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Reactivation of medial temporal lobe and occipital lobe during the retrieval of color information: A positron emission tomography study

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It is widely accepted that memory traces of an event include various types of information about the content of the event and about the circumstances in which the individual experienced it. However, how these various types of information are stored and later retrieved is poorly understood. One hypothesis postulates that the retrieval of specific event information reactivates regions that were active during the encoding of this information, with the aid of binding functions of the medial temporal lobe (MTL) structures. We used positron emission tomography to identify the brain regions related to the encoding and retrieval of color information. Specifically, we assessed whether overlapping activity was found in both the MTL structures and color-related cortical regions during the encoding and retrieval of color information attached with meaningless shapes. During the study, subjects were asked to encode colored (red or green) and achromatic random shapes. At subsequent testing, subjects were presented with only achromatic shapes, which had been presented with or without colors during encoding, and were engaged in retrieval tasks of shapes and colors. Overlapping activity was found in the MTL and occipital lobe (the lingual and inferior occipital gyri) in the right hemisphere during the encoding and retrieval of meaningless shapes with color information compared with those without color information. Although there are some limitations to be considered, the present findings seem to support the view that the retrieval of specific event information is associated with reactivation of both the MTL structures and the regions involved during encoding of the information.

Introduction

Episodic memory is memory that allows one to remember past events in one's life (Tulving, 2001). It is widely accepted that memory traces of an event include various types of information about the content of the event as well as about the circumstances (i.e., temporal and spatial contexts) in which the individual experienced it (Fujii et al., 2004; Nadel and Moscovitch, 1997; Squire and Alvarez, 1995; Tulving, 2002).

However, how the various types of information comprising memory traces of an event are stored and later retrieved is poorly understood. One influential hypothesis postulates that the constituents of the content of a memory are stored in unimodal and heteromodal association cortices of the brain, with the medial temporal lobe (MTL) structures binding these constituents with each other and with event-specific contextual information. At subsequent retrieval, in response to a retrieval cue, reactivations of the MTL and association cortices occur through reciprocal MTL–cortical connections (Alvarez and Squire, 1994; Damasio, 1989; Fujii et al., 2000; Mishkin et al., 1997; Moscovitch, 1995; Nadel and Moscovitch, 1997; Norman and O'Reilly, 2003; Shastri, 2002; Teyler and DiScenna, 1986).

Functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow us to monitor the brain activity associated with encoding and retrieval separately and to identify the brain regions commonly activated during encoding and retrieval. However, to date, only a relatively small number of neuroimaging studies have directly assessed whether the neural activity elicited during encoding is reactivated during retrieval of the encoded information (Nyberg et al., 2000, 2001; Persson and Nyberg, 2000; Vaidya et al., 2002; Wheeler et al., 2000).

In their PET study, Nyberg et al. (2000) reported that what was referred to as the auditory responsive cortex and the left MTL were activated during both the encoding and retrieval of sound information paired with words, relative to words presented alone. Persson and Nyberg (2000) showed that the encoding and retrieval of the spatial location of visually presented words were associated with overlapping regions of the bilateral parietal cortices, compared with information other than spatial location. Wheeler et al. (2000), using fMRI, demonstrated greater activity in the visual associative cortex for the recall of pictures that had been paired with words during encoding and in the auditory associative cortex for the recall of sounds that had been paired with words

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during encoding. Nyberg et al. (2001) used PET to assess whether the verbal retrieval of action phrases was associated with reactivation of motor brain regions if the actions were overtly or covertly (i.e., by imagination) performed during encoding. They found that, common to both the overt and covert conditions, the retrieval of action phrases was associated with activations in the left ventral motor and left inferior parietal cortices. Vaidya et al. (2002), using fMRI, showed that recognition memory judgments about words that were encoded as pictures, relative to those that were encoded as words, activated fusiform and inferior temporal gyri primarily in the left hemisphere, which were involved specifically in the encoding of pictures.

In addition, two recent fMRI studies demonstrated that the visual and olfactory areas are reactivated during memory for pictures, visually presented words, and odors (Gottfried et al., 2004; Woodruff et al., 2005), although these two studies did not directly investigate the overlap between brain regions in activity related to both the encoding and retrieval operations. Gottfried et al. (2004) combined fMRI with a cross-modal paradigm in which objects were presented with odors during memory encoding, and examined the effect of odor context on neural responses at retrieval when the objects were presented alone. The right primary olfactory (piriform) cortex as well as the right anterior hippocampus were activated during the successful retrieval of old (compared to new) objects. Woodruff et al. (2005) identified material-dependent (words vs. pictures) double dissociative activation: recollected words elicited greater activity in the lateral fusiform region than recollected pictures, whereas the reverse effect was evident in the anterior fusiform region. In addition, right MTL activation was observed in the successful recollection (remember responses compared with know responses) of the studied items regardless of whether the items had been encoded as words or pictures.

The results of the above-mentioned studies indicate that some of the association cortices activated during encoding are also activated (reactivated) during retrieval. However, with regard to the reactivation of the MTL structures, the results of previous studies remain controversial. Since there are various constituents of the content of an event, it is worthwhile investigating what circumstances lead to overlapping activation in the MTL and other association cortices during both encoding and retrieval.

The present study further examined the reactivation hypothesis within the same sensory modality (i.e., visual modality) by investigating the encoding and retrieval of color information using PET. Specifically, the research question was whether overlapping activity would be found in both the MTL and color-related cortical regions during the encoding and retrieval of color information attached with meaningless shapes. In most previous imaging studies relevant to the reactivation hypothesis, meaningful stimuli have been used. However, in this study completely arbitrary associative memory tasks involving meaningless shapes and colors were used to avoid a potential confounding effect of preexisting binding between constituents of the memory content.

Materials and methods

Subjects

Fourteen male volunteers with no history of neurological or psychiatric disease were paid for their participation in this study (age range 20–25 years; mean 22 years). There were no pathological findings on the MRIs of any of the subjects' brains. All of the subjects were right-handed and had scores above +90 on the Edinburgh Handedness Inventory (Oldfield, 1971). They gave their written informed consent in accordance with the Declaration of Helsinki and guidelines approved by the Ethical Committee of Tohoku University.

Stimuli

The stimuli were 46 random shapes (Vanderplas and Garvin, 1959): 10 shapes with 6 corners, 12 shapes with 8 corners, 12 shapes with 12 corners, and 12 shapes with 16 corners. For the encoding conditions, two lists (lists A and B) were prepared, each consisting of 20 stimuli. Each list included 5 shapes with 6 corners, 5 shapes with 8 corners, 5 shapes with 12 corners, and 5 shapes with 16 corners. Half of the stimuli in list A were colored red and half of them were green; all those in list B were white. For the retrieval conditions, two lists (lists C and D) were prepared, each consisting of 20 white stimuli. List C consisted of 14 shapes from list A, 3 shapes from list B, and 3 new stimuli (1 with 8 corners, 1 with 12 corners, and 1 with 16 corners). List D consisted of 14 shapes from list B, 3 shapes from list A, and 3 new stimuli (1 with 8 corners, 1 with 12 corners, and 1 with 16 corners).

Tasks

For PET measurement, four conditions were prepared: two encoding conditions followed by two retrieval conditions, the orders of which were counterbalanced across subjects (Fig. 1).

Across all of the conditions, subjects were presented with 20 stimuli (random shapes for the two encoding and two retrieval

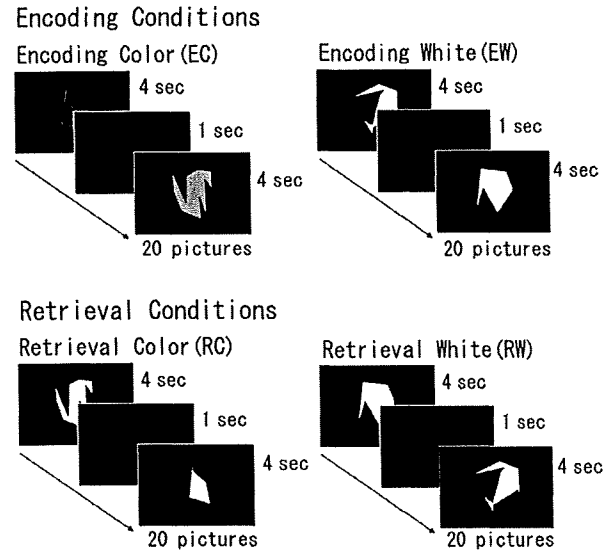

Fig. 1. The experimental design, which involved two encoding conditions (EC and EW) and two retrieval conditions (RC and RW). In each of the encoding conditions, subjects were asked to learn the shapes and colors of 20 stimuli. In each of the retrieval conditions, subjects were asked to judge whether the stimuli had been presented at encoding with red, green, or white, or had not been presented. Note that all stimuli in the retrieval conditions were presented with white. EC, encoding of colored shapes condition; EW, encoding of white shapes condition; RC, retrieval of colored shapes condition; RW, retrieval of white shapes condition.

conditions) one by one at a rate of one stimulus per 5 s (stimulus presentation time=4 s, interstimulus interval=1 s). Stimuli were presented on a black background on a display controlled by a Windows computer.

List A (20 colored random shapes) was presented in one encoding condition (EC; encoding of colored shapes), and list B (20 white random shapes) in the other (EW; encoding of white shapes). During the two encoding conditions, subjects were asked to press a button with the index finger of their left hand as soon as the stimuli were presented and to memorize the shapes and colors of the stimuli. To boost subsequent retrieval, each encoding condition was repeated five times (from the second to the fifth runs: stimulus presentation time=3.5 s, interstimulus interval=0.5 s) and only the first encoding condition was scanned with PET.

List C (14 random shapes which were red or green at encoding, 3 random shapes which were white at encoding, and 3 new random shapes) was presented in one retrieval condition (RC; retrieval of colored shapes), and list D (14 random shapes which were white at encoding, 3 random shapes which were red or green at encoding, and 3 new random shapes) was presented in the other (RW; retrieval of white shapes). During an 80-s PET data acquisition, 14 shapes which were colored at encoding, 1 shape which was white at encoding, and 1 new shape were presented in RC, and 14 shapes which were white at encoding, 1 shape which was green at encoding, and 1 new shape were presented in RW. This procedure ensured that most of the activations occurring during the retrieval conditions were due to the target stimuli, i.e., white shapes which were colored at encoding in RC, and white shapes which were also white at encoding in RW. During the two retrieval conditions, subjects were asked to press one of four buttons with the fingers of their left hand: the index-finger button if they thought the stimulus had been presented in red at encoding, the middle-finger button if they thought it had been presented in green at encoding, the ring-finger button if they thought it had been presented in white at encoding, and the little-finger button if they thought it had not been presented at encoding.

