emotion and sensory integration (44). The parahippocampal gyrus, on the other hand, conducts memory encoding and retrieval in cooperation with other medial temporal regions such as the hippocampus and the amygdala (45). Memory encoding is strengthened by emotion, and adrenaline promotes emotional memory formation (46). Therefore, the right orbitofrontal cortex and the right parahippocampal gyrus may work together to induce arousal of emotion (gut feeling) and memory formation (unpleasant memory) accompanied by an increase in plasma adrenaline during rectal distention.

In our experiments, there were activations in brain regions that were correlated with increases in heart rate, LF/HF ratio and plasma adrenaline. Among them, the thalamus, which is the gate of sensory information to the brain, is well known to be activated by visceral stimulation (16). In addition to the nucleus of the solitary tract, the parabrachial nucleus in the pons and the periaqueductal gray in the midbrain are well-established components of the brain stem autonomic center (40, 47). The periaqueductal gray regulates coordinated behavioral and autonomic responses (48), which can explain the activation of motor-related brain areas accompanied by sympathetic arousal in this study. The cerebellum is also important in autonomic regulation (7). In a recent study, patients with medial cerebellar lesions were shown to have lost fear-conditioned changes in heart rate (49). Co-occurrence of emotional flattening and autonomic reactions have also been seen in a patient after a left cerebellar infarction (50). Brain regions with increased rCBF that were correlated with autonomic arousal were the bilateral putamen, but the right one was located more caudally than the left one. The caudal ventromedial striatum receives inputs from several limbic brain areas like the amygdala and the anterior insula, whereas the rostral striatum primarily regulates motor function (51). However, the majority of patients with pure autonomic failure and multiple system atrophy have an intact striatum (52), and electrical stimulation of the putamen does not induce remarkable changes in blood pressure or heart rate (53). Therefore, activation of the right putamen in our experiments does not directly control sympathetic regulation but may be responsible for other actions accompanied by sympathetic activity. The superior frontal gyrus (BA6) receives inputs from the insula (54), explaining the covariation of BA6 with LF/HF ratio and plasma adrenaline. Therefore, the activated brain regions except for the putamen were in plausible association with autonomic regulation and emotion during the interoception.

RCBF in the amygdala, an important component of autonomic arousal accompanied by emotion, was not correlated with changes in the three autonomic variables. There are two possible explanations for this result. The first is that activation of the amygdala might be transient in our experiments. In a fear conditioning study, firing of the amygdala was limited in the earlier phase of the experiment (55). Because PET brain image needs 70 seconds, the methodology may limit the detection. The second explanation is that the amygdala is not necessary for autonomic and emotional arousal during interoception. Although the amygdala is easily activated by fearful visual stimuli (56), its vulnerability to interoception is unknown. Most functional neuroimaging studies in gastrointestinal stimulation have shown no activation of the amygdala (14–18). Therefore, the amygdala may not play as important a role in sympathetic arousal by visceral sensation as the other activated brain regions.

The important point of our study is the lack of covariation between increased rCBF in the anterior cingulate cortex and changes in the three autonomic variables. The anterior cingulate cortex is known to be a motor center of the limbic system and is responsible for emotional and autonomic arousal (40). One explanation for the lack of detectable covariation of activity in the anterior cingulate cortex is that only male subjects participated in this study. Males show less activation of the anterior cingulate cortex in response to rectal distention than females (57). A second explanation relates to the intensity of stimulation. Vague stimulation can barely activate the anterior cingulate cortex whereas discrete stimulation can easily fire the anterior cingulate cortex (15–17). It has been reported that activity of the anterior cingulate cortex is associated with intensity of urgency during rectal distention with 40 mm Hg in healthy male subjects (16). Thus, the anterior cingulate cortex is activated to process a part of the feeling but it is not associated with autonomic arousal, the bodily state, in healthy male subjects in visceral sensation, the lower hierarchy of emotional processing.

In conclusion, the results of this study support our two hypotheses, i.e., (1) rectal distention provokes changes in heart rate, HRV, and serum catecholamine levels; (2) brain regions that show activity that is correlated with autonomic changes during rectal distention are identifiable. These brain regions are the right insula, thalamus, putamen, periaqueductal gray, pons, and cerebellum as well as the right operculum, the right dorsolateral prefrontal cortex, left insula, right orbitofrontal cortex, and right parahippocampal gyrus.

This study was presented in the 64th Annual Meeting of the American Psychosomatic Society in 2006 and was awarded the Scholar Award of the American Psychosomatic Society.

REFERENCES

1. Kandel ER, Schwartz JH, Jessell TM. Principles of neural science. In; Iversen S, Kupfermann I, Kandel ER., Emotional states and feelings. McGraw-Hill, 2000;pp982–997.
2. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42: 1727–1732.
3. Pool JL, Ransohoff J. Autonomic effects on stimulating the rostral portion of the cingulate gyri in man. J Neurophysiol 1949;12:385–392.
4. Damasio AR. Descarts' Error: Emotion, Reason, and the Human Brain. Putnam, New York, 1993.
5. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 2003;126: 2139–2152.
6. Lane RD. Neural correlates of conscious emotional experience. In; Lane RD, Nadel L, edt., Cognitive Neuroscience of Emotion. Oxford University Press, New York, 2000; pp345–370.
7. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. J Physiol 2000;523:259–270.
8. Critchley HD, Elliot R, Mathias CJ, Dolan RJ. Neural activity relating to

generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J Neurosci 2000;20: 3033–3040.
9. Henderson LA, Macey PM, Macey KE, Frysinger RC, Woo MA, Harper RK, Alger JR, Yan-go FL, Harper RM. Brain responses associated with the Valsalva maneuver revealed by functional magnetic resonance imaging. J Neurophysiol 2002;88:3477–3486.
10. Gianoros PJ, Van der Veen FM, Jennings JR. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: implications for the cortical and subcortical regulation of cardiac autonomic activity. Psychophysiology 2004;41:521–530.
11. Ness TJ, Gebhart GF. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudaffective reflexes in the rat. Brain Res 1988;450:153–169.
12. Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. Anesthesiology 2000;92:1685–1691.
13. Tillisch K, Mayer EA, Labus JS, Stains J, Chang L, Naliboff BD. Sex specific alterations in autonomic function among patients with irritable bowel syndrome. Gut 2005;54:1396–1401.
14. Aziz Q, Andersson JLR, Valind S, Sundin A, Hamdy S, Jones AK, Foster ER, Langstrom B, Thompson DG. Identification of human brain loci processing esophageal sensation using positron emission tomography. Gastroenterology 1997;113:50–59.
15. Ladabaum URI, Minoshima S, Hasler WL, Cross D, Chey WD, Owyang C. Gastric distention correlates with activation of multiple cortical and subcortical regions. Gastroenterology 2001;120:369–376.
16. Hamaguchi T, Kano M, Rikimaru H, Kanazawa M, Itoh M, Yanai K, Fukudo S. Brain activity during distention of the descending colon in humans. Neurogastroenterol Motil 2004;16:299–309.
17. Silverman DHS, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 1997;112:64–72.
18. Mertz H, Morgan V, Tanner G, Pickens D, Price R, Shyr Y, Kessler R. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology 2000;118:842–848.
19. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–222.
20. Kamath MV, Fallen EL. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 1993;21:245–311.
21. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate valiability: Standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–1065.
22. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J 1994;71:1–2.
23. Kano M, Fukudo S, Gyoba J, Kamachi M, Tagawa M, Mochizuki H, Itoh M, Hongo M, Yanai K. Specific brain processing of facial expressions in people with alexithymia: an H2 15O-PET study. Brain 2003;126:1474–1484.
24. Collins RC. Basic aspects of functional brain metabolism. Ciba Found Symp 1991;163:6–22.
25. Fox PT, Mintun MA, Raichle ME, Miezin FM, Allman JM, Van Essen DC. Mapping human visual cortex with positron emission tomography. Nature 1986;6323:806–809.
26. Fox PT, Mintun MA, Reiman EM, Raichle ME. Enhanced detection of focal brain responses using inter subject averaging and change distribution analysis of subtracted PET images. J Cereb Blood Flow Metab 1988;8:642–653.
27. Fujiwara T, Watanuki S, Yamamoto S et al. Performance evaluation of a large axial field-of-view PET scanner: SET-2400W. Ann Nucl Med 1997;11:307–313.
28. Colsher JG. Fully three-dimensional positron emission tomography. Phys Med Biol 1980;25:103–115.
29. Kinhan PE, Rogers JG. Analytic 3D image reconstruction using all detected events. IEEE Trans Nucl Sci 1989;36:964–868.
30. Cherry SR, Dahlbom M, Hoffman EJ. Evaluation of a 3D reconstruction algorithm for multi-slice PET scanners. Phys Med Biol 1992;37:779–790.
31. Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RSJ. The relationship between global and local changes in PET scans. J Cereb Blood Flow Metab 1990;10:458–466.
32. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 1991;11:690–699.
33. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993;13:5–14.
34. Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. Hum Brain Mapp 1994;1:210–220.
35. Friston KJ, Holmes A, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Spatial parametric maps in functional imaging: general linear approach. Hum Brain Mapp 1995;1:189–210.
36. Friston KJ, Ashbuner J, Poline JB, Frith CD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Mapp 1995;2: 165–189.
37. Talairach J, Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Medical Publishers, 1988.
38. Friston KJ, Poline JB, Holmes AP, Frith CD, Frackowiak RSJ. A multivariate analysis of PET activation studies. Hum Brain Mapp 1996;4: 140–151.
39. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000;3:1049–1056.
40. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Neurosci 2002;3:655–666.
41. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci 2004;7: 189–195.
42. Wood JN, Grafman J. Human prefrontal cortex: processing and representational perspectives. Nat Rev Neurosci 2003;4:139–147.
43. Hilz MJ, Dutsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol 2001;49:575–584.
44. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 2005;6:691–702.
45. Larry RS, Craig ELS, Robert EC. The medial temporal lobe. Annu Rev Neurosci 2004;27:279–306.
46. Cahill L, Prins B, Weber M, Mcgaugh JL. Beta-adrenergic activation and memory for emotional events. Nature 1994;371:702–704.
47. Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13:500–505.
48. Bandler R, Carrive P, Zhang SP. Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotopic, somatotopic and functional organization. Prog Brain Res 1991;87:269–306.
49. Maschke M, Schugens M, Kindsvater K, Drepper J, Kolb FP, DienerbH-C, Daum I, Timmann D. Fear conditioned changes of heart rate in patients with medial cerebellar lesions. J Neurol Neurosurg Psychiatry 2002;72:116–118.
50. Annoni JM, Ptak R, Caladara-Schnetzer AS, Khateb A, Pollermann BZ. Decoupling of autonomic and cognitive emotional reactions after cerebellar stroke. Ann Neurol 2003;53:654–658.
51. Fudge JL, Breitbart MA, Danish M, Pannoni V. Insular and gustatory inputs to the caudal ventral striatum in primates. J Comp Neurol 2005; 490:101–118.
52. Brooks DJ, Salmon EP, Mathias CJ, Quinn N, Leenders KL, Bannister R, Marsden CD, Frackowiak RS. The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure, and Parkinson's disease, studied with PET. Brain 1990;113: 1539–1552.
53. Angyan L. Somatomotor and cardiorespiratory responses to basal ganglia stimulation in cats. Physiol Behav 1994;56:167–173.
54. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Rev 1996;22:229–244.
55. Buchel C, Morris J, Dolan R, Friston K. Brain systems mediating aversive conditioning: an event related fMRI study. Neuron 1998;20: 947–957.
56. Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996;383:812–815.
57. Kern M, Jaradeh S, Arndorfer RC, Jesmanowicz A, Hyde J, Shaker R. Gender differences in cortical representation of rectal distension in healthy humans. Am J Physiol Gastrointest Liver Physiol 2001;281: G1512–G1523.

