frontal lobe seem to be especially important in relating information about external sensory stimuli to interoceptive information that represents emotional significance. Intensity of 40 mmHg distention might cause long lasting activation of PFC. An alternative interpretation is that the dorsolateral PFC redirects attention away from pain, as it has been implicated in general attentional processes\textsuperscript{6,18). Prior visceral stimuli with 40 mmHg possibly cause associated learning of the visceral perception through activation of cingulate cortex, insula, PFC, medulla, left OFC. As a result, PFC may be activated by sham distention after 40 mmHg distention.

**REFERENCES**

Fig. 1. Comparisons of visceral perception and emotion during stimulation minus baseline. Sham stimulation after 40 mmHg stimulation v.s. sham without prior stimulation. Solid bars (blue) indicated the combined group 4 and 5. Open bars were combined group 1 and 2 (mean and standard error). Vertical axis indicated the visceral perception and emotion changes from baseline of the ordinate scale. There were no significantly differences in the ordinate scale during sham stimulation between with intense stimuli and without prior stimuli. Statistical analyses was used by Mann-Whitney U-test.
Fig. 2.  Statistical (Z) maps of the rCBF during sham stimulation after 40 mmHg stimulation (group 4 and 5) compared with sham stimuli without prior stimuli (group 1 and 2).  The maps overlaid on a sagittal (above) and verticofrontal (below) view of a single-subject MRI anatomical image, showing the location of significant higher rCBF.  A conjunction analysis were made using ‘multi-group, conditions and covariates’ (uncorrected p < 0.001 for multiple comparisons, threshold of the voxel with alpha level Z = 3.75) SPM model\(^{19}\).  Sham stimulation after the experience of 40 mmHg distention versus sham without the experience of colonic distention (minus baseline respectively).  (a) Right cingulate gyrus, (b) right insula, (c) right middle frontal gyrus were found higher activation comparison of sham distention after the experience of 40 mmHg distention than no experienced sham stimuli.