Data acquisition

All the subjects' responses (and the reaction times) were recorded in a computer as they pressed the buttons, and these data were subsequently used for the evaluation of performance accuracy.

Regional cerebral blood flow (rCBF) was measured using PET (SET2400W Shimadzu, FWHM 4.0 mm) and ^{15}O-labeled water (approximately 180 MBq for each injection). The transaxial sampling field of view (FOV) was 256 mm, and the axial FOV was 190 mm. The thickness of the slices measured was 3.125 mm. Prior to the PET experiments, subjects had a catheter inserted into the right brachial vein for tracer administration, and their heads were fixed to an air-cushioned headrest apparatus. Each task started 10 s before PET data acquisition, and lasted 100 s. PET data acquisition lasted 80 s. A transmission scan was followed by the experiment, and the data were used to obtain corrected emission images. A T1-weighted MRI scan (1.5 T) was performed on a separate occasion for coregistration.

Data analysis

The data were analyzed with Statistical Parametric Mapping (SPM2) (Wellcome Department of Imaging Neuroscience, UK). All rCBF images acquired from each subject were realigned to correct for small movements occurring between scans. This process generated an aligned set of images and a mean image per subject. A T1-weighted structural MRI was coregistered to this mean PET image. Then the coregistered T1 image was normalized to the Montreal Neurological Institute (MNI) templates implemented in SPM2. The parameters from this normalization process were applied to each PET image. The PET images were reformatted to isometric voxels ($2\times2\times2$ mm^3) and smoothed with a Gaussian kernel of FWHM of 10 mm. The rCBF-equivalent measurements were adjusted to a global CBF mean of 50 ml/dl/min. Contrast of the condition effect of each voxel was assessed using *t*-statistics, resulting in a statistical image (SPMt transformed into an SPMz). In both standard pairwise contrasts (i.e., EC vs. EW and RC vs. RW) and a cognitive conjunction analysis (i.e., EC vs. EW conjunct with RC vs. RW) using the "global null" in SPM2 software (Friston et al., 1999, 2005), the threshold of significance was set at $p<0.001$ (uncorrected for multiple comparisons). It should be noted that our "significant conjunction" does not mean all the contrasts were individually significant (i.e., a conjunction of significance). It simply means that the contrasts were consistently high and jointly significant. This is equivalent to inferring that one or more effects were present. To reduce the possibility of false-positive results (Type 1 errors), we regarded clusters of 25 or more voxels as significant. The anatomical identification of activated regions was performed using a standard space of the Talairach and Tournoux (1988) through the transformation from MNI to Talairach space (Brett et al., 2002).

Results

Behavioral measures of task performance

The mean accuracy and reaction time were, respectively, 82.6% (SD=11.3) and 1760 ms (SD=322) for RC, and 76.8% (SD=20.3) and 1758 ms (SD=432) for RW. There were no significant differences (*t*-test) in either accuracy ($p=0.12$) or reaction time ($p=0.49$) (Fig. 2), suggesting that differences in brain activation between EC and EW and between RC and RW cannot be ascribed to a difference in task difficulty.

Brain activation

First, EC was compared with EW. This contrast showed brain activations in the bilateral occipital regions, left supramarginal

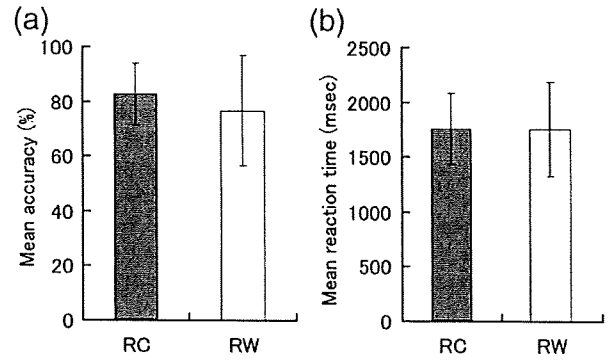

Fig. 2. (a) Mean accuracy of responses and (b) mean reaction times of the two retrieval tasks. Error bars indicate standard deviation. *T*-test showed no significant difference. Abbreviations as in Fig. 1.

Table 1
Brain regions showing activation in EC minus EW

Region (Brodmann's area)	MNI coordinates			Z value	Cluster size
	x	y	z		
R inferior occipital gyrus (BA18)	22	−94	10	4.14	114
L superior frontal gyrus (BA8/6)	−20	22	58	3.77	42
L putamen	−32	8	−4	3.87	34
L supramarginal gyrus (BA40)	−54	−56	46	3.95	26
L inferior occipital gyrus (BA18)	−14	−100	−4	4.37	136

EC, encoding of colored shapes condition; EW, encoding of white shapes condition; R, right; L, left.

gyrus, left superior frontal gyrus, and left putamen (Table 1 and Fig. 3a).

Second, RC was compared with RW. RC, relative to RW, was associated with activations in the right lingual gyrus and left middle occipital gyrus (Table 2 and Fig. 3b).

Finally, to determine whether brain regions activated during encoding were reactivated at retrieval, we used a conjunction analysis (EC vs. EW conjunct with RC vs. RW). This analysis revealed that the right parahippocampal gyrus, right lingual gyrus, right inferior occipital gyrus, and left putamen were active in both the encoding contrast and the retrieval contrast (Table 3 and Fig. 4).

Discussion

The results showed overlapping activity in the MTL and occipital lobe (the lingual and inferior occipital gyri) in the right hemisphere during the encoding and retrieval of meaningless shapes with color information compared with those without color information. In EC all stimuli were colored shapes, and in EW all stimuli were white shapes, whereas all of the stimuli in both of the retrieval conditions (RC and RW) were white shapes. Therefore, encoding-related activations in these regions probably reflect the on-line processing of color information from the external world (i.e., the process of actual color perception) and binding it with shapes. However, retrieval-related activity could not be attributed to the on-line processing of color information from the external world, but rather to the process of retrieval of color information from the recognized shapes. Hence, this finding seems to support the reactivation hypothesis that postulates that the retrieval of specific event information is associated with the reactivation of both the MTL structures and regions that were involved during the encoding of this information.

The overlapping activity found in the MTL during the encoding and retrieval of color information attached with shapes was consistent with the findings of the study by Nyberg et al. (2000), which focused directly on the reactivation of brain regions. Nyberg et al. found left MTL activation during both the encoding and retrieval of sound information paired with words, relative to words presented alone. The results of the present study are also compatible with those of studies of memory retrieval in the context of reactivation (Gottfried et al., 2004; Woodruff et al., 2005) cited in the Introduction. With regard to the successful encoding or retrieval of color information, three neuroimaging studies have demonstrated MTL activation, although overlapping activity between encoding and retrieval was not assessed. Yonelinas et al. (2001), using fMRI, reported that bilateral MTL structures were activated during an associative recognition task (clip-arts with colors) compared with a simple old/new judgment task. Ranganath et al. (2004) showed that activation of two right MTL regions (the posterior hippocampus and

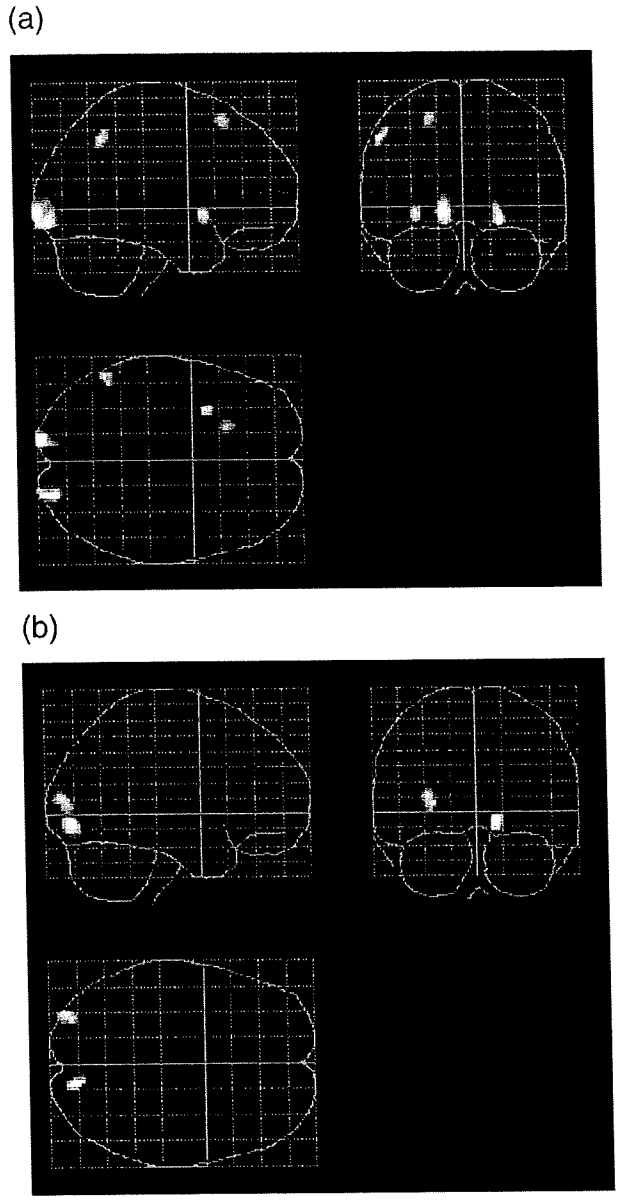

Fig. 3. (a) Brain regions showing activation in comparison of EC with EW. (b) Brain regions showing activation in comparison of RC with RW. The activations are superimposed onto MRIs of Montreal Neurological Institute (MNI) templates. Abbreviations as in Fig. 1.