neurogastroenterology & motility

Neurogastroenterol Motil (2010) **22**, 173–e53 doi: 10.1111/j.1365-2982.2009.01417.x

Site-specific differences in central processing of visceral stimuli from the rectum and the descending colon in men

M. KANAZAWA, T. HAMAGUCHI, S. WATANABE, T. TERUI, H. MINE, M. KANO & S. FUKUDO

Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Abstract

Background *It has been reported that different brain activation areas are demonstrated during somatosensory and visceral stimulation. However, no study thus far has investigated how activated patterns in the human brain differ during visceral stimulation of different sites of the digestive tracts. The aim of this study was to determine possible site-specific differences in brain responses and perceptions during visceral stimulation of two different sites, the intraluminal distentions of the rectum and descending colon.* ***Methods*** *Regional cerebral blood flow was assessed in 32 healthy right-handed male subjects using $H_2{}^{15}O$ positron emission tomography during distention of the rectum (R group, n = 16) or descending colon (DC group, n = 16) at 40 or 20 mmHg.* ***Key Results*** *R group reported significantly higher scores of abdominal pain ($P < 0.05$) and urge to defecate ($P < 0.001$) during the application of stimulus at 40 mmHg compared with DC group but not of abdominal bloating or anxiety. In comparisons of response to the 40-mmHg stimulus, R group showed significantly greater activation in posterior midcingulate cortex (MCC) and right anterior and posterior insula, whereas DC group showed greater activation in subgenual anterior cingulate cortex (ACC), perigenual ACC and left orbitofrontal and superior temporal cortices.* ***Conclusions & Inferences*** *These findings suggest that central projections of painful visceral stimulation from the rectum and descending colon differ in affective, cognitive and nociceptive processing in the brain, which may result in different perceptions of visceral stimulation from different sites.*

Keywords *brain activation, colonic distention, descending colon, positron emission tomography, rectum.*

Abbreviations: R, rectum; DC, descending colon; IBS, irritable bowel syndrome; PET, positron emission tomography; BA, Brodmann area; (s/p) ACC, (subgenual/perigenual) anterior cingulate cortex; (p) MCC, (posterior) midcingulate cortex; (d/v) PCC, (dorsal/ventral) posterior cingulate cortex.

INTRODUCTION

Differentiation of cerebral registration of sensory signals originating from different sites in the digestive tract remains unclear. Subjective perception and responses in smooth muscle tone during intraluminal stimulation between the rectum and the more proximal part of the colon are not always comparable.[1,2] The innervation of the descending colon is considered to be purely visceral (involving the pelvic splanchnic nerves), while the most distal part of the rectum is somatically co-innervated.[3] Thus, a distinct population of low-threshold, slow-adapting mechanoreceptors may be identified within terminal endings in the rectum but not in the descending colon.[3]

Visceral hypersensitivity in the distal colon has been demonstrated in patients with functional gastrointestinal (GI) disorders. In previous studies using a barostat device, pain thresholds to intraluminal distention in the rectum were lower in patients with irritable bowel syndrome (IBS) than in healthy subjects.[4–6] Recently, it has been revealed that the lower pain threshold

Address for correspondence
Motoyori Kanazawa MD, PhD, Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo, Aoba, Sendai 980-8575, Japan.
Tel/fax: +81 22 717 7655
e-mail: mkanazw@mail.tains.tohoku.ac.jp
Received: 8 October 2008
Accepted for publication: 13 September 2009

observed in IBS patients was associated with increased abdominal pain severity not only in the rectum[7,8] but also in the descending colon.[9]

The development of brain imaging techniques [e.g. positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)] in recent years has helped us assess central processing of emotional, cognitive, somatosensory and visceral inputs.[10,11] Previous brain imaging studies confirmed that brain responses to intraluminal distention of the rectum are observed in certain areas such as the anterior cingulate cortex (ACC), prefrontal cortex, insula and thalamus in healthy subjects, which is summarized in a systematic review of 10 studies.[12] On the other hand, there have been only a few studies that investigated brain activations during distention of the descending colon.[13,14] Thus, little is known how visceral perceptions and brain responses to visceral stimulation are different between the rectum and descending colon.

It has been reported that different brain activation patterns in the ACC were demonstrated during somatosensory and visceral stimulation of the upper (proximal and distal oesophagus)[15] or lower digestive tracts (anus and rectum).[16,17] These studies revealed that visceral stimulation (e.g. distal oesophageal or rectal distention) elicited a response in the more rostral part of the cingulate cortex compared with somatic stimulation (e.g. proximal oesophageal or anal distension), suggesting that perceptions of visceral and somatic sensations are differentiated in the limbic system. Therefore, central processing and cortical representation of visceral stimulation may differ even in close but different sites of the colon. However, no study has so far investigated similarities or differences in brain activated or deactivated areas during visceral stimulation between the rectum and descending colon.

The aim of this study was to determine possible site-specific differences in brain responses and subjective perception during visceral stimulation of two different sites by intraluminal distention of the rectum and the descending colon. We tested the following hypotheses: (i) that there are differences in cerebral activations during both painful and non-painful stimulation of the rectum and descending colon and (ii) that subjective perception induced by intraluminal distention of the rectum is different from that of the descending colon in healthy male subjects.

METHODS

Subjects

Thirty-two healthy right-handed male subjects (mean age, 22 ± 2 years; 19–29 years) were recruited from Tohoku University Campus in Sendai, Japan. All participants had no GI complaints and had not taken any medications within 4 weeks prior to testing. Each participant underwent a medical history evaluation and was given a physical examination. Subjects were randomly allocated into the rectum group (R group; $n = 16$; mean age, 21 ± 1 years) and descending colon group (DC group; $n = 16$; mean age, 22 ± 2 years). Written informed consent was obtained from all participants, and this study was approved by the Ethics Committee of Tohoku University School of Medicine.

Distention protocol

The distention protocol performed in this study followed previously reported methods.[13] In brief, on the day before examination, the subjects were required to follow a low residue diet and ingest 17 g (13.6%) of magnesium citrate, 75 mg of sodium picosulphate and 24 mg of sennosides A & B to cleanse the colon. On the day of the experiment, a colonoscope was inserted into the splenic flexure in DC group and a splinting device was inserted along the scope. After removal of the scope, a catheter with a thin polyethylene bag (Synectics Medical, Stockholm, Sweden) was inserted into the descending colon. The maximal volume of the bag was 600 mL and the maximal diameter at full inflation was 10 cm. The location of the bag was confirmed by X-ray fluoroscopy. In the R group, the same catheter was inserted into the rectum without X-ray fluoroscopy and placed with the distal end of the bag 5 cm from the anal verge.

Colonic distention stimuli were induced with a computerized barostat pump (Medtronics Synectics, Shoreview, MN, USA), which inflated the taped bag at a rate of 38 mL s^{-1}. Firstly, the subjects underwent no stimulation with a bag pressure of 0 mmHg (baseline). Thereafter, the colon was stimulated with bag pressures of 20 and 40 mmHg for 80 s. The intensity of each stimulus was pseudorandomized to avoid an order effect. There was a time lag of 6 s before reaching peak pressures after initiation of the highest intensity stimulus. After each stimulus, the subjects were asked to report the following items of visceral perception: abdominal pain, urge to defecate, abdominal bloating and anxiety. Each sensation was verbally evaluated on an ordinate scale from 0 (no sensation) to 10 (maximal sensation), namely, an 11-point Likert scale as previously described.[13]

Positron emission tomography scanning

A plaster head support was set for each subject to minimize head movements during PET imaging. [^{15}O]-labelled water (Tohoku University Cyclotron Radioisotope Center) was injected into a vein in the right arm at the beginning of colonic distention. Scans were started about 10 s after the beginning of colonic balloon distensions, at which both radioactivity peak and peak pressure of the bag reached simultaneously a plateau. As the radioactivity detected in the brain is proportional to the volume of cerebral blood flow, an increase in regional cerebral blood flow (rCBF) is seen as an index of neural activity evoked by stimulation. Using a ^{68}Ge/^{68}Ga radiation source, the transmission scan for γ-ray absorption was corrected before PET scanning. The PET scanning room was darkened and the subjects were instructed to keep their eyes closed but remain awake for the whole period of the scan (70 s). rCBF was measured during scans (70 s each) using a PET scanner in the three-dimension sampling mode (HEADTOME V SET-2400W; Shimadzu, Kyoto, Japan).[18] The scanner operated on high-sensitivity three-dimensional (3D) mode with an axial resolution of 3.9 mm. To ensure that radioactivity levels in each subject returned to baseline before starting a new scan, a 10-min interval was given between successive scans.

Analysis

The PET data were transferred to a super computer (NEC, SX-4/128H4; Tohoku University Computer Center) and PET images were reconstructed using a 3D filtered back projection algorithm. PET images were analysed according to the method of Friston *et al.*[19] using statistical parametric mapping software (SPM2, Wellcome; Department of Cognitive Neurology, London, UK). PET images were realigned, spatially normalized, and transformed into approximates in Talairach–Tournoux stereotactic space. Finally, the images were smoothed using a $7 \times 7 \times 7$ mm Gaussian filter and proportionally scaled to account for global confounders.

To estimate rCBF differences between 20- and 40-mmHg distention periods and the baseline period, an intra-group comparison (distention minus baseline images, or baseline minus distention images) was conducted using 'population main effect: two conditions, one scan/condition (paired *t*-test)' in the SPM model. To compare regional brain activities in response to each stimulus between groups, a between-group comparison of the contrasts was applied. The level of significance was set at voxel level of $P_{uncorrected} < 0.001$, with an extent threshold of 20 voxels as the region of significant correction. Talairach Daemon database[20] was used to complement transformation of the coordinates in Talairach space[21] and to determine precise cortical activated regions.

