Towards an integrated psychoneurophysiological approach of irritable bowel syndrome

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TESTING A BIOBEHAVIORAL MODEL OF IRRITABLE BOWEL SYNDROME

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ABSTRACT

Background: The pathogenesis of irritable bowel syndrome (IBS) is probably multifactorial with dysfunction at different levels of the brain-gut axis. The aim of this study was to evaluate an existing biobehavioral model of IBS symptom generation in a large group of patients.

Methods: In 104 IBS patients, we assessed symptom severity by a symptom diary, age and gender, visceral hypersensitivity using a barostat, autonomic function by measuring arterial baroreflex sensitivity and psychological functioning using questionnaires. Structural Equation Modeling was used to calculate reciprocal and chronological relationships between model variables.

Results: Analysis of the adjusted original model indicated poor fit (Satorra-Bentler scaled chi-square *p*-value .019, comparative fit index (CFI) .842), which was caused by omission of 2 paths (illness behavior-IBS symptoms and trauma-IBS symptoms). The revised model yielded good fit (Satorra-Bentler, *p*=.274; CFI=.967). The trimmed model, obtained by deleting non-significant paths, explained 16.2% of the variance in IBS symptoms. Illness behavior completely mediated the effect of cognitions on IBS symptoms and partly mediated the effect of trauma on IBS symptoms. The fit of this alternative model was significantly better than the fit of the non-trimmed model (Satorra-Bentler, *p*=.43; CFI=.996). The trimmed alternative model explained 16.0% of the variance in IBS symptoms.

Conclusion: The proposed biobehavioral model could not be validated. Whereas visceral hypersensitivity and IBS symptom severity significantly correlate, autonomic function and IBS symptoms do not. Cognitive-behavioral aspects are important in the clinical expression of IBS, with illness behavior playing an intermediate and central role.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic functional bowel disorder characterized by recurrent abdominal pain and altered bowel habits such as diarrhea and/or constipation[1]. IBS is the most frequent functional gastrointestinal disorder with an estimated prevalence of 6 to 22%[2,3] and substantial economic impact[4,5]. Despite the growing body of literature, the pathophysiology of IBS remains poorly understood and a variety of mechanisms have been proposed in symptom generation. These include enhanced visceral sensitivity[6,7], disturbed intestinal motility[8,9], autonomic dysfunction[10,11], inflammatory processes[12,13], altered immune activity[14,15], altered processing of afferent sensory information[16,17] and psychological disturbances[18,19]. These alterations probably reflect dysfunction at different levels of the brain-gut axis, a conceptual framework which has recently emerged in an attempt to improve our understanding of the etiology, pathogenesis and clinical expression of IBS[20]. Although a biobehavioral model of IBS based on the brain-gut axis would be of great assistance to gain further insight in the relationship between these disturbances, few attempts have been made to construct such a model.

In 1998, Naliboff and colleagues proposed an initial but comprehensive working model of IBS, incorporating the central nervous system, visceral sensory and motor functioning, and cognitive-behavioral systems[21]. This biobehavioral model implies that internal or external stimuli, for example dysenteric illness or sexual or physical abuse, affect visceral sensory and motor function either directly or by an arousal-induced autonomic response ('ANS stress response'), that is, hypervigilance. Furthermore, the model suggests that visceral motor and sensory disturbances subsequently give rise to IBS symptoms, and that prolonged symptom duration will lead to alterations in illness behavior, environmental responses and health beliefs. These biobehavioral changes in turn increase hypervigilance and, ultimately, deteriorate IBS symptoms. Thus, the proposed model represents the clinical manifestation of IBS as interplay between biological and psychological factors, which is in agreement with the current concept of IBS as a multifactorial condition[22,23]. It also provides a verifiable theoretical framework that may improve our understanding of the pathophysiological mechanisms involved in IBS.