Table 2
Brain regions showing activation in RC minus RW

Region (Brodmann's area)	MNI coordinates			Z value	Cluster size
	x	y	z		
R lingual gyrus (BA18)	14	−86	−6	4.02	69
L middle occipital gyrus (BA18)	−32	−90	10	3.73	72

RC, retrieval of colored shapes condition; RW, retrieval of white shapes condition; R, right; L, left.

Table 3
Brain regions showing overlapping activity during encoding and retrieval of color information

Region (Brodmann's area)	MNI coordinates			Z value	Cluster size
	x	y	z		
R parahippocampal gyrus (BA28)	18	−22	−16	3.68	25
R lingual gyrus (BA18)	18	−88	−6	4.12	83
R inferior occipital gyrus (BA18)	34	−88	−16	4.45	58
L putamen	−30	10	0	3.78	36

R, right; L, left.

posterior parahippocampal cortex) at encoding predicted subsequent successful retrieval of color information attached with words. Weis et al. (2004) found increased activity in bilateral MTL structures in successful color retrieval attached with buildings/landscapes at encoding. Collectively, the present findings and the data from these previous studies suggest that the MTL structures are engaged in binding specific event information with items during encoding and in recovering the same information from items during later retrieval.

Interestingly, overlapping MTL activity was identified in the right hemisphere in the present study. One possible reason for this is that the constituents of the materials encoded and retrieved in this study were non-verbal (the association between random shapes and colors). This explanation is consistent in part with some previous studies showing right MTL activation during memory for pictures and odors (Gottfried et al., 2004), bilateral MTL activation during the retrieval of colors from clip-arts (Yonelinas et al., 2001) and of colors from buildings/landscapes (Weis et al., 2004), and left MTL activation during memory for words and sounds (Nyberg et al., 2000). Two studies, however, have not reported right MTL activation during the successful encoding of words and colors (Ranganath et al., 2004) and during the retrieval of pictures from words (Woodruff et al., 2005). This may be related to the fact that these two studies found MTL activation in a somewhat different comparison (recollection-related activity; i.e., remember responses vs. know responses) from that used in others.

On the other hand, some studies have found no activation in the MTL in the context of reactivation (Nyberg et al., 2001; Persson and Nyberg, 2000; Vaidya et al., 2002; Wheeler et al., 2000). Persson and Nyberg (2000) and Wheeler et al. (2000) compared associative tasks with each other, a situation in which activation of the MTL might be cancelled out. Similarly, in the study by Nyberg et al. (2001), since the baseline condition was an associative learning task (rehearsing verb–noun commands), comparison between the target conditions (overt enactment and covert enactment) and the baseline condition might weaken the differences in activation of the MTL. Vaidya et al. (2002) compared recognition memory judgments related to words that were encoded as pictures with those that were encoded as words, and reported no activation in the MTL structures. However, their study did not involve any explicit associative learning, and it is possible that an associative learning procedure might be necessary to trigger MTL activation. The precise circumstances in which MTL activations are found (including, for example, combinations of constituents to be remembered, task procedures, and the method used for statistical comparisons) should be determined carefully in future studies.

The right occipital lobe (the lingual and inferior occipital gyri) also showed overlapping activity during the encoding and retrieval of color information attached with shapes. These sites are close to the color perception areas (V4; 28, −78, −14/−30, −76, −16) demonstrated by Bartels and Zeki (2000). Chao and Martin (1999) reported that the right lingual gyrus is associated with color perception. Moreover, Howard et al. (1998) showed that color perception activated the bilateral posterior fusiform gyri (area V4), as well as the right-sided anterior fusiform and lingual gyri, striate cortex (area V1), and bilateral insula. However, as mentioned above, whereas encoding-related activations could be attributed to the on-line processing of color information from the external world and the binding of color with shapes, this is not the case for retrieval-related activity, which is attributable to the processes of retrieval of color information from recognized shapes. Related to this, Miceli et al. (2001) reported two brain-damaged patients who exhibited an unusual pattern of object color knowledge loss but spared color perception and naming, suggesting that the brain regions subserving color retrieval and color perception are not the same. Therefore, the overlapping activity in the occipital lobe found in the present study probably reflects processes necessary for association between the color and shape of stimuli rather than processes of color perception itself.

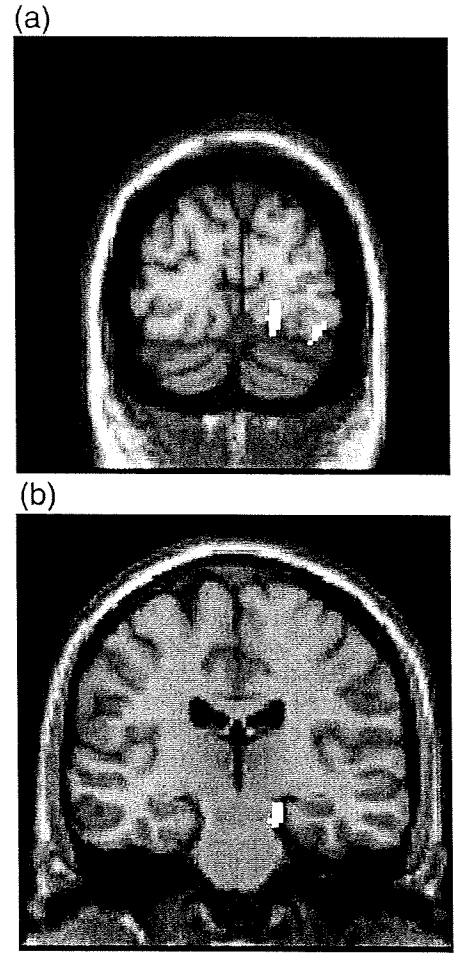

Fig. 4. Brain activations common to the encoding and retrieval of color information (EC vs. EW conjunct with RC vs. RW). The activations are superimposed onto MRIs of Montreal Neurological Institute (MNI) templates. (a) Right lingual gyrus (18, −88, −6), right inferior occipital gyrus (34, −88, −16). (b) Right parahippocampal gyrus (18, −22, −16). Abbreviations as in Fig. 1.

Other than our hypothesized regions, overlapping activation of the left putamen, one component of the basal ganglia, was found during the encoding and retrieval of color information attached with shapes. Although the basal ganglia are usually thought to have a role in regulating motor behavior, previous studies have clarified their role in language processing such as word fluency, sentence comprehension, and verbal long-term memory (D'Esposito and Alexander, 1995; Grossman, 1999; Risse et al., 1984). One possible interpretation is that the activation of the left putamen might be associated with an increased cognitive demand of language processing during EC and RC (relative to EW and RW), where subjects might inwardly generate two color names throughout the conditions.

Finally, it is necessary to mention the limitations of the present study. First, we used PET and a blocked design as a measure of brain activation. Compared with fMRI, PET has the advantage of detecting some regional activation (e.g., orbitofrontal cortex, anterior temporal lobe structures, and other regions showing magnetic susceptibility-induced signal losses due to the sinus cavities), but the blocked design raises issues of expectation or effects of selective attention on activation patterns. Second, the use of multiple encoding procedures makes the relevance of the present results to episodic memory or semantic memory uncertain. A similar criticism can be applied to other previous studies (Gottfried et al., 2004; Vaidya et al., 2002; Wheeler et al., 2000). To clarify this point, it might be useful to assess the difference in brain activation between a single-study procedure and a multiple-study procedure. Alternatively, in the present study, a remember/know procedure during retrieval could have been informative. Third, to achieve our goal, it might not be necessary to use two different colors (red or green) as specific event information attached with shapes. Encoding or retrieval, or both, of two different colors might be more demanding for cognitive processes than encoding and/or retrieval of a single color, and this might be a confounding factor in the interpretation of the data, although there were no significant differences in the behavioral measures between the two retrieval conditions (RC and RW). Finally, it is not clear whether activation in the MTL is preceded by activation in the occipital lobe or vice versa during the encoding and retrieval conditions. In order to prove the validity of the reactivation hypothesis, it is critical to determine the time course of activation in each region. The animal study conducted by Naya et al. (2001) showed that the memory-retrieval signal appeared earlier in the perirhinal cortex, and neurons in the inferior temporal cortex were then gradually recruited to represent the sought target. They suggested that this finding underlies the activation (reactivation) of neurons in the inferior temporal cortex that represent a visual object retrieved from long-term memory. Also, recent studies (Dhond et al., 2005; Masumoto et al., 2006) using magnetoencephalography (MEG) have reported the time course of activation patterns in some brain regions during a recognition test, although MEG does not easily detect signals in deep or medial brain structures. If the temporal resolution of non-invasive neuroimaging techniques such as event-related fMRI improves, it will be possible to determine the time course of activation patterns in several memory-related regions, including the MTL in the human brain.

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Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity

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NEUROGASTROENTEROLOGY

Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity

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Objective: The aim was to determine whether lower visceral pain thresholds in irritable bowel syndrome (IBS) primarily reflect physiological or psychological factors.

Methods: Firstly, 121 IBS patients and 28 controls underwent balloon distensions in the descending colon using the ascending methods of limits (AML) to assess pain and urge thresholds. Secondly, sensory decision theory analysis was used to separate physiological from psychological components of perception: neurosensory sensitivity (p(A)) was measured by the ability to discriminate between 30 mm Hg vs 34 mm Hg distensions; psychological influences were measured by the report criterion—that is, the overall tendency to report pain, indexed by the median intensity rating for all distensions, independent of intensity. Psychological symptoms were assessed using the Brief Symptom Inventory (BSI).

Results: IBS patients had lower AML pain thresholds (median: 28 mm Hg vs 40 mm Hg; $p<0.001$), but similar neurosensory sensitivity (median p(A): 0.5 vs 0.5; $p=0.69$; 42.6% vs 42.9% were able to discriminate between the stimuli better than chance) and a greater tendency to report pain (median report criterion: 4.0 ("mild" pain) vs 5.2 ("weak" pain); $p=0.003$). AML pain thresholds were not correlated with neurosensory sensitivity ($r=-0.13$; $p=0.14$), but were strongly correlated with report criterion ($r=0.67$; $p<0.0001$). Report criterion was inversely correlated with BSI somatisation ($r=-0.26$; $p=0.001$) and BSI global score ($r=-0.18$; $p=0.035$). Similar results were seen for the non-painful sensation of urgency.