Subjective perception score was analysed using with one-way analysis of variance (ANOVA) for comparisons between groups. Data were expressed as mean with standard deviation (SD). For the analyses, a *P*-value of 0.05 defined statistical significance.

RESULTS

All subjects in both the R and DC groups completed the study protocol. No aversive effects or complications were observed throughout the study.

Subjective visceral perception

There was no difference in symptom score of abdominal pain [0.3 ± 0.8 *vs* 0.1 ± 0.5, $F(1, 30) = 0.29$], urge to defecate [0.8 ± 1.3 *vs* 0.8 ± 1.2, $F(1, 30) = 0.00$], abdominal bloating [0.3 ± 0.8 *vs* 0.7 ± 1.1, $F(1, 30) = 1.62$], or even anxiety [0.4 ± 0.7 *vs* 1.1 ± 1.4, $F(1, 30) = 3.09$] between the R and DC groups during the baseline non-stimulation period (Table 1). During the 20-mmHg distention period, scores for abdominal pain [2.8 ± 2.3 *vs* 0.9 ± 1.1, $F(1, 30) = 9.18$, $P < 0.01$] and urge to defecate [5.1 ± 2.3 *vs* 2.6 ± 1.9, $F(1, 30) = 10.43$, $P < 0.01$] were significantly higher in the R group than those in the DC group (Table 1). There was no difference in score of abdominal bloating [3.6 ± 1.9 *vs* 2.8 ± 1.9, $F(1, 30) = 1.44$] or anxiety [1.8 ± 1.8 *vs* 1.6 ± 1.4, $F(1, 30) = 0.11$] to the 20-mmHg stimulus between the R and DC groups. During the distention period at 40 mmHg, the R group reported significantly higher scores of abdominal pain [5.3 ± 3.3 *vs* 3.2 ± 2.2, $F(1, 30) = 4.56$, $P < 0.05$] and urgency [9.3 ± 0.9 *vs* 4.4 ± 3.5, $F(1, 30) = 29.67$, $P < 0.001$] but not of abdominal bloating [6.0 ± 2.9 *vs* 5.2 ± 2.3, $F(1, 30) = 0.76$] or anxiety [4.5 ± 2.7 *vs* 3.1 ± 2.7, $F(1, 30) = 2.12$] compared with those in the DC group (Table 1).

Table 1 Differences in subjective symptoms induced by intraluminal distention

Symptom score (0–10)	Stimulus intensity	Rectum Mean (SD) ($n = 16$)	Descending colon Mean (SD) ($n = 16$)	*P*-value
Abdominal pain	Baseline	0.3 (0.8)	0.1 (0.5)	0.592
	20 mmHg	2.8 (2.3)	0.9 (1.1)	0.005
	40 mmHg	5.3 (3.3)	3.2 (2.2)	0.041
Urge to defecate	Baseline	0.8 (1.3)	0.8 (1.2)	1.00
	20 mmHg	5.1 (2.3)	2.6 (1.9)	0.003
	40 mmHg	9.3 (0.9)	4.4 (3.5)	<0.001
Abdominal bloating	Baseline	0.3 (0.8)	0.7 (1.1)	0.214
	20 mmHg	3.6 (1.9)	2.8 (1.9)	0.240
	40 mmHg	6.0 (2.9)	5.2 (2.3)	0.390
Anxiety	Baseline	0.4 (0.7)	1.1 (1.4)	0.089
	20 mmHg	1.8 (1.8)	1.6 (1.4)	0.748
	40 mmHg	4.5 (2.7)	3.1 (2.7)	0.156

Abdominal pain, urge to defecate, abdominal bloating and anxiety were assessed using an 11-point ordinate scale (0, no sensation; 10, maximal sensation). SD, standard deviation.

Brain regions activated during intraluminal distention

Rectal distention at a pressure of 40 mmHg significantly activated the right anterior insula and the bilateral thalamus (Fig. 1 and Table 2). Brain regions comprising the right inferior parietal lobule and thalamus were significantly activated during rectal distention at 20 mmHg (Table 2). During the 40-mmHg stimulus of the descending colon, significant brain activations of the posterior midcingulate cortex (pMCC), perigenual ACC (pACC), subgenual ACC (sACC) and right supramarginal gyrus were observed (Fig. 2A–D and Table 3). The 20-mmHg stimulus of the descending colon significantly induced the pACC, sACC, pMCC and right supramarginal gyrus (Table 3).

Brain regions deactivated during intraluminal distention

Visceral stimulation with an intensity of 40 mmHg in the rectum caused a significant and broad deactivation of regions of the occipital, middle temporal [including the posterior cingulate cortex (PCC)] and medial prefrontal cortices (Fig. 3A and Table S1). During the 20-mmHg stimulus of the rectum, significant brain deactivations were also observed in the occipital, middle temporal and medial prefrontal cortices (Table S1). During the 40- or 20-mmHg distentions of the

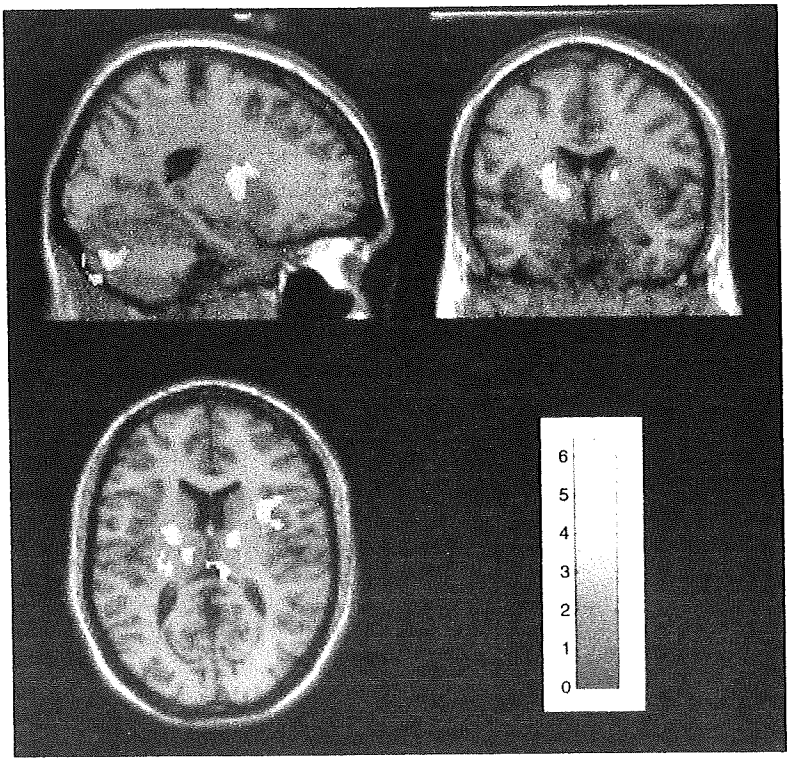

Figure 1 Regions of cerebral activation induced by intraluminal distention in the rectum with a bag pressure of 40 mmHg. Brain regions activated during intraluminal distentions of the rectum were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. Significant activations during 40-mmHg stimulus in the rectum (x,y,z = 32,8,8) are shown. The level of significance was set at 0.1% or less (voxel level).

Table 2 Brain regions activated during intraluminal distention in the rectum

Cordinate of local maximum x,y,z (mm)	Tentative anatomical localization	t-Value (voxel level)	$P_{FWE\text{-corrected}}$ (voxel level)	$P_{FDR\text{-corrected}}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
40-mmHg stimulus						
8,−26,8	Right thalamus	6.02	0.029	0.003	306	<0.001
32,8,8	Right anterior insula (BA13)	5.40	0.165	0.004	193	<0.001
−26,−20,10	Left thalamus	5.39	0.167	0.004	57	0.181
−20,−2,12	Left thalamus	4.78	0.636	0.009	369	<0.001
20-mmHg stimulus						
48,−56,48	Right inferior parietal lobule (BA40)	4.87	0.547	0.038	75	0.068
8,−26,12	Right thalamus	4.63	0.778	0.058	37	0.519
52,−30,30	Right inferior parietal lobule (BA40)	4.36	0.952	0.089	26	0.809

Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level). Degree of freedom = [1, 45]. BA, Brodmann area.

descending colon, significant deactivation occurred in brain regions similar to those deactivated during the rectal stimulus (Fig. 3B and Table S2).

Comparisons of contrasts in activated brain regions

In response to the intraluminal distention at 40 mmHg, the R group showed greater activation in the pMCC and right anterior and posterior insula (Fig. 4A,B and Table 4), whereas the DC group showed greater activation in the sACC, pACC, and left orbitofrontal and superior temporal cortices (Fig. 4C,D and Table 4). There was little significant difference in regional contrasts during the application of stimulus at 20 mmHg between the groups (Table 4).

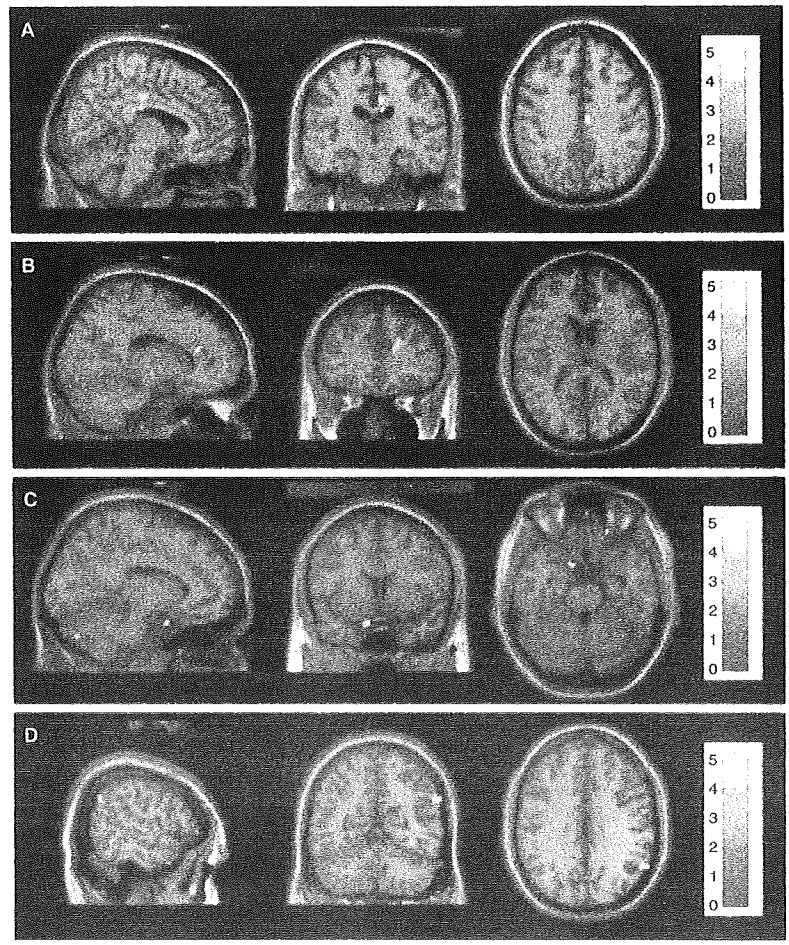

Figure 2 Regions of cerebral activation induced by intraluminal distention in the descending colon with a bag pressure of 40 mmHg. Brain regions activated during intraluminal distentions of the descending colon were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. Significant activations during 40-mmHg stimulus in the descending colon (x,y,z = 8,−18,38: A; 16,32,16: B; −12,10,−24: C; and 60,56,32: D) are shown. The level of significance was set at 0.1% or less (voxel level).