The aim of the present study was to evaluate this biobehavioral model of IBS[21] in a large group of patients. We tested the validity of the model using Structural Equation Modeling (SEM), as it allows calculation of reciprocal and chronological relationships between the model variables. Lackner and colleagues have recently shown that SEM is a valid method to test a sequential model of pain processing in IBS[24]. The ratio between the number of observed variables and the number of patients restricted testing possibilities using a model with latent variables and therefore constrained us

to perform a path analysis (as was done by Lackner et al.). To apply a path analysis to the working model proposed by Naliboff et al., we modified the model slightly, that is, we eliminated the feedback loop from IBS symptoms, illness behavior, environmental responses, health beliefs, and vigilance back to IBS symptoms[21] (see Fig 1). Furthermore, as IBS has a female predominance of unknown origin[25] and is less common in the elderly[26], we included age and gender in the model. Based on the proposed model, the existing literature, and the abovementioned statistical restrictions, we built the following hypotheses (Fig 1):

1. Trauma involving the abdomen, e.g., acute gastroenteritis, abdominal surgery, or sexual or physical abuse, will influence IBS symptom severity by modification of autonomic functioning and/or visceral sensitivity[27-29].
2. Autonomic dysfunction (reflected by low baroreflex sensitivity (BRS)-values) is associated with increased visceral sensitivity and hypervigilance[30-32].
3. Hypervigilance will lead to increased IBS symptom severity, either directly or by influencing visceral sensitivity.
4. Dysfunctional cognitions regarding functional bowel disorders lead to hypervigilance and increased IBS symptom severity[33].
5. Illness behavior aggravates dysfunctional cognitions[34].
6. Visceral hypersensitivity will lead to increased IBS symptom severity[6,35-37].
7. In older patients, autonomic functioning (BRS) is impaired[38], while vigilance is increased.
8. Levels of vigilance are higher in female patients[39].

METHODS

Participants

Between March 2001 and July 2002, IBS patients between 18 and 65 years of age were invited to participate in a clinical trial assessing the effect of a brief psychological intervention on IBS symptom severity. This trial included baseline psychological assessment, combined autonomic nerve functioning and rectal sensitivity testing (day 0), and IBS symptom severity measurements (day 1 to 14). All these data were used for the present study.

Patients were recruited through a tertiary referral centre (the outpatient department of Gastroenterology of the Leiden University Medical Center (LUMC)) and through local advertisement. All eligible participants were screened by one of the investigators (PvdV). All patients met Rome II criteria for IBS[1]. Exclusion criteria were organic disease, previous abdominal surgery (except cholecystectomy and appendectomy),

and pregnancy. Use of antispasmodics, laxatives, bulking agents and occasional use of analgesics was permitted. We used the Mini International Neuropsychiatric Interview (Dutch version 5.0.0)[40] to exclude patients with psychotic disorder, or risk of suicide. Informed consent was obtained from each participant. The LUMC ethics committee had approved the study protocol.

Measures

IBS symptom severity

Patients rated the severity of 5 symptoms, i.e. discomfort, abdominal pain, constipation, diarrhea, and bloating, daily for 14 days, on a 5-point Likert scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe symptoms) using a symptom diary card. A composite score was computed by summing up the 14-day mean scores for each symptom (range 0-20).

Visceral sensitivity

An electronic barostat (Synectics Visceral Stimulator, Synectics Medical, Stockholm, Sweden) was used to assess visceral perception. This device maintains constant pressure within an infinitely compliant balloon by injecting air when the rectal wall relaxes and aspirating air during rectal contraction[41]. A slow rectal ramp distension procedure was performed (1 mmHg increase/min, maximum 30 mmHg), during which rectal pain perception was quantified on a 100-mm Visual Analogue Scale (VAS)[42] at every even pressure. End points ranged from 'none' to 'intolerable'.

Autonomic function

Autonomic function was assessed by measuring arterial baroreceptor reflex sensitivity (BRS). BRS is defined as the prolongation of the interval between heart beats (milliseconds) induced by aorta and carotid baroreceptor activation when, due to any cause (e.g. stress or pain), arterial blood pressure rises by 1 mmHg. We chose to use BRS rather than more conventional autonomic measures, such as heart rate variability, because the arterial baroreflex not only modulates sympathetic and parasympathetic autonomic outflow, which governs gastrointestinal motor function, but also affects cortical arousal[31,32] and somatic[32,43] and visceral[30] pain perception. Thus, BRS may well be involved in conditions associated with altered visceral sensory and motor function, such as IBS. BRS measurements were performed as described previously[44].