Conclusion: Increased colonic sensitivity in IBS is strongly influenced by a psychological tendency to report pain and urge rather than increased neurosensory sensitivity.

During balloon distension of the rectum or colon patients with irritable bowel syndrome (IBS) report pain and discomfort at abnormally low volumes or pressures.[1–3] These lower pain thresholds have been interpreted to represent visceral hypersensitivity[4 5] and have been attributed to physiological differences in IBS patients.[6–8] Mertz *et al* even proposed that lower pain thresholds are "a reliable biological marker of IBS."[9] However, it is impossible to attribute lower IBS pain thresholds specifically to underlying physiological mechanisms[3 10] since cognitive and psychological influences affect the reporting of pain and, by extension, affect threshold measurements.[1 11 12]

The physiological and psychological components that determine pain thresholds can be separately quantified by sensory decision theory analysis (SDT).[13] In SDT stimuli of different intensities are presented in an unpredictable order and subjects rate the intensity of each stimulus. Statistical decision theory is then used to determine:

(1) The *discrimination index (p(A))*: a measure of neurosensory sensitivity (physiological) that is based on the subject's ability to discriminate between two stimuli of similar, yet distinct, intensities. The discrimination index is reduced by local nerve blocks and analgesics, but is immune to cognitive and psychological manipulations.[14 15]

(2) The *report criterion (B)*: a measure of the subject's overall tendency to label any stimuli as weak vs intense, independent of the actual stimulus intensity. The report criterion is susceptible to cognitive and psychological manipulations such as suggestion and placebo, but is not affected by analgesics.[14–16]

The primary aim of this study was to determine whether differences in pain thresholds between patients with IBS and healthy controls are explained primarily by differences in neurosensory sensitivity (physiological differences) or differences in the overall tendency to report pain (psychological differences). The secondary aim was to determine and explain differences in urge thresholds. Ultimately, a better understanding of the factors that affect these thresholds will improve our understanding of the mechanisms responsible for hypersensitivity and might help to direct therapy. Accordingly, we used AML to compare sensory thresholds in both IBS patients and healthy controls, and SDT supplemented by psychological questionnaires to determine how physiological and psychological factors contribute to these thresholds. We hypothesised that, compared to healthy controls, IBS patients would have: (1) lower AML determined pain and urge thresholds; (2) similar levels of neurosensory sensitivity; and (3) a lower report criterion (that is, an increased overall tendency to report stimuli as intense). (4) We also hypothesised that AML pain thresholds and the report criterion would be inversely correlated with levels of psychological distress.

Abbreviations: AML, ascending methods of limits; BSI, Brief Symptom Inventory; IBS, irritable bowel syndrome; IBS-C, constipation predominant irritable bowel syndrome; IBS-D, diarrhoea predominant irritable bowel syndrome; IOP, individual operating pressure; ROC, receiver operator characteristic; SDT, sensory decision theory analysis

METHODS

Subjects

Subjects were recruited by advertisements or physician referrals and screened by telephone. The study was approved by the institutional review board of the University of North Carolina (UNC) and all subjects provided informed consent.

IBS patients

The study population consisted of 132 patients (84% female; median age 35 years) who met Rome II criteria for IBS[17] and had current symptom activity (abdominal pain at least once a week in the past month). Twenty-seven IBS patients were constipation predominant (IBS-C), 31 were diarrhoea predominant IBS (IBS-D), and 61 were not classifiable as either. These subjects had no history of gastrointestinal resection (other than appendectomy or cholecystectomy), known IBS, coeliac disease, lactose malabsorption, heart disease, or diabetes mellitus, and they were not pregnant at the time of study. IBS patients were required to stop the following medications—antidepressants (seven days before study), antispasmodics, muscle relaxants or narcotic analgesics (three days); and non-steroidal anti-inflammatory agents (one day).

Controls

The control population consisted of 31 subjects (71% female; median age 40 years) without any significant or recurring gastrointestinal symptoms; exclusion criteria were average stool frequency of less than three per week or more than three per day, abdominal pain, use of a laxative or anti-diarrhoeal agent on more than two occasions over the previous year, history of alcohol or substance abuse, a psychiatric diagnosis, or any of the medical conditions listed above for the IBS patients. None of these healthy subjects had used any antidepressants, antispasmodics, muscle relaxants, or narcotic analgesics for at least one year. Non-steroidal anti-inflammatory agents were not permitted for at least one day before the study. There were no significant differences between the IBS group and healthy controls for age ($p = 0.72$) or sex ($p = 0.12$).

Psychological evaluation

On the first day of the study subjects reported to the UNC General Clinical Research Center (GCRC) at 11 am where they completed the Brief Symptom Inventory-18 (BSI-18). This is an 18-item measure of psychological distress along three primary symptom dimensions: somatisation, anxiety, and depression.[18] The BSI-18 was also scored for the global severity index. The rationale for including the BSI somatisation scale is that somatic hypervigilance is hypothesised to play a part in visceral hypersensitivity.[12] The BSI depression, anxiety, and global scales were included based on the convention of regarding depression and anxiety as the primary dimensions of psychological distress.

Colonic sensory testing

At approximately 4 pm subjects underwent bowel preparation with 3 oz of Fleets Phospho-Soda followed by an overnight fast. On the morning of the second day (approximately 8 am) a barostat catheter was placed into the descending colon for sensory testing. Firstly, a guide wire was inserted to the level of the splenic flexure using a flexible sigmoidoscope. The sigmoidoscope was then withdrawn and a barostat catheter (Model No C7-CB-0026, Mui Scientific, Mississauga, Ontario, Canada) was inserted over the guide wire. The guide wire was then withdrawn and barostat placement was confirmed by fluoroscopy. No sedation was used throughout the duration of this procedure. A 600 ml plastic bag (Model No CT-BP600R, Mui Scientific, Mississauga, Ontario, Canada) was attached to the catheter, and the catheter was connected to a computer controlled piston type pump (barostat) that was capable of inflating and deflating the bag at a rate of 38 ml/s (G&J Electronics, Willodale, Ontario, Canada). The pump was interfaced to a computer running a software program that recorded the pressure inside the bag 16 times per second.

Subjects were instructed to give separate ratings of the intensity of pain and urgency to defecate experienced at the end of each distension, using a six point scale (0 = no sensation; 1 = weak; 2 = mild; 3 = moderate; 4 = strong; 5 = intense) (fig 1). The scale was visible to subjects during the procedure. Sample distensions were then performed during which the barostat bag was inflated in a stepwise fashion by increasing bag pressure by 4 mm Hg every 15 seconds until the subject reported moderate pain (rating of 3). The purpose of the sample distensions was threefold: (1) to insure that the barostat bag was unfolded; (2) to teach the subject how to use the rating scale to rate the intensity of colonic sensations; and (3) to decrease anticipatory anxiety. The barostat bag was then slowly inflated with 30 ml of air and the pressure was allowed to equilibrate for 3 minutes. The average pressure during the last 15 seconds defined the individual operating pressure (IOP): the minimum pressure required to overcome mechanical forces and inflate the bag with 30 ml of air.

	Numeric rating	Descriptor	Beta value
	5	Intense	1
Boundary 5			
	4	Strong	2
Boundary 4			
	3	Moderate	3
Boundary 3			
	2	Mild	4
Boundary 2			
	1	Weak	5
Boundary 1			
	0	None	6

Figure 1 Subjects rated the intensity of each stimulus on the six point rating scale showed above. The corresponding descriptor and beta value for each numeric rating are shown. Boundaries separate consecutive ratings.

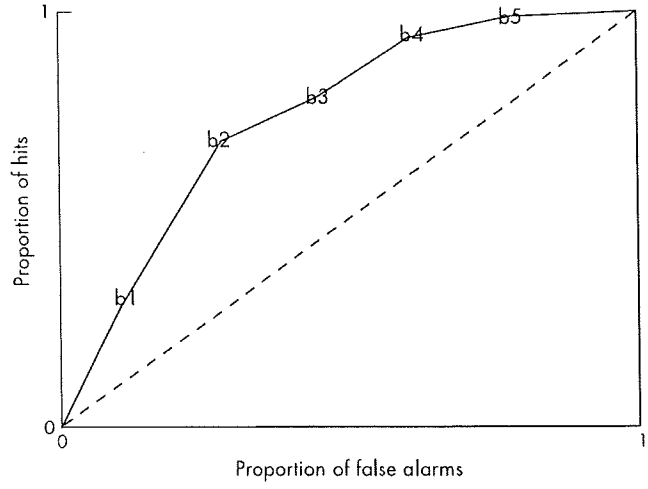

Figure 2 Receiver operator characteristic curve (ROC curve): each point represents the proportion of hits and false alarms for a given boundary (b1–b5). The total area under the ROC curve represents p(A).

Ascending method of limits (AML) protocol

This protocol started approximately 90 minutes following barostat placement. Phasic distensions were 30 seconds in duration and were separated by 30-second rest intervals starting at the IOP and progressively increasing in 2 mm Hg steps until either the subject requested the research nurse to stop the protocol or 48 mm Hg was reached. The pain threshold was defined as the amount of pressure above IOP at which the subject first reported moderate pain (absolute distending pressure minus the IOP). If the subject requested that the research nurse stop the trial before moderate pain was reported (for example, because of urge to defecate) then the pain threshold was not determined. If the subject reached 48 mm Hg without reporting moderate pain, then the pain threshold was defined as 50 mm Hg minus the IOP. The urge threshold was defined analogously.

Sensory decision theory (SDT) protocol

This protocol started approximately 100 minutes following barostat placement. Subjects were instructed that the purpose was to evaluate how well they could discriminate between different balloon pressures. Twenty-four 30-second phasic distensions (eight at 30 mm Hg, eight at 32 mm Hg, and eight at 34 mm Hg) were presented in an unpredictable order separated by 30-second rest intervals at the IOP. These stimulus intensities were selected to bracket the average pain threshold determined by AML in a previous study of SDT.[14] The choice of 2 mm Hg increments between stimuli was based on this previous study in which this difference was found to work well (that is, subjects made some errors of classification but discrimination was better than chance).[19] This protocol followed the recommendation of McNicol[20] and one of the co-investigators who is an expert on SDT (WCC). The subjects were able to stop the protocol at any time.