Table 3 Brain regions activated during intraluminal distention in the descending colon

Cordinate of local maximum x,y,z (mm)	Tentative anatomical localization	t-Value (voxel level)	$P_{FWE-corrected}$ (voxel level)	$P_{FDR-corrected}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
40-mmHg stimulus						
8,−18,38	Right pMCC (BA24)	5.18	0.263	0.250	32	0.635
22,32,28	Right pACC (BA32)	4.65	0.736	0.250	26	0.796
60,−56,32	Right supramarginal gyrus (BA40)	4.42	0.910	0.250	36	0.531
6,−22,26	Right pMCC (BA23)	4.35	0.943	0.250	37	0.506
−12,10,−24	Left sACC (BA25)	4.22	0.982	0.250	27	0.770
20-mmHg stimulus						
−10,30,38	Left pACC (BA32)	5.28	0.210	0.212	38	0.483
64,−56,32	Right supramarginal gyrus (BA40)	4.62	0.757	0.397	27	0.770
4,−20,40	Right pMCC (BA24/23)	4.25	0.975	0.397	27	0.770
−12,10,−24	Left sACC (BA25)	4.07	0.997	0.397	34	0.582

Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level). Degree of freedom = [1, 45]. BA, Brodmann area; ACC, anterior cingulate cortex (s, subgenual; p, perigenual); MCC, midcingulate cortex (p, posterior).

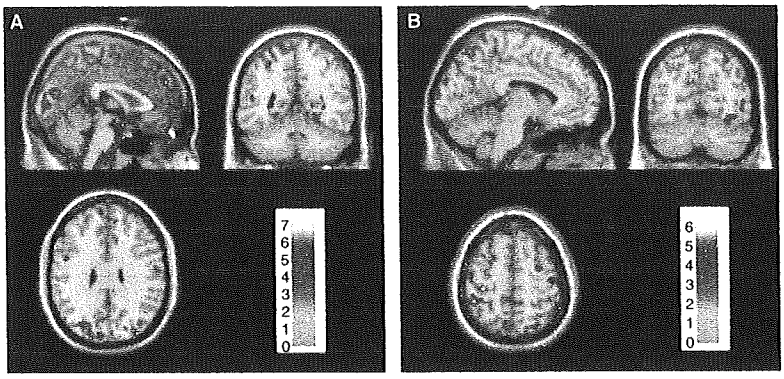

Figure 3 Regions of cerebral deactivation induced by intraluminal distention in the rectum and descending colon with a bag pressure of 40 mmHg. Brain regions deactivated during intraluminal distentions of the rectum and descending colon were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. Significant deactivations during 40-mmHg stimulus in the rectum (*x,y,z* = 2,−50,30: A) and the descending colon (*x,y,z* = −6,−66,58: B) are shown. The level of significance was set at 0.1% or less (voxel level).

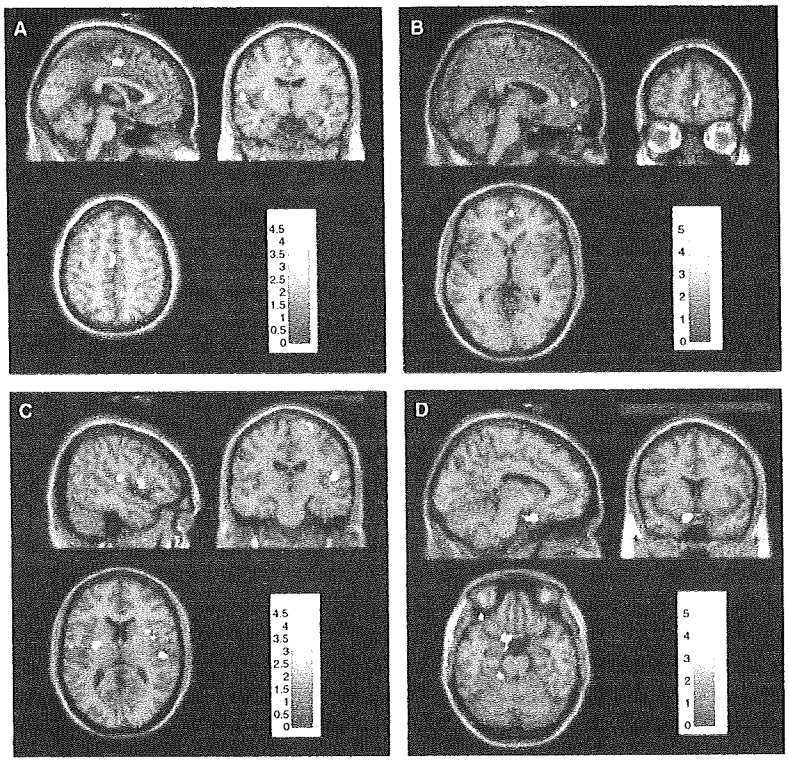

Figure 4 Comparisons of activated cerebral regions during intraluminal distention at 40 mmHg between the rectum and the descending colon. Dominant brain activations during intraluminal distentions of the rectum (*x,y,z* = 0,8,50: A and 50,−18,12: B) and the descending colon (*x,y,z* = 4,52,0: C and −8,10,−22: D) were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. To compare regional brain activities in response to each stimulus between groups, a between-group comparison of the contrasts (distention minus baseline images) was applied. The level of significance was set at 0.1% or less (voxel level).

DISCUSSION

This is the first study to demonstrate the differences in subjective perception and central activation during intraluminal distention of the rectum and descending colon. Pain and the urge to defecate perception were more sensitive to distention in the rectum than in the descending colon, while the abdominal bloating sensation was similar. Differences in regions of brain activation, especially regions associated with affective, cognitive and/or nociceptive networks (i.e. pMCC, pACC, sACC),[22] were shown during a 40-mmHg distention of the rectum compared with the descending colon. Greater activation of the pMCC was demonstrated during the intense rectal stimulus, whereas greater activation in the more anterior part of the cingulate cortex was demonstrated during stimulation of the descending colon. There was little difference in brain activation pattern during the weak distention between the rectum and descending colon. In contrast, broad deactivation of the occipital, middle temporal (including PCC) and medial prefrontal cortices during

Table 4 Comparisons of brain regions activated during intraluminal distention

Cordinate of local maximum x,y,z (mm)	Tentative anatomical localization	t-Value (voxel level)	$P_{FWE-corrected}$ (voxel level)	$P_{FDR-corrected}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
Rectum (40-mmHg baseline) > descending colon (40-mmHg baseline)						
−32,−28,66	Left precentral gyrus (BA4)	4.88	0.206	0.078	101	0.026
50,−18,12	Right posterior insula (BA13)	4.67	0.372	0.078	64	0.154
−62,2,28	Left precentral gyrus (BA6)	4.65	0.387	0.078	36	0.583
52,8,6	Right anterior insula (BA13)	4.58	0.460	0.078	47	0.355
54,−68,36	Right angular gyrus (BA39)	4.58	0.469	0.078	31	0.706
−56,−6,6	Left superior temporal gyrus (BA22)	4.44	0.623	0.078	36	0.583
−30,−6,8	Left putamen	4.39	0.687	0.084	67	0.132
0,−8,50	Left pMCC (BA24)	4.27	0.811	0.086	99	0.028
24,−16,72	Right precentral gyrus (BA6)	4.1	0.936	0.093	45	0.391
34,10,14	Right anterior insula (BA13)	3.85	0.997	0.113	71	0.109
Rectum (20-mmHg baseline) > descending colon (20-mmHg baseline)						
54,6,6	Right anterior insula (BA13)	4.53	0.515	0.855	30	0.731
Descending colon (40-mmHg baseline) > rectum (40-mmHg baseline)						
−8,10,−22	Left rectal gyrus, sACC (BA11)	5.66	0.013	0.013	145	0.004
−58,−36,6	Left superior temporal gyrus (BA22)	5.26	0.059	0.014	43	0.429
−44,0,−14	Left superior temporal gyrus (BA38)	4.56	0.486	0.049	73	0.099
4,52,0	Right pACC (BA32)	4.26	0.817	0.076	61	0.179
−38,34,−22	Left orbitofrontal gyrus (BA47)	3.94	0.987	0.123	35	0.607
−38,−60,38	Left inferior parietal lobule (BA40)	3.90	0.993	0.127	29	0.755
Descending colon (20-mmHg baseline) > rectum (20-mmHg baseline)						
−8,8,−20	Left sACC (BA25)	4.54	0.505	0.341	44	0.409
12,−62,34	Right precuneus (BA7)	4.36	0.717	0.341	28	0.779
−40,−8,−12	Left middle temporal gyrus (BA21)	3.91	0.992	0.408	36	0.583

A between-group comparison of the contrasts (distention minus baseline images) was applied. Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level). Degree of freedom = [1, 90]. BA, Brodmann area; ACC, anterior cingulate cortex (s, subgenual; p, perigenual); MCC, midcingulate cortex (p, posterior).

the intense stimulus in the rectum and descending colon were observed respectively.

These two closely linked parts of the large bowel seem to show similar central projections with respect to visceral perception. Previous PET/fMRI studies in healthy subjects during rectal stimulation have quite consistently shown cerebral activations in the anterior insula and thalamus.[23–25] We have previously reported that stimulation of the descending colon in healthy volunteers activated similar brain regions (i.e. thalamus, pACC, inferior parietal gyrus).[13] In this study, the activated brain regions during each stimulus are almost concordant with these findings. On the other hand, the different activation patterns of the cingulate cortex to visceral stimulation of the rectum and descending colon from the present findings are intriguing.

A systematic review of previous brain imaging studies during visceral stimulation revealed that lower GI stimulus results noticeably in more effects in the anterior and ventral part of the prefrontal cortex and more anterior insula than upper GI stimulus.[26] Differences in the distribution of activated brain areas may reflect characteristics of the afferent innervations, suggesting that these findings support the concept of 'visceral homunculus' (i.e. functional anatomical distinction for visceral perception)[27] like a relative body representation in the sensorimotor cortex.[28] In this study, comparisons of the contrasts in brain activation during the intense stimulus between the rectum and descending colon revealed differential neural enhancement in the cingulate cortex. Therefore, our findings support a novel hypothesis that parts of the visceral signals from the different sites in the gut may be conveyed to the different brain regions to discriminate visceral perceptions.

