fMRI Studies of Visceral and Cutaneous Pain in IBS Patients and Normal Subjects

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Introduction
The specific cortical areas that mediate visceral pain in humans have been poorly understood until recently. Neuroimaging in humans employing functional magnetic resonance imaging (fMRI) has begun to provide insight into cortical participation in the processing of visceral pain. Recent studies have explored these cortical areas specifically in subjects with irritable bowel syndrome (IBS), a common gastrointestinal disease. They suggest that lower visceral pain thresholds of IBS patients reflect altered cerebral processing of visceral pain. A summary of these results to date suggests that various components of acute pain are mainly processed in the regions of the somatosensory cortices, thalamus, prefrontal cortex, anterior insula cortex, and the anterior cingulate cortex [1,2]. We used fMRI to evaluate differences in activation of these cerebral regions across IBS patients and control subjects in response to painful visceral and cutaneous stimuli.

Methods
Subjects: Nine healthy subjects (6 female, 3 male) and nine patients with IBS (6 female, 3 male), all right-handed and appropriately age-matched, were studied. Visceral pain stimulation was administered by rectal balloon distension with pressure pulses of 55 mmHg delivered using an automated barostat producing 6.5 cycles of alternating deflation and inflation periods of 20 sec each. Cutaneous pain was induced by immersing the right foot into 47 deg C water for 6.5 cycles, with alternating 20 sec periods during which the foot was out of or in the hot water.
Image Acquisition: Images were obtained using a 1.5T GE Signa with a 2-spiral gradient echo scan, 22 contiguous sagittal or coronal 5-7 mm thick slices of the whole brain, 180 mm FOV, 128 x 128 matrix, TR/TE/FA = 1666ms/20ms/80deg. Five functional runs were acquired with 78 images per run. Total time to acquire a functional data set was 4 min 28 sec. Anatomic images were obtained with a 3D-SPGR sequence (TR/TE/FA = 27ms/7ms/45deg), voxel size = 0.94 mm x 0.94 mm x 1.3 mm).
Image Analysis: Analysis was performed with AFNI [3]. Voxel intensities in the 78 serial images were correlated with phase-shifted sinusoidal reference waveforms to produce magnitude of least squares fit functional image intensities. Images were AC-PC aligned, warped into standard Talairach atlas space, and blurred with a 6 mm fwhm filter. The t test ($p < 0.01$) was used to check for significant differences between IBS patients versus control subjects for both the 55 mmHg rectal distension and 47 deg C thermal stimuli. Corrections were made for multiple comparisons.

Results and Discussion
Analysis of the functional imaging data revealed that a number of cerebral cortical and subcortical areas exhibited significant activation to both visceral and cutaneous pain stimuli. Increased activity occurred in areas previously demonstrated to be responsive to painful stimulation including the prefrontal cortex, anterior cingulate cortex, somatosensory cortex, thalamus, and insula for both the IBS patients and control subjects. However, as indicated by Tables 1 and 2, activation was significantly greater for IBS patients than for controls in all areas during both visceral and cutaneous pain stimuli. Particularly robust activation for IBS patients over control subjects was present in the anterior cingulate cortex for visceral pain stimuli and the thalamus for cutaneous pain stimuli (Fig. 1).

Table 1. T-test values of IBS vs. control subjects for 55 mmHg balloon distension

Region	x	y	z	P	T
Prefrontal Cortex	15	51	26	0.010	3.35
Anterior Cingulate Cortex	-6	25	16	0.006	3.66
Somatosensory Cortex	11	-41	40	0.010	3.36
Thalamus	10	-4	17	0.004	3.96
Insula	-32	1	20	0.006	3.73

Table 2. T-test values of IBS vs. control subjects for 47°C hot water stimuli

Region	x	y	z	P	T
Prefrontal Cortex	0	48	21	0.010	3.35
Anterior Cingulate Cortex	3	18	29	0.007	3.61
Somatosensory Cortex	7	-26	45	0.008	3.53
Thalamus	-4	-12	14	0.002	4.40
Insula	-32	-1	12	0.005	3.78

Locations (x, mediolateral; y, rostrocaudal; z, dorsal-ventral) are according to Talairach coordinate system.

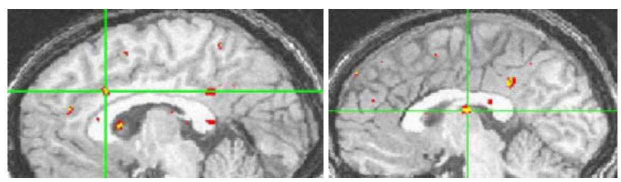

Figure 1. Sagittal view of activation map for t-test comparison of IBS patients vs. controls for the visceral pain (rectal balloon distension; left) and the cutaneous pain (hot water; right) stimuli. IBS patients demonstrated more activation in the anterior cingulate cortex (left; crosshairs) and in the thalamus (right; crosshairs) than did normals.

Conclusions
Compared to control subjects, IBS patients have increased regional cerebral activation in response to experimental cutaneous and visceral pain stimuli. The larger magnitudes of activation in pain-related brain areas of IBS patients as compared to controls are consistent with their higher pain ratings to these same visceral and cutaneous stimuli (i.e., allodynia/hyperalgesia).

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