Discrimination index (p(A)) and report criterion (B) values for the 30 mm Hg vs 34 mm Hg stimuli were calculated for each subject using a computer program developed by MN Janal and WC Clark (personal communication). This program was based on formulas taken from McNicol for non-parameteric SDT analysis of rating scale data.[20]

The meaning of the discrimination index (p(A)) is clear: it is a measure of the ability to distinguish between the two stimulus intensities, based on the sensory intensity ratings reported in response to them. However, the computational formula is complex: (1) ratings on the rating scale used by the subject to subjectively rate the intensity of stimuli that are presented, are separated by multiple boundaries (fig 1). (2) For each boundary one calculates the proportion of all the higher intensity stimuli (that is, 34 mm Hg distensions) that received ratings above this boundary (this is the "hit" rate for this boundary) and one separately calculates the proportion of the lower intensity stimuli (that is, 30 mm Hg distensions) that received ratings above this boundary (this is the "false alarm" rate for this boundary). Thus, in this study hit rates and false alarm rates were calculated for each of five boundaries. (3) These hit rates and false alarm rates are plotted against each other to create a receiver operator characteristic curve (ROC curve) as shown in figure 2. The curve is drawn by connecting the different intersections of hit and false alarm rates calculated for each boundary (shown by the solid line in fig 2). (4) P(A) is the total area under the ROC curve (shaded area in fig 2) expressed as a proportion of the maximum possible area. The broken diagonal line in figure 2 goes through all the points for which the hit rate and the false alarm rates are equal; this represents chance performance or no discrimination, and the index, p(A) is 0.5. All values less than 0.5 are considered chance performance and are rounded up to 0.5. Thus, p(A) is a number between 0.5 (chance) and 1.0 (perfect discrimination) that measures the ability to discriminate between the two intensities independently of what rating labels the subject uses to describe the stimuli.

The report criterion (B) is the median rating assigned by the subjects to all stimuli. Firstly, the ratings assigned to the

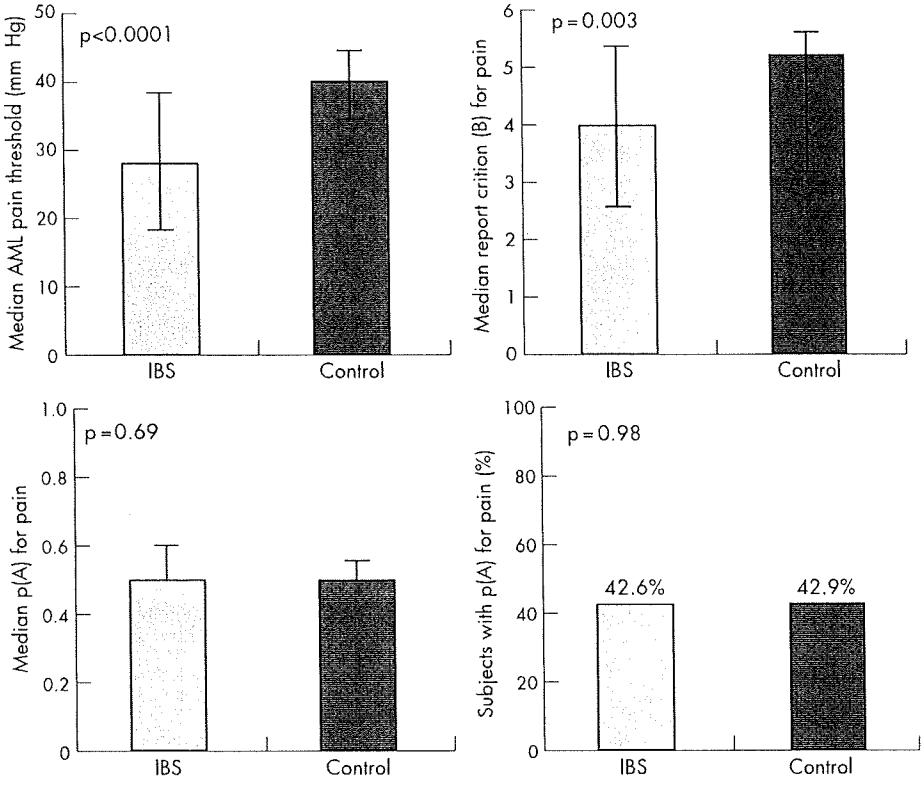

Figure 3 (Top left) Median AML pain thresholds: thresholds were significantly higher in healthy controls than in IBS subjects. (Top right) The pain report criterion (B) across both 30 mm Hg and 34 mm Hg stimuli: IBS patients had a lower criterion, which reflects their increased tendency to report pain irrespective of stimulus intensity. (Bottom left) The median pain neurosensory sensitivity (p(A)). There were no differences between the two groups. (Bottom right) The percentage of subjects whose ability to discriminate painful sensations between 30 mm Hg and 34 mm Hg stimuli was better than chance (p(A)>0.5): there was no difference between the two groups. The bars on each graph represent the interquartile range.

30 mm Hg distensions were pooled with ratings for the 34 mm Hg distensions. Secondly, each response on the six-point rating scale was assigned an individual report criterion (B) value. Based on SDT convention, a numerically low criterion means a "liberal" tendency to rate most of the stimuli as intense, whereas a numerically high criterion means a "conservative" or "stoic" tendency to label most stimuli as less intense. Therefore, higher (that is, more intense) subject ratings are assigned lower B values and vice versa (fig 2). Thirdly, the overall report criterion (B) was determined as the B value on the six point rating scale for which half of total responses to *both* stimulus intensities were to categories above the criterion and half were to categories below the criterion.[13]

There was a strong correlation between AML pain thresholds and pain report criterion ($r = 0.67$ $p<0.0001$). On the contrary, AML pain thresholds did not correlate with neurosensory sensitivity for pain ($r = -0.13$; $p = 0.14$).

Data analysis

The data were not normally distributed. Consequently, non-parameteric statistical tests were used. Significance was set at a p value of 0.05. Firstly, Wilcoxon rank sum tests were used to compare IBS patients to controls with respect to the following measures: AML determined pain and urge thresholds; SDT determined pain and urge discrimination index (p(A)) and report criterion values (B); BSI anxiety, depression, somatisation, and global severity index scores. Secondly, Spearman correlations were used to determine associations between AML pain thresholds with SDT determined pain discrimination index (p(A)) and report criterion (B). Thirdly, Spearman correlations were used to determine associations between both AML pain thresholds and pain report criteria (B) with the following measures: p(A), BSI anxiety, depression, somatisation, and global severity index scores.

RESULTS

Excluded subjects

In all, 119 IBS patients and 29 control subjects underwent colonic sensory testing. Of the 13 IBS patients who did not undergo colonic sensory testing, three withdrew consent after the first day, possibly because of apprehension regarding the pain test procedure, three refused flexible sigmoidoscopy, two did not tolerate sigmoidoscopy, one had an extremely elevated blood pressure, and one had colonic inflammation detected on sigmoidoscopy. Of the three excluded control subjects, one did not tolerate the flexible sigmoidoscopy and two had exclusionary medical conditions that were detected during the study (lactose intolerance in one and previous colonic surgery in the other).

Pain thresholds, neurosensory sensitivity, and report criterion

On the AML protocol IBS patients had lower pain thresholds (median 28 mm Hg vs 40 mm Hg; $p = 0.0002$). On sensory decision theory analysis there were no differences in pain neurosensory sensitivity (median p(A): 0.5 vs 0.5; $p = 0.69$; 42.6% of IBS patients vs 42.9% of healthy controls had p(A) >0.5 (chance); $p = 0.98$). Conversely, IBS patients had a lower pain report criterion, which represents their increased tendency to report stimuli as being relatively painful irrespective of the actual intensity of the stimulus (median B: 4.0 (median response = mild pain) vs 5.2 (median response = weak pain); $p = 0.003$) (fig 3).

Table 1 Psychological profiles of IBS and control populations

	IBS median (range)	Controls median (range)	p Value
BSI global severity index	49 (33–78)	42 (33–63)	<0.0001
BSI anxiety	50 (38–74)	39 (38–61)	<0.0001
BSI depression	48 (40–81)	42 (40–61)	=0.006
BSI somatisation	55 (41–74)	41 (41–66)	<0.0001

Psychometric scores and pain report criterion

IBS patients scored higher than controls on all psychometric scales (table 1). There were modest inverse correlations between pain report criterion (B) and BSI global score ($r = -0.18$; $p = 0.035$) and BSI somatisation ($r = -0.26$; $p = 0.001$) (table 2). Higher psychological distress correlated with an increased tendency to report pain.

Urge thresholds, neurosensory sensitivity, and report criterion

Sensory thresholds for urge were lower than those for pain. On the AML protocol IBS patients had lower urge thresholds than controls (median: 18 mm Hg vs 34 mm Hg; $p = 0.002$), but on sensory decision theory analysis there were no differences in urge neurosensory sensitivity (median p(A): 0.55 vs 0.50; $p = 0.17$; 63.1% of IBS patients vs 46.4% of healthy controls had urge p(A) >0.5 (chance); $p = 0.10$). Conversely, IBS patients had a lower urge report criterion, which represents their increased tendency to report relatively intense urge irrespective of the actual intensity of the stimulus (median B: 3.0 (median response = "moderate" urge) vs 4.2 (median response = "mild"); $p = 0.006$) (fig 4).

There was a strong inverse correlation between AML urge thresholds and urge report criterion ($r = -0.51$; $p<0.0001$) and a weaker but significant inverse correlation with neurosensory sensitivity to urge ($r = -0.22$; $p = 0.007$).

Psychometric scores and urge report criterion

There were modest inverse correlations between urge report criterion (B) and BSI global score ($r = -0.19$; $p = 0.03$), BSI somatisation ($r = -0.18$; $p = 0.04$), and BSI anxiety ($r = -0.17$; $p = 0.05$) (table 3). Higher psychological distress correlated with an increased tendency to report urge.

Additional analyses of SDT data

There was a moderately strong positive correlation between pain and urge discrimination (p(A)) ($r = 0.50$; $p<0.0001$). Similarly, there was a moderately strong positive correlation between pain and urge report criteria (B) $r = 0.44$; $p<0.0001$).