This study also provides novel findings of similar and different patterns of brain deactivation to visceral stimulation of the rectum and descending colon. This is the first report to investigate in detail brain deactivation areas responding to visceral stimulation of the distal colon. Van Oudenhove *et al.*[29] found a pattern of cortical deactivation during unpleasant/painful gastric distention in healthy subjects by a PET study (i.e. the occipital and adjacent lateral parietal and temporal cortices, medial parietal cortex including PCC, medial prefrontal cortex). Occipital deactivation may be explained as attentional processes filtering out other sensory processing.[30] Medial prefrontal deactivation is thought to be an antinociceptive response for cognitive–affective evaluation of the painful sensation or the neural substrate of the coping strategy towards a predictable but unavoidable pain stimulus.[30] On the

other hand, the PCC and adjacent precuneus are thought to be tonically active regions of the brain that continuously gather information about the world around and, possibly, within us.[31] This appears to be the 'default network' brain activity, which may be especially associated with the shift from exteroceptive to interoceptive processing.[29] The results of cerebral deactivation during the stimulus to the rectum and descending colon in this study support the previous findings investigated with different methodologies,[29,30,32] suggesting that relatively constant deactivation patterns despite stimulation of different sites of the gut are more likely.

LIMITATIONS

To avoid frequent exposure to the radioisotope, an intra-personal comparison of rCBF during intraluminal distention in both the rectum and descending colon was not performed. However, the characteristics of both groups were not significantly different and the findings of activated brain regions in each group were almost in concordance with the results from previous studies.[12,13] Thus, sampling bias appears to be unlikely in this study. In addition, healthy female subjects were not investigated. Women are more likely to suffer from IBS than men, and gender differences in activated brain regions during painful rectal distention in IBS patients and healthy subjects have been reported.[33] In this PET study, a lot of clusters detected at the significant level of $P_{uncorrected}$ did not reach significance after either FDR or FWE correction at voxel level. Moreover, most of them were relatively small and therefore did not reach significance at cluster level either. This may be due to a small sample size in each group and/or methodological differences with the previous studies (e.g. stimulus intensity/duration and PET imaging analyses). Furthermore, it remains unclear whether abnormal brain activations are caused by hypersensitive nerves via mechanoreceptors within the gut, by abnormal processing of afferent inputs at the level of the dorsal horn neurons in the spinal cord, or by abnormal processing in the brain. Further investigations are therefore warranted to understand the pathophysiology of the brain–gut link in patients with functional GI disorders.

CONCLUSIONS

The findings in this study provide us with a new understanding of central discrimination during visceral perception. Despite the fact that pain perception and the urge to defecate were more sensitive in the rectum, central activations to a 20-mmHg distention of the rectum and the descending colon were alike, suggesting that assessment of brain imaging during mild to moderate stimulation of the rectum may correspond to that in other sites of the distal colon. In contrast, central projections of intense visceral stimuli from the rectum and descending colon differ to some extent in affective, cognitive, and nociceptive processing in the brain, which may result in different discriminative sensory perceptions.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan, and a Grant-in-Aid for Scientific Research from the Ministry of Health, Welfare, and Labor, Japan.

REFERENCES

1 Petersen P, Gao C, Rössel P *et al.* Sensory and biomechanical responses to distension of the normal human rectum and sigmoid colon. *Digestion* 2001; **64**: 191–9.
2 Drewes AM, Petersen P, Rössel P, Gao C, Hansen JB, Arendt-Nielsen L. Sensitivity and distensibility of the rectum and sigmoid colon in patients with irritable bowel syndrome. *Scand J Gastroenterol* 2001; **36**: 827–32.
3 Lynn PA, Olsson C, Zagorodnyuk V, Costa M, Brookes SJ. Rectal intraganglionic laminar endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum. *Gastroenterology* 2003; **125**: 786–94.
4 Whitehead WE, Holtkotter B, Enck P *et al.* Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 1990; **98**: 1187–92.
5 Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 1995; **109**: 40–52.
6 Bouin M, Plourde V, Boivin M *et al.* Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology* 2002; **122**: 1771–7.
7 Zar S, Benson MJ, Kumar D. Rectal afferent hypersensitivity and compliance in irritable bowel syndrome: differences between diarrhoea-predominant and constipation-predominant subgroups. *Eur J Gastroenterol Hepatol* 2006; **18**: 151–8.
8 Posserud I, Syrous A, Lindström L, Tack J, Abrahamsson H, Simrén M. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. *Gastroenterology* 2007; **133**: 1113–23.
9 Kanazawa M, Palsson OS, Thiwan SIM *et al.* Contributions of pain sensitivity and colonic motility to IBS symptom severity and predominant

bowel habits. *Am J Gastroenterol* 2008; **103**: 2550–61.
10 Aziz Q, Thompson DG. Brain-gut axis in health and disease. *Gastroenterology* 1998; **114**: 559–78.
11 Mayer EA, Naliboff BD, Craig AD. Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders. *Gastroenterology* 2006; **131**: 1925–42.
12 Rapps N, van Oudenhove L, Enck P, Aziz Q. Brain imaging of visceral functions in healthy volunteers and IBS patients. *J Psychosom Res* 2008; **64**: 599–604.
13 Hamaguchi T, Kano M, Rikimaru H *et al.* Brain activity during distention of the descending colon in humans. *Neurogastroenterol Motil* 2004; **16**: 299–309.
14 Kano M, Hamaguchi T, Itoh M, Yanai K, Fukudo S. Correlation between alexithymia and hypersensitivity to visceral stimulation in human. *Pain* 2007; **132**: 252–63.
15 Aziz Q, Thompson DG, Ng VW *et al.* Cortical processing of human somatic and visceral sensation. *J Neurosci* 2000; **20**: 2657–63.
16 Hobday DI, Aziz Q, Thacker N, Hollander I, Jackson A, Thompson DG. A study of the cortical processing of ano-rectal sensation using functional MRI. *Brain* 2001; **124**: 361–8.
17 Lotze M, Wietek B, Birbaumer N, Ehrhardt J, Grodd W, Enck P. Cerebral activation during anal and rectal stimulation. *Neuroimage* 2001; **14**: 1027–34.
18 Fujiwara T, Watanuki S, Yamamoto S *et al.* Performance evaluation of a large axial field-of-view PET scanner: SET-2400W. *Ann Nucl Med* 1997; **11**: 307–13.
19 Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 1991; **11**: 690–9.
20 Lancaster JL, Woldorff MG, Parsons LM *et al.* Automated Talairach Atlas labels for functional brain mapping. *Hum Brain Mapp* 2000; **10**: 120–31.
21 Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain.* New York: Thieme Medical Publishers, 1998.
22 Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 2005; **6**: 533–44.
23 Silverman DH, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 1997; **112**: 64–72.
24 Mertz H, Morgan V, Tanner G *et al.* Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000; **118**: 842–8.
25 Naliboff BD, Derbyshire SW, Munakata J *et al.* Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. *Psychosom Med* 2001; **63**: 365–75.
26 Derbyshire SW. A systematic review of neuroimaging data during visceral stimulation. *Am J Gastroenterol* 2003; **98**: 12–20.
27 Drewes AM, Dimcevski G, Sami SA *et al.* The "human visceral homunculus" to pain evoked in the oesophagus, stomach, duodenum and sigmoid colon. *Exp Brain Res* 2006; **174**: 443–52.
28 Penfield W, Boldray E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 1937; **60**: 389–443.
29 van Oudenhove L, Vandenberghe J, Dupont P *et al.* Cortical deactivations during gastric fundus distension in health: visceral pain-specific response or attenuation of 'default mode' brain function? A $H_2{}^{15}O$-PET study. *Neurogastroenterol Motil* 2009; **21**: 259–71.
30 Aziz Q, Andersson JL, Valind S *et al.* Identification of human brain loci processing esophageal sensation using positron emission tomography. *Gastroenterology* 1997; **113**: 50–9.
31 Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2001; **2**: 685–94.
32 Mayer EA, Berman S, Suyenobu B *et al.* Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain* 2005; **115**: 398–409.
33 Berman S, Munakata J, Naliboff BD *et al.* Gender differences in regional brain response to visceral pressure in IBS patients. *Eur J Pain* 2000; **4**: 157–72.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Brain regions deactivated during intraluminal distention in the rectum.

Table S2. Brain regions deactivated during intraluminal distention in the descending colon.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Appl Psychophysiol Biofeedback
DOI 10.1007/s10484-009-9125-y

Effect of Autogenic Training on General Improvement in Patients with Irritable Bowel Syndrome: A Randomized Controlled Trial

Masae Shinozaki · Motoyori Kanazawa · Michiko Kano · Yuka Endo · Naoki Nakaya · Michio Hongo · Shin Fukudo

Abstract Autogenic training (AT) is a useful and comprehensive relaxation technique. However, no studies have investigated the effects of AT on irritable bowel syndrome (IBS). In this study we tested the hypothesis that AT improves symptoms of IBS. Twenty-one patients with IBS were randomly assigned to AT ($n = 11$, 5 male, 6 female) or control therapy ($n = 10$, 5 male, 5 female). AT patients were trained intensively, while the control therapy consisted of discussions about patients' meal habits and life styles. All patients answered a question related to adequate relief (AR) of IBS symptoms and four questionnaires: Self-induced IBS Questionnaire (SIBSQ), Self-reported Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and Medical Outcome Short Form 36 Health Survey (SF-36). The proportion of AR in the last AT session in the AT group (9/11, 81.8%) was significantly higher than that in the controls (3/10, 30.0%, Chi-square test, $p = 0.048$). Two subscales of the SF-36, i.e., social functioning and bodily pain, were significantly improved in the AT group ($p < 0.05$) as compared to the control group. Role emotional ($p = 0.051$) and general health ($p = 0.068$) showed a tendency for improvement in the AT group. AT may be useful in the treatment of IBS by enhancing self-control.