Trauma

A history of trauma involving the abdomen was assessed by asking patients whether they ever experienced 1) sexual abuse, 2) physical violence or abuse involving the abdomen, and/or 3) abdominal illness, e.g. acute gastroenteritis, appendicitis etc. Scores ranged from 0 (no trauma, answer is 'no' to all questions) to 3 (answer is 'yes' to all questions).

Vigilance

We used the Somatosensory Amplification Scale (SAS)[45,46] to determine the extent to which an individual is likely to report enhanced perception of physical symptoms (i.e. lower cognitive perception thresholds). This scale comprises 10 items, with each item being scored on a 0 ('this statement does not apply to me') to 4 ('this statement is fully applicable to me') scale, yielding a total score range from 0 (best score) to 40 (worst score).

Dysfunctional cognitions

The recently developed 31-item Cognitive Scale for Functional Bowel Disorders (CS-FBD) was used to measure patients' levels of dysfunctional cognitions concerning their IBS[47]. Scores for individual items range from 1 (I completely agree) to 7 (I completely disagree), which yields a total score ranging from 31 (best) to 217 (worst).

Illness behavior

Illness behavior was assessed using the 6-item illness behavior subscale of the Illness Attitude Scale (IAS) [45,48]. Scores for individual items range from 0 ('not at all') to 4 ('very much'). The total score was divided by the number of items, yielding an illness behavior subscale score ranging from 0 (best score) to 4 (worst score).

RESULTS

Subjects

We screened 130 patients of whom 26 did not meet Rome II criteria[1], so that 104 patients were included in the analysis. Mean age was 42.0 ± 13.9 years. Seventy-four patients (71%) were female. Thirty-three patients (32%) were recruited through the outpatient department and 71 patients (68%) were recruited through advertisement in a local newspaper.

Preliminary analyses

Descriptive statistics and normality

Means, standard deviations, skewness and kurtosis values for each quantitative variable are displayed in Table 1. We used standard errors of $\sqrt{(6/N)}$ and $\sqrt{(24/N)}$ to evaluate the skewness and kurtosis values, respectively. Two variables showed both a significant positive skewness and kurtosis value: BRS, and vigilance ($z > |3.29|$; $p < .001$). Visceral pain showed a significant positive skewness value ($z = 3.97$; $p < .001$).

Missing data

Table 1 shows the number of patients (n) per variable. Only BRS had a high number of missing values (20, being 19.2%). Little's test of missing completely at random (MCAR) revealed that this assumption was not rejected ($\chi^2 = 77.395$, DF = 72, $p = .311$). Missing values were imputed before the path model analysis using an Expectation Maximization approach (see the Computational Note). Because of the existence of non-normally distributed variables, the corrections of Satorra and Bentler (1988) to the test statistics of the path model were computed (see the Computational Note).

Outliers

We examined model based outliers using linear regression analyses for each of the regression equations derived from the path model (see Fig 1). For each subject in each regression equation, we inspected Cook's distance, a measure of the change in regression coefficients produced by leaving out that subject. No outliers (i.e., a Cook's distance > 1) were detected. The normalized estimate of the multivariate kurtosis was 1.52, indicating no multivariate outliers were present.

Table 1. Descriptive statistics of the quantitative model variables in 104 IBS patients

Variable	n	Mean	SD	Skewness	Kurtosis
Trauma (0-3)	103	0.64	0.67	0.76	0.30
BRS	84	7.93	5.42	1.64	4.35
Visceral pain (0-10)	101	2.50	2.67	0.97	-0.31
Vigilance (0-40)	103	9.68	5.75	1.48	3.87
Cognitions (31-217)	101	110.57	35.56	0.36	-0.28
Illness behavior (0-4)	103	1.88	0.63	0.25	-0.22
IBS symptoms (0-20)	98	4.43	2.52	0.69	0.73
Age	104	41.67	13.83	0.01	-1.05

Score range for each variable is denoted between parentheses when applicable.