The SDT test involved 24 distensions at pressures, which were painful for most subjects, and consequently some subjects did not complete all trials. The accuracy of discrimination index (p(A)) and report criterion (B) values in subjects who underwent fewer SDT distension trials might have been lower because of increased variance. We therefore excluded subjects who completed fewer than one-half (<12) of all trials (33 IBS, 4 controls, $p = 0.158$) and repeated the comparison between IBS patients and controls for pain p(A) and report criterion (B). The pattern of results and the significance of the differences did not change for pain p(A) (median p(A) 0.5 vs 0.5; $p = 0.31$; % with pain p(A) > chance: IBS = 47.1%; control = 41.7%; $p = 0.63$;) or pain report criterion (median B: IBS = 4.4; control = 5.4; $p = 0.0001$).

Repeated distension of the colon has been previously shown to induce hyperalgesia ("sensitisation") in IBS patients.[8] Thus, it is possible that as a result of this potential sensitisation, the intensity ratings made by IBS patients to late SDT trials may

Table 2 Spearman's correlations: AML pain threshold and pain report criterion (B)

	Correlation (rho) with AML pain threshold	Correlation (rho) with SDT pain report criterion (B)
Pain p(A)	−0.13 p=0.1	−0.16 p=0.04
Pain B	0.67 p<0.0001	–
BSI global severity index	−0.22 p=0.01	−0.18 p=0.04
BSI anxiety	−0.11 p=0.2	−0.04 p=0.7
BSI depression	−0.11 p=0.2	−0.07 p=0.4
BSI somatisation	−0.28 p=0.001	−0.26 p=0.001

Table 3 Spearman's correlations: AML urge threshold and urge report criterion (B)

	Correlation (rho) with AML urge threshold	Correlation (rho) with SDT urge report criterion (B)
Urge p(A)	−0.22 p=.007	−0.09 p=0.3
Urge B	−0.51 p<0.0001	–
BSI global severity index	−0.19 p=0.03	−0.18 p=0.04
BSI anxiety	−0.17 p=0.05	−0.15 p=0.07
BSI depression	−0.07 p=0.4	−0.12 p=0.15
BSI somatisation	−0.18 p=0.04	−0.16 p=0.06

have been affected. In order to test for this we first determined the change in pain intensity ratings between the first and the last 30 mm Hg and 34 mm Hg trials (change in ratings = pain intensity rating to the last 30 mm Hg stimuli plus pain intensity rating to the last 34 mm Hg stimuli minus pain intensity ratings to the first 30 mm Hg stimuli minus pain intensity rating to the first 34 mm Hg stimuli). We then used the Wilcoxon rank sum test of differences to compare change in intensity ratings between IBS patients and controls who completed at least one-half (≥12) of all trials. There was no difference between the two groups (p = 0.22).

Finally, the intensities of the three SDT stimuli (30 mm Hg, 32 mm Hg, 34 mm Hg) were below AML pain thresholds for some subjects (mostly controls) and above threshold for other subjects (mostly IBS patients). Therefore, it was possible that certain subjects failed to demonstrate discrimination (p(A)) because they assigned the same ratings to all stimuli (either calling all of them "intense" or calling all of them non-painful). We identified nine (7.4%) IBS patients and nine (35%) healthy controls who rated each SDT stimulus as zero pain intensity. One IBS patient rated all stimuli as "intense." All other subjects varied their pain intensity ratings. When we excluded the 10 IBS patients and nine healthy controls who did not vary their pain intensity ratings and repeated the analysis, the pattern of results and the significance of the differences did not change for pain p(A) (median p(A) 0.5 vs 0.52; p = 0.8); percentage with pain p(A) > chance: IBS = 45.6%; control = 52.2%; p = 0.57) or pain report criterion (median B: IBS = 3.9; control = 4.52; p = 0.04).

DISCUSSION

In this study we first used AML to measure pain and urge thresholds and we then used SDT to determine the two components of these thresholds: physiologically determined neurosensory sensitivity and psychologically determined report criterion. Using these techniques, we demonstrated that lower AML determined pain and urge thresholds in patients with IBS are explained primarily by an increased tendency to report pain and urge, not increased neurosensory sensitivity. Since this lower report criterion reflects psychological phenomena, increased colonic sensitivity in IBS appears to be determined more by psychological factors than by physiological factors.

Pain is a complex perceptual experience that can only be measured indirectly.[21] Gastrointestinal pain sensitivity is typically measured by pain thresholds, which are defined as the lowest stimulus intensity to which subjects report pain. However, pain

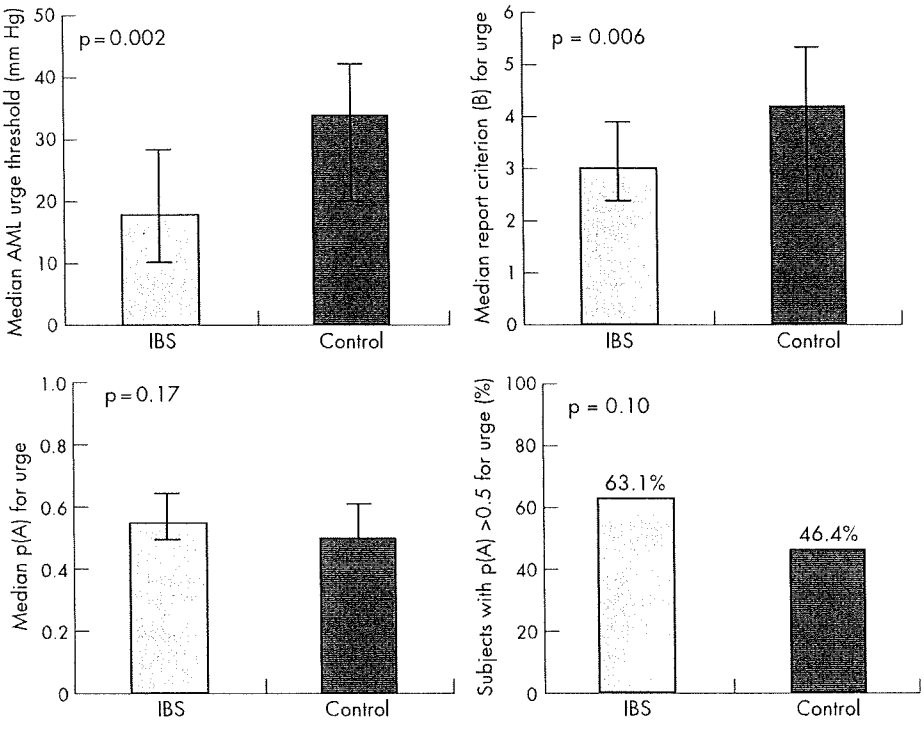

Figure 4 (Top left) Median AML urge thresholds: thresholds were significantly higher in healthy controls than IBS subjects. (Top right) The median urge report criterion (B) to 30 mm Hg and 34 mm Hg stimuli: IBS patients had a lower criterion which reflects their increased tendency to report urge irrespective of stimulus intensity. (Bottom left) The median urge neurosensory sensitivity (p(A)). There were no differences between the two groups. (Bottom right) The percentage of subjects whose ability to discriminate urge sensations between 30 mm Hg and 34 mm Hg stimuli was better than chance (p(A)>0.5): there was no difference between the two groups. The bars on each graph represent the interquartile range.

thresholds are not equivalent with painful sensations since pain reports are influenced by non-neurosensory factors such as placebo, emotion, attention, and distraction.[13]

SDT is an alternative pain measurement technique that separately quantifies the individual components of the pain response: neurosensory sensitivity (p(A)), a measure of neurosensory function based on the ability to discriminate between stimuli; and report criterion (B), a measure of stoicism based on the overall tendency to report pain.[14] Importantly, previous research has shown that only the criterion is susceptible to changes in cognitive or psychological variables.[13–15] The discrimination index, p(A), changes in response to analgesic drugs but is not influenced by psychological manipulations.[15 16] In this study, IBS patients had similar pain neurosensory sensitivity and lower pain report criterion compared to healthy controls. In other words, their tendency to report pain at lower thresholds related not to increased neural sensitivity, but rather to their predilection towards reporting pain.

Whereas SDT has been widely used in somatic pain research[13] it has been used only rarely in previously published studies on visceral pain sensitivity in functional gastrointestinal disorders. Bradley *et al* observed lower AML pain thresholds, similar neurosensory sensitivity, and decreased report criterion for balloon distensions of the oesophagus in patients with non-cardiac chest pain,[22] which is similar to the findings of this study. Whitehead *et al* observed lower AML pain thresholds and similar neurosensory sensitivity for rectal distensions in women with IBS,[19] which is also similar to the findings of this study. However, they did not measure the report criterion.