Keywords Adequate relief (AR) · Autogenic training (AT) · Irritable bowel syndrome (IBS) · Quality of life (QOL) · Randomized controlled trial (RCT)

Abbreviations

SIBSQ	Self-reported Irritable Bowel Syndrome Questionnaire
SDS	Self-reported Depression Scale
STAI	State-trait anxiety inventory
SF-36	Medical Outcome Short Form 36 Health Survey
PF	Physical functioning
RP	Role physical
BP	Bodily pain
GH	General health
VT	Vitality
SF	Social functioning
RE	Role emotional
MH	Mental health

Introduction

Irritable bowel syndrome (IBS) is a very common gastrointestinal disorder characterized by recurrent abdominal

M. Shinozaki · M. Kanazawa · M. Kano · S. Fukudo (✉)
Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo, Aoba, Sendai 980-8575, Japan
e-mail: sfukudo@mail.tains.tohoku.ac.jp

Y. Endo
Department of Psychosomatic Medicine, Tohoku University Hospital, 1-1 Seiryo, Aoba, Sendai 980-8575, Japan

N. Nakaya
Division of Epidemiology, Department of Public Health & Forensic Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo, Aoba, Sendai 980-8575, Japan

M. Hongo
Department of Comprehensive Medicine, Tohoku University Hospital, 1-1 Seiryo, Aoba, Sendai 980-8575, Japan

Published online: 08 December 2009

pain and altered bowel habits without major organic diseases as assessed by routine gastroenterological examination (Drossman 2006). The prevalence of IBS in the general population is high in western countries as well as in Japan (Thompson et al. 2002; Kanazawa et al. 2004). In addition, IBS is recognized as one of the most common diseases in primary care (Thompson et al. 2000). Rome III diagnostic criteria based on subjective gastrointestinal (GI) complaints is the current standard for IBS diagnosis (Drossman 2006; Longstreth et al. 2006a, b).

Although regarded as a digestive disease, IBS is a syndrome that fits well the definition of a biopsychosocial model, in which the relationship between physiological factors, GI symptoms, psychosocial factors, and clinical outcome reciprocally influence their expression (Drossman 2006). These phenomena are conceptualized as a "brain-gut" interaction (Fukudo et al. 1993). From the psychosocial viewpoint, IBS has a negative impact on subjects' daily activity and quality of life as it incurs substantial health-care seeking (Drossman et al. 1993). Patients with IBS frequently show exaggerated gastrointestinal motility under stress (Fukudo et al. 1993), have psychiatric comorbidities, especially depressive disorders, anxiety disorders, and somatoform disorders (Drossman 2006), and reveal psychosocial risk factors including sexual/physical abuse, economical loss, and social withdrawal (Drossman 2006). Although several new pharmacological agents for IBS have been developed (Camilleri et al. 2000; Chey et al. 2004; Chang et al. 2005; Tack et al. 2005; Reilly et al. 2005), there are still patients who do not respond to pharmacotherapy (Levy et al. 2006). For these patients, psychotherapy might be useful. Therefore, the development of a treatment for IBS based on a biopsychosocial model is indispensable.

Hypnotherapy has been shown to improve IBS-induced GI symptoms (Whorwell et al. 1984; Gonsalkorale et al. 2003; Gonsalkorale et al. 2004; Lea et al. 2003), and is now a valid alternative in the treatment of IBS (American Gastroenterological Association 2002; Drossman et al. 2002; Drossman 1999). However, hypnotherapy requires a long treatment period and its success is highly dependent on the skills of the therapist. On the other hand, autogenic training (AT), which is often used to treat different types of psychosomatic disorders (Stetter and Kupper 2002), is easier for physicians and allied health providers to perform and more accessible than hypnotherapy. Besides, after a few sessions, it is possible for patients to carry out AT by themselves. Despite these advantages, there is no evidence that AT is effective in treatment of IBS symptoms. Based on this background information, we hypothesized in this study that AT would improve GI symptoms, negative emotion, and health related quality of life (HR-QOL) in patients with IBS.

Methods

Study Sample Size

The desired sample size in this study was calculated using $\alpha = 0.05$ significance level and $\beta = 0.75$. Based on our clinical experience, we hypothesized that the improvement rate in subjects that received autogenic training would be 85% and that the improvement rate in the control subjects would be 25%. The difference (d) between the AT and control groups can therefore be calculated as $d = 0.85 - 0.25 = 0.6$. With this assumption, the sample size in this study was estimated as 10.

Study Subjects

Out of all IBS outpatients who visited the Department of Psychosomatic Medicine in Tohoku University Hospital from December 2001 to July 2005, 21 patients (10 males and 11 females) were enrolled at random in this study. Eligible patients strictly fulfilled the Rome II criteria (Thompson et al. 1999). Before the beginning of this study, the patients completed a series of tests, including blood count, C-reactive protein blood chemical analysis, thyroid hormones test, thyroid stimulating-hormone test, urinalysis, fecal occult blood test, colonoscopy and/or Ba enema. After diagnosis of IBS, patients were prescribed trimebtrine or polycalbophil calcium. Probiotics for diarrhea, anticholinergics for abdominal pain, or laxatives for constipation were prescribed depending on the dominant symptoms. The drug prescribed to each patient was not changed during this study. After treatment for 8 weeks, patients were asked whether they had adequate relief (AR) or not (Camilleri et al. 2000). Only patients who showed no adequate relief were enrolled in this study. All patients gave informed consent, and this study was approved by the Ethics Committee of Tohoku University School of Medicine (No. 2001-223).

Pharmacotherapy Outcome

Subjects were asked to answer one oral question and complete four validated questionnaires. The oral question was used as a primary endpoint, and the four validated questionnaires were used as secondary endpoints for quantification of IBS (Irvine et al. 2006).

Adequate Relief

AR is clinically useful to assess improvement of abdominal pain and/or discomfort (Camilleri et al. 2000; Chey et al. 2004). In this study, AR addressed improvement in IBS-induced GI symptoms following pharmacotherapy with a

single question ("Did you have adequate relief of IBS-related abdominal pain or discomfort?") scored on a dichotomous scale. The question was asked during the patient's medical visit, and the answer was either "Yes" or "No".

Self-reported Irritable Bowel Syndrome Questionnaire

The self-reported irritable bowel syndrome questionnaire (SIBSQ) (Endo et al. 2000) is a validated disease-specific questionnaire. SIBSQ is based on the Rome II criteria and consists of 14 GI symptoms-related questions and seven additional questions. The 14 questions are related to the following: abdominal pain, discomfort, defecation frequency, improved pain or discomfort, gas or defecation state, existence of sticky stool, feeling of residual stool, bloating, straining, defecation urgency, anticipated anxiety because of bowel symptoms, abdominal dysfunction with perceived stress, and abdominal dysfunction after meal. The 14 GI symptom-related questions are used to evaluate severity of GI symptoms on a seven-point Likert scale (1: nothing at all, 2: almost nothing, 3: slightly present 4: present, 5: moderately present 6: severely present 7: extremely present). The sum of scores for the 14 GI symptoms-related questions gives a total score for SIBSQ.

The seven additional questions are used to obtain more detailed characterization of IBS symptoms (Appendix).

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) is a well-validated 40 item self-reported questionnaire. STAI is used to measure state anxiety (20 items) and trait anxiety (20 items), wherein subjects choose one of four levels of anxiety for each item. State anxiety reflects a "transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity." State anxiety may fluctuate over time and can vary in intensity. In contrast, trait anxiety denotes "relatively stable individual differences in anxiety proneness." The Japanese version of STAI has already been validated (Nakazato and Mizuguchi 1982).

Self-Rating Depression Scale

The Self-Rating Depression Scale (SDS) consists of 20 questions scored on four-point Likert scale (Zung 1965). The Japanese version of SDS is well-validated and commonly used (Fukuda and Kobayashi 1973).

Medical Outcome Study 36-Items Short-Form Health Survey

The Medical Outcome Study 36-Items Short-Form Health Survey (SF-36) is a non-specific questionnaire for health-related quality of life (HR-QOL) (Ware and Sherbourne 1992). The SF-36 consists of eight subscales as follows: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The Japanese version of SF-36 has been validated (Fukuhara et al. 1998; Fukuhara et al. 2001).

Autogenic Training

The Autogenic Training (AT) used in this study was based on the Schultz-style (Schultz 1987). AT was performed individually for eight sessions in eight weeks (Schultz 1987; Kermani 2001). Each session consisted of 30–40 min of full exercise. Although some studies described AT session time between a few minutes (Kermani 2001) and 60 min (Mitani et al. 2006), we gave priority to patient comfortableness (Kermani 2001). The standard session of AT used in this study is shown in Table 1 (Kermani 2001; Mitani et al. 2006). In brief, traditional AT consists of 6 standard exercises after the formula "I am at peace". The first exercise aims at muscular relaxation by repetition of a verbal formula, "My right arm is heavy" emphasizing heaviness. Subsequent passive concentration is focused on feeling warm, initiated by the instruction "My right arm is warm", followed by cardiac activity using the formula "My heartbeat is calm and regular". Then follows passive concentration on the respiratory mechanism with the formula "It breathes me", then on warmth around the abdominal region with "My solar plexus is warm" and finally on coolness in the cranial region with "My forehead is cool and clear" (Kanji and Ernst 2000).

Control Session

The control session was aimed at discussing diet therapy. The session time and frequency were the same as those in

Table 1 AT standard exercise

1. My right (left) arm (leg) is heavy
2. My right (left) arm (leg) is warm
3. My heart beat is calm and regular
4. It breathes me
5. My solar plexus is warm
6. My forehead is cool and clear
7. Cancellation

the AT sessions. All control patients were given the original textbook for the session. The table of contents for the textbook used in this study is shown in Table 2.

Procedure

The study protocol is shown in Fig. 1. About 21 eligible patients were randomly assigned to the AT group ($n = 11$, 5 males, 6 females) or the control group ($n = 10$, 5 males, 5 females). Patients in the AT group completed a standard course of AT sessions eight times. The interval between AT sessions was two to four weeks, depending on the patient's social situation. A specialized psychologist (MS) performed AT in a quiet, sheltered, temperature- and humidity-controlled room. During the interval between sessions, home-exercise was recommended. AT patients were given a set of explanatory leaflets and an audiotape for home exercise. Patients in the control group had discussions about their meal habits with the psychologist and were given booklets about meal habits to prepare for the discussion. The patients were not informed which group he/she would be assigned to. However, they were not completely blinded because they could understand the contents of treatments after the beginning of the intervention (Whitehead 2004).

Table 2 Table of contents for control session textbook

1. What is IBS?
2. Treatment of IBS
3. Nutrients and dietary fibers
4. Diet therapy for IBS
5. Diet therapy for diarrhea-predominant IBS
6. Diet therapy for constipation-predominant IBS
7. Diet therapy for alternating IBS
8. Summary

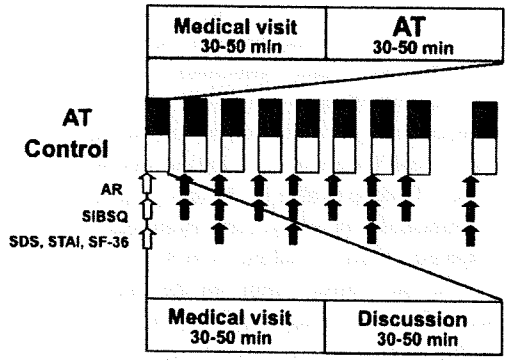

Fig. 1 Study protocol. The *white* and *black arrows* indicate points of measurement of Adequate Relief (AR), Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ), Self-reported Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and The MOS 36-item short-form health survey (SF-36). *Black square*—AT session (including details of the session). *White square*—control session (including details of the session). *White arrow*—point of measurement of baseline. *Black arrow*—point of measurement of a regular session

Statistical Analysis

The proportion of patients with AR was calculated and analyzed by Chi-square test. The difference of proportion of patients with AR, the rate ratio (RR) of AR between the AT and control groups, and the 95% confidence interval (95%CI) of these parameters were also calculated. Scores of before and after pharmacotherapy were compared using both analysis of variance (ANOVA) and Wilcoxon signed-rank test.