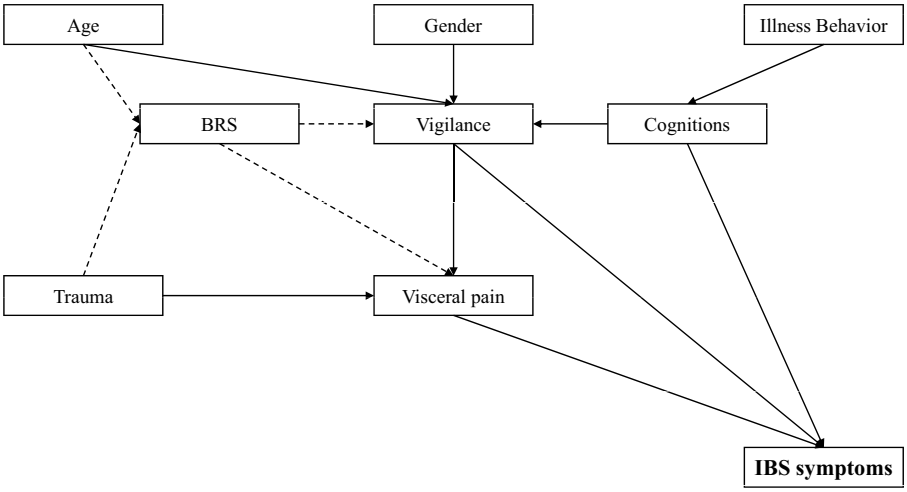

Figure 1. The biobehavioral testmodel of IBS adapted by Naliboff et al. Dashed arrows indicate a negative coefficient. Note the sequential links between a) trauma, visceral pain, and IBS (visceral component); b) trauma, BRS, vigilance, visceral pain, and IBS (central nervous system component); c) illness behavior, cognitions, and IBS (cognitive-behavioral component). The model contains four exogenous variables (i.e., trauma, age, gender and illness behavior).

Model tests

Figure 1 shows the biobehavioral model of IBS that was tested. A dashed arrow is displayed if a negative coefficient was expected for that path. Important features of the model are the sequential links between a) trauma, visceral pain, and IBS (comparable to the 'visceral' component in Naliboff's model); b) trauma, BRS, vigilance, visceral pain, and IBS (the 'central nervous system' component in Naliboff's model); c) illness behavior, cognitions, and IBS (the 'cognitive-behavioral' component in Naliboff's model). The model contains four exogenous variables (i.e., trauma, age, gender and illness behavior), which were assumed to be uncorrelated. The *p*-value of the Satorra-Bentler scaled chi-square was .019 (χ^2 = 39.22; *df* = 23), indicating poor model fit. The robust estimates of the non-normed fit index (NNFI) and comparative fit index (CFI) were .752 and .842, respectively, also indicating a poor fit.

The standardized residual matrix revealed that the ill fit was caused by the omission of two paths, one between illness behavior and IBS symptoms, and one between trauma and IBS symptoms (the corresponding residuals were .274 and .258). The model was revised accordingly. The revised model yielded good fit, indicated by the robust estimates of the test-statistics (Satorra-Bentler χ^2 = 24.40, *df* = 21, *p* = .274; robust NNFI = .943; robust CFI = .967; robust RMSEA = .040). The model explained 18.9% of the variance in IBS symptoms. The path coefficients of this model were examined and those being not statistically significant were deleted in a special way. To control the False Discovery Rate (FDR) in the case of multiple testing, we used a procedure described by Benjamini and Hochberg. Because we hypothesized

a priori the sign of the path coefficients, we computed for each path coefficient a one-sided *p*-value, using the robust estimates of the standard errors. In line with Lackner et al.[24], a family of tests was defined as the path coefficients leading from the exogenous variables to a given endogenous variable. The within-family error rates were controlled using the FDR method. The trimmed model was re-fit and the test statistics yielded a comparable fit as the non-trimmed model (Satorra-Bentler χ^2 = 30.76, *df* = 27, *p* = .28; robust NNFI = .951; robust CFI = .963; robust RMSEA = .037). The standardized path coefficients of this trimmed model are shown in Figure 2. Three of the values of the path coefficients differed a value of .01 with those of the non-trimmed model, the remaining path coefficients were equal. The values of the standardized error variances are displayed in the circles. The trimmed model explained 16.2% of the variance of IBS symptoms.