Similar to pain, our findings also suggest that lower AML determined urge thresholds in patients with IBS are largely explained by an increased tendency to report urge. However, the finding that urge thresholds and urge neurosensory sensitivity were inversely correlated ($r = -0.22$, $p<0.005$) suggests that lower urge thresholds in IBS may also be attributable—albeit to a lesser extent—to increased urge neurosensory sensitivity. These findings contrast with those reported by Corsetti *et al* who, using non-painful, barely perceivable balloon distensions, found that patients with IBS had increased neurosensory sensitivity and similar report criterion. However, unlike our study, their study involved a small population (22 patients and 13 controls) in which there were no psychological differences between the IBS and control groups.[23]

The increased tendency to report pain and urge in patients with IBS may be the downstream result of multiple cognitive and psychological processes. Firstly, patients with IBS appear to be hypervigilant to gastrointestinal sensations.[12 24] For example, on functional brain imaging they show similar, abnormal cortical responses to both actual and anticipated (sham) distensions.[25 26] Secondly, hypervigilance may reduce the intensity at which they notice gut distensions[28] and sensations. Thirdly, once perceived, subjects with IBS interpret these sensations through a generally negative schema (framework for explaining reality),[28] which leads them to attribute their sensations to disease.[29] Finally, disease attribution in turn further increases attention to gastrointestinal symptoms[30] through which a cycle of gastrointestinal sensory amplification is ultimately established.[31] Along these lines, in our study somatisation was more common in IBS and was correlated inversely with pain thresholds and directly with the response criterion. This is similar to findings that in Gulf War veterans with IBS, lower pain thresholds could be largely explained by increased somatic focus.[32] Other investigators have also found that global psychological distress is correlated with the amount of brain activation in response to painful rectal distension[33] and is inversely correlated with tolerance for painful balloon distension of the rectum.[34]

In order to assess visceral sensitivity independently from these cognitive processes, some have proposed measuring cortical activity during subliminal distensions (that is, not consciously perceived).[35 36] Lawal *et al* used this approach and found increased cortical activation in subjects with IBS. They interpreted this as evidence for neural hypersensitivity that is independent of cognitive input.[37] However, it is unclear whether these distensions were truly subliminal since most individuals can perceive distensions as small as 5 mm Hg[38]; the distensions in their study ranged from 10 mm Hg to 20 mm Hg. Secondly, their observation that cerebral activation in IBS patients did not increase in a positive dose-response fashion suggests that IBS patients were globally hypersensitive at baseline. This global hypersensitivity was attributed by Naliboff and Mayer to cognitive and psychological processes such as uncertain expectation and hypervigilance, that could not be completely controlled for in the study.[39]

Although our data demonstrate that psychological phenomena strongly influence pain thresholds, our experimental methods may not have been sensitive enough to detect subtle differences in neurosensory sensitivity. Thus, we cannot rule out the effects of peripheral physiological mechanisms, such as sensitisation of colonic afferent pathways.[6 42 43] This afferent hypersensitivity has been credited to inflammation based on evidence that experimentally induced colonic inflammation lowers rectal pain thresholds in animal models.[42] Nonetheless, inflammation has not been shown to explain lower thresholds in IBD patients.[43 44]

Study limitations

Two potential limitations to this study were posed by the repeated balloon distensions required by the SDT protocol. Firstly, certain subjects failed to complete all 24 SDT trials because of intolerable levels of pain or urge. We estimated the effects of this by repeating our analyses without including those subjects who completed fewer than half of the trials. The results were the same. Secondly, the process of repeated very intense colonic distensions (60 mm Hg) has been previously shown to induce rectal hypersensitivity in subjects with IBS.[8] We estimated the effects of this by comparing the change in pain intensity ratings between early and late stimuli in IBS patients and healthy controls. There was no difference between the two groups.

SDT, which quantifies the ability of subjects to discriminate between very similar stimuli, required that we use stimulus intensities that were very close to each other (30 mm Hg vs 34 mm Hg). This might have been too close to allow for adequate discrimination—that is, the measurement of neural sensitivity may have been insensitive. However, most subjects can perceive a 5 mm Hg increase in stimulus intensity.[19] In this study 43% of both IBS patients and healthy controls were able to discriminate between the 30 mm Hg and 34 mm Hg distensions at better than chance levels (p(A) values above 0.5).

Calculation of the report criterion required us to use the same stimuli for all subjects, irrespective of their AML thresholds. As a result, the ability of some subjects to discriminate between SDT stimuli might have been affected either because the test stimuli were well above their pain threshold or they were so far below their pain threshold that none of them were perceived as painful. We tested for this by excluding subjects who rated all stimuli as equally painful and repeating the analysis. The results did not change. Furthermore, in our previous smaller study where we individualised SDT stimulus intensities for each patient based on their AML determined pain threshold (though we did not compute a report criterion), we still found

that subjects with IBS and healthy controls had similar neurosensory sensitivity to pain.[14]

A theoretical limitation is that we used pressure rather than volume based balloon distensions. Some investigators prefer volume based distensions or indices that integrate pressure and volume into estimates of wall tension.[45] We followed the recommendations of an international consensus committee[40] by scaling our distensions in pressure rather than volume because it is recognised that volume thresholds are influenced by muscle tone, which varies from hour to hour in response to meal ingestion and anxiety. Individual differences in pain thresholds are believed to be more stable and reproducible when measured on a pressure scale rather than a volume scale.

Conclusion

These data show that lower pain and urge thresholds in subjects with IBS are strongly influenced by cognitive and psychological factors. Peripheral physiological events such as inflammation[42] and temporal summation[8] have also been shown to influence pain sensitivity. However, these data suggest that, when explaining the differences between IBS patients and healthy controls, the contribution of peripheral physiological events may be relatively small compared to the cognitive and psychological influences that are reflected in the report criterion index, which reflects the generalised tendency to report pain. The implications of this finding are far reaching. Firstly, it underscores the importance of accounting for psychological factors when interpreting tests of sensory function. Secondly, it highlights the important part played by centrally mediated processes in the pathophysiology of visceral sensitivity in IBS and suggests that novel therapies for pain in IBS should target centrally mediated mechanisms.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1190

The echocardiogram demonstrates a pericardial effusion with cardiac tamponade. This resulted in ischaemic hepatitis (IH) and acute liver failure (ALF). An emergency pericardiocentesis was performed, and circulatory function immediately improved. Liver and renal function normalised over the next 15 days (fig 1).

IH is an uncommon but well described cause of ALF. In this case, ischaemic liver injury occurred because of a combination of factors: right heart failure (acute hepatic congestion) and decreased hepatic arterial perfusion, secondary to hypotension from cardiac tamponade.

IH occurs in the setting of the following predisposing factors: reduced hepatic arterial flow states, passive liver congestion and arterial hypoxaemia. Aetiologies include cardiac arrest and intraoperative hypotension (eg, cardiac bypass) on a background of respiratory or left ventricular failure.

Treatment aims at removing the insult to the liver and maximising cardiac output, thus improving oxygenation. Fulminant hepatic failure is uncommon, and usually occurs with pre-existing cirrhosis. The condition is reversible, depending on the underlying cause of the circulatory insult. Because of the setting of major circulatory failure (eg, cardiac arrest) and good prognosis if circulation is restored, liver transplantation is rarely indicated.

When presented with ALF, it is important to consider ischaemia, a reversible condition. Although cardiac tamponade is a rare cause of IH, this case demonstrates the benefit of early diagnosis and removing the insult to the liver with resultant rapid and complete clinical improvement of the IH.

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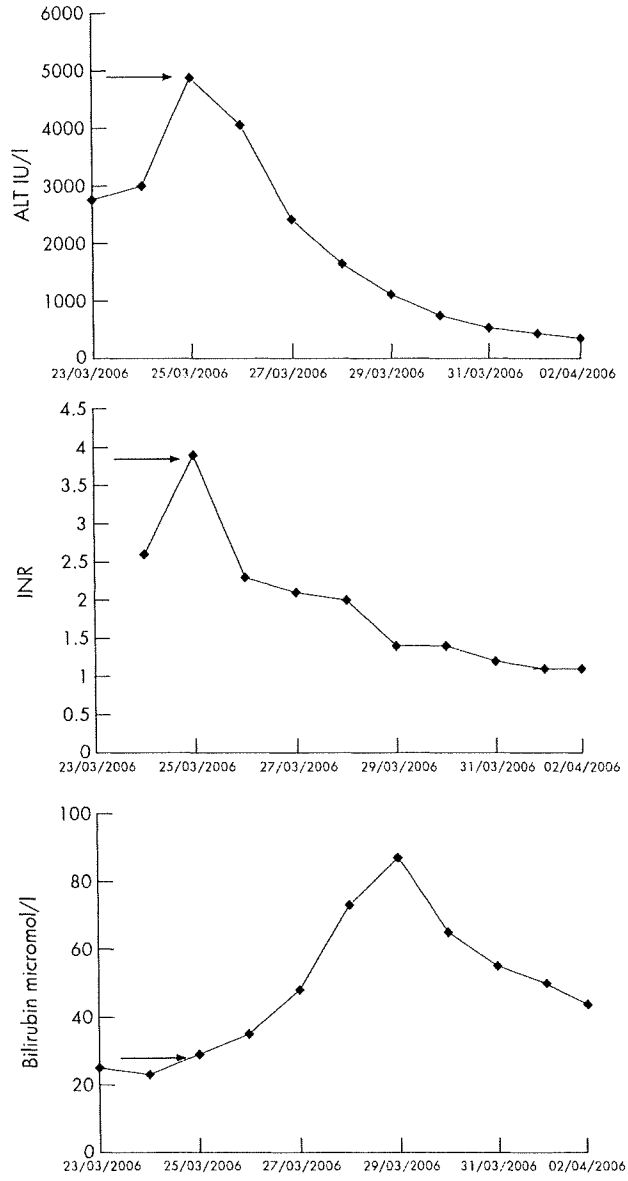

Figure 1 Graphs showing the biochemical changes in the reported case. The acute rise and fall in alanine aminotransferase (ALT) and international normalised ratio (INR), with a delayed rise in bilirubin, are characteristic of ischaemic hepatitis. The arrows denote when pericardiocentesis was performed.

High Prevalence of Irritable Bowel Syndrome in Medical Outpatients in Japan

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Background and Goals: The prevalence of irritable bowel syndrome (IBS) among Japanese patients who visit hospitals departments of internal medicine is thought to be high. However, no clear statistical evidence has been provided to support such a claim. We tested the hypotheses that the prevalence of IBS in medical outpatients clinics in Japan is high, and that IBS patients feel more psychosocial stress than patients without IBS.

Study: The subjects in this study were 633 patients who visited participating physicians. Patients were asked to fill in the Japanese version of the Rome II Modular Questionnaire (RIIMQ) for IBS diagnosis, the Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ) for severity of the disease and the demographic questionnaire for perceived stress and life style.

Results: Rome II-defined IBS was diagnosed in 196 patients (31%). Analysis of variance revealed significant difference in the IBS scores of SIBSQ among IBS subjects (39.0 ± 11.1, mean ± SD), functional bowel disorder subjects (27.1 ± 10.2), and normal subjects (24.0 ± 10.0, $P < 0.01$). The prevalence of IBS depending on age formed 2 peaks, one among adolescents and the other among the elderly. IBS patients had significantly more perceived stress ($P < 0.0001$), irregular sleep habit ($P < 0.0001$), and irregular meal habit ($P < 0.0001$) than those without IBS.

Conclusions: The prevalence of IBS among medical outpatients in Japan is high (31%). IBS subjects among medically ill patients are thought to have more perceived stress and less regular life styles.