Results

Subjects Demographic Data

Demographic data for the patients are shown in Tables 3 and 4. No difference in age, sex, IBS subtype, SIBSQ, SDS, and STAI between the AT group and the control group was observed. In addition, SF-36 subscales were almost identical between the AT group and the control group. Only social functioning in the AT group was significantly lower than that in the control group ($p < 0.05$).

Adequate Relief

The proportion of patients with AR in the AT group (9/11, 81.8%) was significantly higher than that in the control group (3/10, 30.0%) in the last AT session as indicated by

Table 3 Subjects demographic data

Variable	AT ($N = 11$)	Control ($N = 10$)	p-Value
Demographic data			
Age	32.8 ± 2.8	30.3 ± 15.4	0.7
Sex			0.83
Male	5	5	
Female	6	5	
IBS subtype			0.58
Alternating	5	5	
Constipation	3	1	
Diarrhea	3	4	

Data are given as mean ± SD

Sex: degree of freedom = 1, p-value was calculated by a 2 × 2 Chi square

IBS subtype: degree of freedom = 2, p-value was calculated by a 2 × 3 Chi square

Table 4 IBS symptoms, negative emotion, and HR-QOL before and after treatment

	AT			Control		
	Baseline	End of treatment	*p*-Value	Baseline	End of treatment	*p*-Value
SIBSQ(Q1-14)	52.1 ± 11.6	48.9 ± 6.1	0.473	55.9 ± 13.9	36.3 ± 23.4	0.008*
SDS	46.4 ± 5.9	44.6 ± 7.4	0.315	45.9 ± 5.9	45.8 ± 9.4	0.553
STAI						
State anxiety	50.0 ± 9.1	47.2 ± 7.9	0.755	54.6 ± 11.0	51.4 ± 10.5	0.173
Trait anxiety	56.0 ± 8.1	54.5 ± 9.4	0.102	56.8 ± 11.4	52.8 ± 14.5	0.097
SF-36						
PF	47.7 ± 14.3	51.2 ± 8.3	0.600	48.9 ± 7.8	46.4 ± 13.7	0.655
RP	26.9 ± 18.9	35.6 ± 20.4	0.310	23.7 ± 19.2	33.8 ± 24.6	0.293
BP	36.8 ± 7.8	45.6 ± 11.7	0.012*	38.5 ± 9.6	41.3 ± 10.7	0.735
GH	30.9 ± 10.6	34.7 ± 9.4	0.069§	32.8 ± 10.4	33.8 ± 17.4	0.484
VT	35.4 ± 8.3	37.1 ± 6.6	0.463	36.6 ± 6.3	34.5 ± 10.7	0.097
SF	27.0 ± 12.0	41.1 ± 19.6	0.021*	43.4 ± 9.0	42.6 ± 15.7	0.866
RE	34.2 ± 14.5	46.4 ± 15.5	0.051§	33.9 ± 16.0	41.2 ± 18.2	0.575
MH	36.6 ± 9.0	42.0 ± 4.9	0.239	35.9 ± 8.5	35.6 ± 13.5	0.889

PF physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health

Data are given as mean ± SD

* $p < 0.05$, § $p < 0.1$

Chi-square test ($\chi^2 = 5.74$, $p < 0.05$, Fig. 2). The difference of proportion of patients with AR in the last AT session was 51.8% and the 95%CI ranged from 17.0 to 86.6%. The rate ratio of AR between the AT group and the control group in the last AT session was 2.73 (95%CI, 1.02–7.32).

Also, the proportion of patients with AR in the AT group was significantly higher than that in the control group in the fourth ($p < 0.05$), seventh ($p < 0.001$), and eighth ($p < 0.05$) AT session.

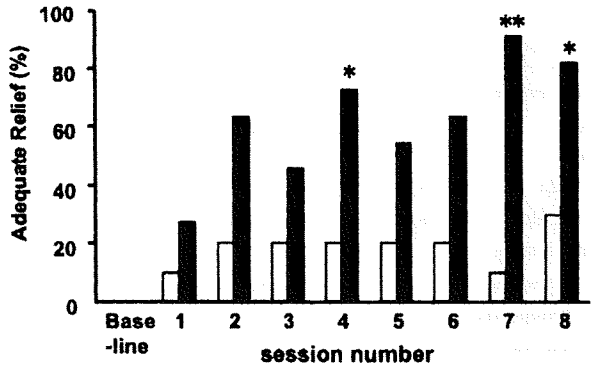

Fig. 2 AT-induced changes in adequate relief (%).*White bar*—control group ($n = 10$), *Black bar*—AT group ($n = 11$). * $p < 0.05$, ** $p < 0.001$: vs. control. Baseline means before the first session. The *white* and *black bars* indicate the proportion of adequate relief (AR) "yes". Session number is for both AT and control sessions

SIBSQ, SDS, and STAI

SIBSQ subscores, SDS, and STAI did not differ between the AT group and the control group (Table 4). ANOVA of SIBSQ total scores showed no significant difference between the AT group and the control group.

HR-QOL

No significant group effect, period effect, or group x period interaction in SF-36 subscores was detected by two-way ANOVA. However, some post-treatment SF-36 scores in the AT group significantly improved as indicated by Wilcoxon signed-rank test. Role emotional score ($p = 0.051$) and general health score ($p = 0.069$) tended to be improved only in the AT group (Table 4). Bodily pain score in the AT group significantly increased after treatment (45.6 ± 11.7) as compared with baseline (36.8 ± 7.8, $p = 0.012$, Table 4). In the control group, on the other hand, bodily pain score did not change throughout the study. Social functioning score in the AT group was significantly improved by treatment (baseline: 27.0 ± 12.0, after treatment: 41.1 ± 19.6, $p = 0.021$, Table 4). However, no change in social functioning score was detected in the control group. There were no significant changes in the other subscales of the SF-36 in both groups.

There was no difference in visiting interval between the AT group and the control group. Besides, no relationship

was noted between the length of visit interval and clinical effect.

Discussion

This is the first study to demonstrate that AT is effective in the general improvement of IBS. As shown in our results, the proportion of AR in the last AT session in the AT group was significantly higher than that in the controls. In addition, two subscales of the SF-36, i.e. social functioning and bodily pain, were significantly improved in the AT group as compared to the control group. Role emotional and general health showed a tendency for improvement in the AT group, although without statistical significance. SIBSQ, SDS, and STAI, on the other hand, did not differ between the AT group and the control group. AT has long been used as a relaxation technique (Günter and von Eye 2006), and has been reported to reduce anxiety (Kanji et al. 2006a; Jorm et al. 2004), chronic pain (Jensen and Patterson 2006), and headache (ter Kuile et al. 1994). AT has also been shown to improve some aspects of HR-QOL in patients with multiple sclerosis (Sutherland et al. 2005). However, systematic studies on headache, chronic pain, and anxiety indicate that the effects of AT on these conditions are limited (Jorm et al. 2004; Jensen and Patterson 2006; Sutherland et al. 2005). On the other hand, psychophysiological studies revealed that AT has a distinct effect on autonomic function (Kanji et al. 2006a, b; Sakakibara et al. 1994; Mishima et al. 1999). AT has been shown to increase cardiac parasympathetic tone (Sakakibara et al. 1994) and prolong the ECG R–R interval electrocardiogram (Kanji et al. 2006a, b; Mishima et al. 1999).

Emotional memory has two major forms: a conscious (explicit) memory for facts and personal events and an unconscious (implicit) memory for motor and sensory experience (Iversen et al. 2000). Autonomic function reflects typical implicit processing of emotion. Thus, grading GI symptoms, grading anxious symptoms, and grading depressive symptoms may mainly be executed by explicit brain processing, while judging AR may be based on implicit brain processing. Based on this reasoning, it is suggested that the effect of AT on general improvement of IBS is due to changes in implicit processing of emotion.

AT is one of the methods of self-induced hypnotherapy (Schultz 1987). Hypnotherapy has been used for treating refractory IBS (Whorwell et al. 1984; Whorwell 1989; Prior et al. 1990). Although the mechanism by which hypnotherapy affects IBS has not been clarified, there are several reports indicating that abdominal rectal sensitivity in IBS patients can be normalized by hypnotherapy (Lea et al. 2003; Prior et al. 1990). In addition, hypnotic suggestions are capable of changing activity of the anterior cingulate cortex as detected by positron emission tomography (Rainville et al. 1997). Therefore, the hypnotic element of AT, at least, may have changed rectal sensitivity and/or limbic brain activity in IBS patients in our study. The advantage of AT over usual hypnotherapy is that AT is easier to perform for therapists than hypnotherapy and that patients can acquire AT techniques and use them in their daily lives. Although we did not measure patients' self-efficacy in performing AT, AT might improve self-control resulting in more AR, less bodily pain, and improved social functioning. There are several protocols of hypnotherapy for IBS (Palsson 2006; Palsson et al. 2006) and gut directed hypnotherapy is one of them (Lea et al. 2003; Gonsalkorale 2006; Roberts et al. 2006; Smith 2006). In this study the AT used did not follow the gut-directed approach. However, it is of interest to search for what is the best method of inducing remission of IBS among the therapies in the hypnosis category.

In this study, socres for SIBSQ, anxiety, and depression did not change with AR. However, this is not surprising because in clinical trials of IBS, AR is not always proportional to the summation of individual GI symptoms (Irvine et al. 2006). In contrast, bodily pain score and social functioning of SF-36 were improved in the AT group. Patients with IBS in this study might regard QOL as a more important factor for AR than GI symptoms per se. This is because IBS is usually a chronic process and patients tend to have maladjusted coping style with catastrophizing (Drossman et al. 2002). In other words, most IBS patients have no adequate strategy to control their emotion and behavior before treatment. AT is one of the options that offer IBS patients a technique to control their emotion and behavior. In this study, self-efficacy may have been at the origin of improved social functioning. This notion can be examined in studies with larger sample sizes.

There are several limitations to this study. First, the degree of self-performed AT (AT home exercise) might have affected the results, although this possibility was not examined in this study. Second, longterm effects were not assessed. Although several anecdotal reports revealed effects of AT lasted for years, the long-term effects of AT clearly need to be quantified.

We believe we have shown in this study that AT may be a promising psychological treatment for IBS. Further studies with larger sample sizes and evaluation of the long-term effects of AT are warranted.