Key Words: irritable bowel syndrome (IBS), Rome II Modular Questionnaire, outpatient, stress

(*J Clin Gastroenterol* 2008;42:1010–1016)

Irritable bowel syndrome (IBS) is a very common and a chronic gastrointestinal (GI) disorder characterized by recurrent abdominal pain and altered bowel habits without major organic diseases by routine gastroenterologic examination.[1] IBS is a highly common disorder with a prevalence in Europe and North America of about 10% to 15% of the population.[2,3] In GI practice, however, the prevalence of IBS accounts for 30% of patients in the United Kingdom.[4] IBS has, therefore, become a serious issue for the medical economy in developed countries, including the United States and the United Kingdom,[5,6] where a decline in the quality of life associated with disturbed activities at work,[7] school, and daily life has been reported.[8–10] In those countries, IBS is known to affect the negative impact on their quality of life.[11] In fact, psychosocial stress is repetitively reported as an aggravating factor of IBS.[12,13]

For exact investigation of IBS, worldwide diagnostic criteria are indispensable.[14] These criteria were proposed after the International Congress of Gastroenterology was held in Rome (Rome I).[15] Rome II criteria[16,17] were then established after a 7-year validation and evaluation period of Rome I. These criteria include the Rome II Modular Questionnaire (RIIMQ) developed by Rome Committee for clinical investigation and/or epidemiologic surveys.[18,19]

Japan is a highly developed country with a culture, including diet and human relationships, different from

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those of western countries. Japan is also known as a country with increased level of psychosocial stress.[20] Despite predictions of high prevalence of IBS in Japan, an earlier preliminary study showed that the prevalence of Rome I-defined IBS in the consulters for healthcheck was only 3.6%, predominantly in males.[21] However, this study was not based on a standardized method. In addition, in epidemiologic surveys in western countries, the prevalence of IBS was shown to be high among females.[1–5] As the establishment of a highly reliable and valid questionnaire for IBS in Japanese language was needed to compare data between western countries and Japan, we have recently established the Japanese version of RIIMQ. This Japanese version of RIIMQ has been shown to be reliable and valid.[22] Although the prevalence of IBS among Japanese patients who visit hospitals departments of internal medicine is thought to be high, no clear statistical evidence, until now, has been provided to support such a claim.

The objectives of this study were (1) to confirm that the prevalence of IBS in Japanese outpatients who visit hospitals departments of internal medicine is high and (2) to verify the hypothesis that IBS subjects feel more psychologic stress than subjects without IBS.

SUBJECTS AND METHODS

Subjects

The subjects were patients who visited participating physicians in a Nation-wide Epidemiological Research Study conducted by the IBS Club in September 2002. Both urban and rural samples were included. The term of the study was 1 day only, and all patients who visited the participating physicians on the study day were enrolled in the study. The physicians explained the purpose of the study and written informed consents were obtained from the patients. This study was approved by the Ethics Committee of Tohoku University School of Medicine (approval number 2001-223). The number of subjects necessary to enroll was estimated according to the theory of experimental design. Taking into account that the prevalence of IBS at a hospital department of gastroenterology in the United Kingdom is 30%,[4] a sample size of over 400 subjects was enough for data analysis.

Questionnaire

RIIMQ, Respondent Form

This self-administered questionnaire for IBS diagnosis is based on the Rome II criteria.[18] Reliability and validity of both the English and Japanese versions of RIIMQ had already been established.[19,22] The questionnaire is composed of 4 crucial questions and 11 additional questions. The 4 crucial questions determine whether the patient has IBS or not. The 11 additional questions are about supporting symptoms and they are used to determine subgroups of IBS. The subgroups are classified as constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and others classified neither IBS-C nor IBS-D (alternating, IBS-A). The Japanese version of RIIMQ can be provided by the corresponding author.

In this survey, patients who reported no bowel symptoms were classified as normal and patients who had signs of bowel symptoms but did not satisfy Rome II criteria were regarded as having functional bowel disorder (FBD).

Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ)

This modified version of the self-reported IBS symptom evaluation scale consisting of a total of 21 items was prepared at Tohoku University.[23] SIBSQ is based on the Rome II criteria, and its Japanese version has already been validated.[22] The subjects answered 14 questions about their GI symptoms and 7 questions about the characteristics and number of stools, the presence or absence of stress, and the frequency of hospital visitations during a period of 1 week in their daily lives. Regarding GI symptoms, the questions included abdominal pain, abdominal discomfort, frequency of defecation, characteristics of stools (2 questions), feeling of residual stools, feeling of abdominal distention, bloating, feeling of incomplete evacuation, straining during defecation, anxiety for abdominal pain, relation between stress and bowel symptoms, and the relation between meals and bowel symptoms. Answers to SIBSQ were rated by Likert's scale from 1 (nothing at all) to 7 (extremely present), and the sum of the 14 questions about GI symptoms was taken as IBS score, which reflects the severity of IBS in Japan.[23] The other 7 questions had 7 options grading the frequency or severity by frequency, and the subjects were asked to select one option among them.

Demographic Data

The following 10 items were investigated: (1) sex, (2) age, (3) occupation, (4) smoking, (5) alcohol, (6) diet, (7) sleeping, (8) perceived stress, (9) analysis of medical visits, and (10) name of the disease or condition the patient was diagnosed with during past visits. Demographic items were shown in Table 1.

Methods

After receiving patients' informed consents, the physicians handed the questionnaires to the patients who completed them during their waiting time. Diagnoses of each patient's past visits were recorded by the physician. Clinical diagnosis of IBS was made by the physicians based on Rome II criteria or on each physician own criteria, including complete blood counts, blood chemical examination, plasma inflammatory response, fecal occult blood, and colon-fiberscopy or Ba enema and flexible sigmoidoscopy if necessary. Diagnosis for other diseases was made by accurate clinical examinations.

Statistical Analysis

SPSS 11.0J for Windows was used for statistical analysis. Analysis of variance (ANOVA), χ^2 test, and the Kruskal-Wallis test were performed to evaluate differences

TABLE 1. Demographic Data

Items	Unit	Male	Female	Total
Sex	%	305 (48.2)	328 (51.8)	633 (100.0)
Age	yo/range	16-96	15-93	15-96
	yo/mean ± SD	57.1 ± 16.3	58.3 ± 20.1	57.6 ± 18.4
Occupation				
Full-time	n (%)	139 (22.0)	62 (9.8)	201 (31.8)
Part-time	n (%)	22 (3.5)	51 (8.1)	73 (11.5)
Retire	n (%)	64 (10.1)	19 (3.0)	83 (13.1)
No occupation, layoff	n (%)	49 (7.7)	46 (7.3)	95 (15.0)
Homemaker	n (%)	4 (0.6)	118 (18.6)	122 (19.3)
Student	n (%)	5 (0.8)	12 (1.9)	17 (2.7)
Others	n (%)	22 (3.5)	20 (3.2)	42 (6.6)
Smoking				
No	n (%)	188 (29.7)	276 (43.6)	464 (73.3)
Yes	n (%)	117 (18.5)	52 (8.2)	169 (26.7)
Cigarette/d	d/mean ± SD	20.6 ± 10.6	15.9 ± 9.3	19.2 ± 10.8
Alcohol				
No	n (%)	124 (19.6)	214 (33.8)	338 (53.4)
Drink sometimes	n (%)	80 (12.6)	87 (13.7)	167 (26.4)
Drink everyday	n (%)	101 (16.0)	27 (4.3)	128 (20.2)
Diet				
Always regular	n (%)	93 (14.7)	144 (22.7)	237 (37.4)
Sometimes irregular	n (%)	161 (25.4)	153 (24.2)	314 (49.6)
Always irregular	n (%)	51 (8.1)	31 (4.9)	82 (13.1)
Sleeping				
Always regular	n (%)	93 (14.7)	144 (22.7)	237 (37.4)
Sometimes irregular	n (%)	170 (26.9)	169 (26.7)	339 (53.6)
Always irregular	n (%)	55 (8.7)	59 (9.3)	114 (18.0)
Perceived stress				
No	n (%)	200 (31.6)	190 (30.0)	390 (61.6)
Yes	n (%)	105 (16.9)	138 (21.8)	243 (38.4)
Initial visit				
No	n (%)	45 (7.1)	152 (24.0)	197 (31.1)
Yes	n (%)	260 (41.1)	176 (27.8)	436 (68.4)
Cause of consultation				
Hypertension	n	50	57	107
Diabetes	n	60	46	106
Peptic ulcer	n	47	15	62
IBD	n	22	36	58
Hepatitis/cirrhosis	n	23	19	42
Pancreatitis	n	13	19	32
Insomnia	n	5	10	15
Angina pectoris	n	8	6	14
Gallstone	n	2	7	9
Others	n	18	52	70

IBD indicates inflammatory bowel disease; SD, standard deviation; yo, years old.

among the study subjects. Statistical significance was regarded at P value less than 0.05.

RESULTS

Answers to the study questionnaires were obtained from 1045 patients. Seven hundred ninety-one patients (75%) completely answered the RIIMQ, 639 (61%) patients completely answered the SIBSQ, and 689 (66%) patients answered the demographic questionnaire. Of the 1045 patients, 633 patients (61%) completely answered all of the questionnaires. The demographic data of 633 patients are shown in Table 1. The patients were aged 57.6 ± 18.4, with 305 males and 328 females, 68.4% of the patients visited the hospital initially, and the causes of their visits were common diseases related to internal medicine. Of those patients, 196 (31%) were diagnosed as having IBS (Fig. 1). The prevalence of IBS among females (34.1%) tended to be more than that among males (27.5%, χ^2 value = 2.92, $P < 0.1$, Fig. 1). Two hundred seventy-six patients (44%) were diagnosed as having FBD and 161 patients (25%) were classified as normal. There was no significant difference in the prevalence of FBD between males and females.

ANOVA revealed a significant difference in IBS scores of SIBSQ among IBS subjects (39.0 ± 11.1, mean ± standard deviation), FBD subjects (27.1 ± 10.2) and normal subjects (24.0 ± 10.0, $P < 0.01$, Fig. 2). A post hoc test confirmed that IBS scores in IBS subjects were significantly higher than those in normal subjects