Acknowledgments This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Ministry of Health, Welfare, and Labor, Japan.

Appendix

Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ)

(Date / /)

Name (male • female) age years old
(Date of birth / /)

Please read the following questions and choose one answer from the seven choices. Mark your answer with an open circle o.

(1) Please answer all of the following 14 questions. In the last one week, you generally had・・・.

	nothing at all	almost nothing	slightly present	present	moderately present	severely present	extremely present
① abdominal pain.	1	2	3	4	5	6	7
② abdominal discomfort.	1	2	3	4	5	6	7
③ a change in your usual number of bowel movement (either more or fewer), when the pain or discomfort started.	1	2	3	4	5	6	7
④ softer stools than usual, when the pain or discomfort started.	1	2	3	4	5	6	7
⑤ harder stools than usual, when the pain or discomfort started.	1	2	3	4	5	6	7
⑥ improvement of abdominal pain or abdominal discomfort after a bowel movement.	1	2	3	4	5	6	7
⑦ pasting mucus during a bowel movement.	1	2	3	4	5	6	7
⑧ feeling of incomplete emptying after a bowel movement.	1	2	3	4	5	6	7
⑨ feeling of abdominal distention.	1	2	3	4	5	6	7
⑩ straining anring bowel movement and/or difficulty to defecate.	1	2	3	4	5	6	7
⑪ urgency of defecation	1	2	3	4	5	6	7
⑫ anxiety about occurrence of bowel symptoms even when you have no bowel symptoms.	1	2	3	4	5	6	7
⑬ occurrence of bowel symptoms when you feel stress	1	2	3	4	5	6	7
⑭ occurrence of bowel symptoms after you take meals.	1	2	3	4	5	6	7

(2) In the last one week, what kind of stool form did you have generally?

1 separate lumpy stool
2 hard stool with aggregated lumpy stool
3 banana-like stool with cracks
4 smooth and soft stool
5 loose stool with blobs
6 mushy stool
7 watery stool

(3) In the last one week, what kind of bowel movement did you have generally?	1 no spontaneous bowel movement and used laxatives 2 no bowel movement 3 once or twice/week 4 3-4 times/week 5 5-6 times/week 6 2-3 times/day 7 over 4 times/day
(4) In the last one week, how often did you have abdominal pain or abdominal discomfort?	1 nothing 2 once/week 3 twice/week 4 3-4 times/week 5 5-6 times/week 6 once/day 7 twice/day
(5) In the last one week, how often did you visit an emergency room of the hospital because of bowel symptoms?	1 not at all 2 visited once/week 3 visited twice/week 4 visited 3-4 times/week 5 visited 5-6 times/week 6 visited once/day 7 visited over twice/day
(6) In the last one week, how often did you visit your usual outpatient clinic (except emergency room) because of bowel symptoms?	1 not at all 2 visited once/week 3 visited twice/week 4 visited 3-4 times/week 5 visited 5-6 times/week 6 visited once/day 7 visited over twice/day
(7) In the last week, how often did you feel stress?	1 not at all 2 felt once/week 3 felt twice/week 4 felt 3-4 times/week 5 felt 5-6 times/week 6 felt once/day 7 felt over twice/day
(8) In the last one week, how was your life disturbed because of bowel symptoms? (e.g. absent from job, unable to get in or on a vehicle, etc...)	1 not at all 2 no disturbance despite slight symptoms 3 no disturbance despite symptoms once 4 no disturbance with slight bearing symptoms 5 no disturbance with bearing symptoms 6 sometimes disturbed 7 disturbed

References

American Gastroenterological Association. (2002). American Gastroenterological Association medical position statement: Irritable bowel syndrome. *Gastroenterology, 123*, 2105–2107.

Camilleri, M., Northcutt, A. R., Kong, S., Dukes, G. E., McSorley, D., & Mangel, A. W. (2000). Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. *Lancet, 25*, 1035–1040.

Chang, L., Ameen, V. Z., Dukes, G. E., McSorley, D. J., Carter, E. G., & Mayer, E. A. (2005). A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *American Journal of Gastroenterology, 100*, 115–123.

Chey, W. D., Chey, W. Y., Heath, A. T., Dukes, G. E., Carter, E. G., Northcutt, A., et al. (2004). Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *American Journal of Gastroenterology, 99*, 2195–2203.

Drossman, D. A. (1999). Review article: An integrated approach to the irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics, 13*(suppl 2), 3–14.

Drossman, D. A. (2006). The functional gastrointestinal disorders and the Rome III process. *Gastroenterology, 130*, 1377–1390.

Drossman, D. A., Camilleri, M., Mayer, E. A., & Whitehead, W. E. (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology, 123*, 2108–2131.

Drossman, D. A., Li, Z., Andruzzi, E., Temple, R. D., Talley, N. J., Thompson, W. G., et al. (1993). U.S. householder survey of functional gastrointestinal disorders: Prevalence, sociodemography and health impact. *Digestive Diseases & Science, 38*, 1569–1580.

Endo, Y., Yoshizawa, M., Fukudo, S., Sasaki, M., & Hongo, M. (2000). Panic disorder in irritable bowel syndrome (in Japanese). *Shinsin-Igaku [Japanese Journal of Psychosomatic Medicine], 40*, 339–346.

Fukuda, K., & Kobayashi, S. (1973). A study of Self-rating depression scale (in Japanese). *Seishin Shinkeigaku Zasshi [Japanese Journal of Psychiatry], 75*, 673–679.

Fukudo, S., Nomura, T., Muranaka, M., & Taguchi, F. (1993). Brain-gut response to stress and cholinergic stimulation in irritable bowel syndrome. A preliminary study. *Journal of Clinical Gastroenterology, 17*, 133–141.

Fukuhara, S., Bito, S., Green, J., Hsiao, A., & Kurokawa, K. (1998). Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *Journal of Clinical Epidemiology, 51*, 1037–1044.

Fukuhara, S., Suzukamo, Y., & Bito, S. (2001). *Manual of SF-36 Japanese version 1.2* (pp. 1–105). Tokyo: Public Research Foundation.

Gonsalkorale, W. M. (2006). Gut-directed hypnotherapy: The Manchester approach for treatment of irritable bowel syndrome. *The International Journal of Clinical and Experimental Hypnosis, 54*, 27–50.

Gonsalkorale, W. M., Miller, V., Afzal, A., & Whorwell, P. J. (2003). Long term benefits of hypnotherapy for irritable bowel syndrome. *Gut, 52*, 623–629.

Gonsalkorale, W. M., Toner, B. B., & Whorwell, P. J. (2004). Cognitive change in patients undergoing hypnotherapy for irritable bowel syndrome. *Journal of Psychosomatic Research, 56*, 271–278.

Günter, K., & von Eye, A. (2006). Treatment motives as predictors of acquisition and transfer of relaxation methods to everyday life. *Journal of Clinical Psychology, 62*, 83–96.

Irvine, E. J., Whitehead, W. E., Chey, W. D., Matsueda, K., Shaw, M., Talley, N. J., et al. (2006). Design of treatment trials for functional gastrointestinal disorders. *Gastroenterology, 130*, 1538–1551.

Iversen, S., Kupfermann, I., & Kandel, E. R. (2000). Emotional states and feelings. In E. R. Kandel, J. H. Schwartz, & T. M. Jessel (Eds.), *Principles of neural science* (4th ed., pp. 982–997). New York: McGraw-Hill.

Jensen, M., & Patterson, D. R. (2006). Hypnotic treatment of chronic pain. *Journal of Behavioral Medicine, 29*, 95–124.

Jorm, A. F., Christensen, H., Griffiths, K. M., Parslow, R. A., Rodgers, B., & Blewitt, K. A. (2004). Effectiveness of complementary and self-help treatment for anxiety disorders. *The Medical Journal of Australia, 181*(suppl 7), S29–46.

Kanazawa, M., Endo, Y., Whitehead, W. E., Kano, M., Hongo, M., & Fukudo, S. (2004). Patients and nonconsulters with irritable bowel syndrome reporting a parental history of bowel problems have more impaired psychological distress. *Digestive Diseases & Science, 49*, 1046–1053.

Kanji, N., & Ernst, E. (2000). Autogenic training for stress and anxiety: A systematic review. *Complementary Therapies in Medicine, 8*, 106–110.

Kanji, N., White, A. R., & Ernst, E. (2006a). Autogenic training to reduce anxiety in nursing students: Randomized controlled trial. *Journal of Advanced Nursing, 53*, 729–735.

Kanji, N., White, A. R., & Ernst, E. (2006b). Autogenic training for tension type headaches: A systematic review of controlled trials. *Complementary Therapies in Medicine, 14*, 144–150.

Kermani, K. (2001). Part 2 autogenic training, step by step. In *Autogenic training-the effective holistic way of better health* (pp. 39–145). London: Souvenir Press.

Lea, R., Hougton, L. A., Calvert, E. L., Larder, S., Gonsalkorale, W. M., Whelan, V., et al. (2003). Gut-focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics, 17*, 635–642.

Levy, R. L., Olden, K. W., Naliboff, B. D., Bradley, L. A., Francisconi, C., Drossman, D. A., et al. (2006). Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology, 130*, 1447–1458.

Longstreth, G. F., Thompson, W. G., Chey, W. D., Houghton, L. A., Mearin, F., & Spiller, R. C. (2006a). Functional bowel disorders. In D. A. Drossman, E. Corazziari, M. Delvaux, R. C. Spiller, N. J. Talley, W. G. Thompson, W. E. Whitehead (Eds.), *Rome III*. McLean: Degnon Associates.

Longstreth, G. F., Thompson, W. G., Chey, W. D., Houghton, L. A., Mearin, F., & Spiller, R. C. (2006b). Functional bowel disorders. *Gastroenterology, 130*, 1480–1491.

Mishima, N., Kubota, S., & Nagata, S. (1999). Psychological correlates of relaxation induced by standard autogenic training. *Psychotherapy and Psychosomatics, 68*, 207–213.

Mitani, S., Fujita, M., Sakamoto, S., & Shirakawa, T. (2006). Effect of autogenic training on cardiac autonomic nervous activity in high-risk fire service workers for posttraumatic stress disorder. *Journal of Psychosomatic Research, 60*, 439–444.

Nakazato, K., & Mizuguchi, T. (1982). Development and validation of Japanese version of state-trait anxiety inventory (in Japanese). *Shinsin-Igaku [Japanese Journal of Psychosomatic Medicine], 22*, 107–112.

Palsson, O. S. (2006). Standardized hypnosis treatment for irritable bowel syndrome: The North Carolina protocol. *The International Journal of Clinical and Experimental Hypnosis, 54*, 51–64.

Palsson, O. S., Turner, M. J., & Whitehead, W. E. (2006). Hypnosis home treatment for irritable bowel syndrome: A pilot study. *The International Journal of Clinical and Experimental Hypnosis, 54*, 85–99.