Ancillary analyses

The biobehavioral model proposed by Naliboff et al. suggests that the effect of illness behavior on IBS symptoms is possibly mediated by environmental response and health beliefs (operationalized as "cognitions" in the present study). The model tests of Figure 1 revealed that a direct path was needed from illness behavior to IBS symptoms. By adding this path to the model, the coefficient of the path from cognitions to IBS symptoms was no longer significant (see Figure 2). This result lead

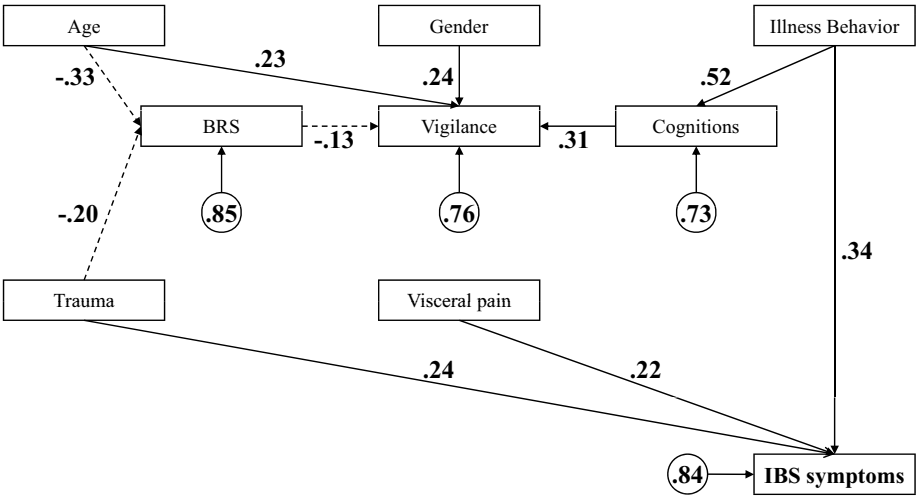

Figure 2. Trimmed model showing the standardized path coefficients after deleting non-significant paths and addition of a path between illness behavior and IBS symptoms and a path between trauma and IBS symptoms. This was necessary due to ill model fit in the initial analysis, in which these paths were omitted. The values of the standardized error variances are displayed in the circles. The trimmed model explains 16.2% of the variance of IBS symptoms.

us to formulate the following alternative hypothesis: the effect of cognitions on IBS symptoms is *mediated* by illness behavior.

We tested if illness behavior met the conditions to be considered as a mediator by means of four linear regression analyses (also see the Computational Note). Cognitions were significantly associated with both illness behavior and IBS symptoms (two-tailed $p < .05$). Illness behavior was significantly associated with IBS symptoms. The effect of cognitions on IBS symptoms was no longer significant (two-tailed $p = .82$) when the effect of illness behavior on IBS symptoms was controlled. The corresponding standardized regression coefficient decreased from .21 to .03 when illness behavior was added to the regression analysis. These findings support the hypothesis that illness behavior mediates the effect of cognition on IBS symptoms completely.

Investigation of the standardized residuals of the trimmed model (Fig 2) revealed a relatively large residual (0.21) between trauma and illness behavior. This result indicated that the model could be improved by adding an additional path from trauma to illness behavior. The addition of this path gave us the possibility to investigate whether the effect of trauma on IBS symptoms was also mediated by illness behavior. We tested this hypothesis by a series of linear regression analyses as mentioned above (also see the Computational Note). Trauma was significantly associated with both illness behavior and IBS symptoms (two-tailed $p < .05$). The effect of trauma on IBS symptoms was no longer significant ($p = .06$) when the effect of illness behavior on IBS symptoms was controlled. The corresponding standardized regression coefficient decreased from .24 to .18 when illness behavior was added to the regression analysis. These findings support the hypothesis that illness behavior mediates partly the effect of trauma on IBS symptoms.

On the basis of the results, we formulated an alternative model to Figure 1. We added three paths, one from trauma to illness behavior, one from trauma to IBS symptoms and one from illness behavior to IBS symptoms. Furthermore, we reversed the direction of the path from cognition to illness behavior. The fit of this model was significantly better than the fit of the non-trimmed model of Figure 2 (Satorra-Bentler $\chi^2 = 20.42$, $df = 20$, $p = .43$; robust NNFI = .993; robust CFI = .996; robust RMSEA = .014). We used the within-family FDR-procedure to remove non-significant path coefficients from this model. The fit of the trimmed model, displayed in Figure 3, was also good (Satorra-Bentler $\chi^2 = 26.93$, $df = 26$, $p = .41$; robust NNFI = .987; robust CFI = .991; robust RMSEA = .019). The model explained 16.0% of the variance in IBS symptoms.

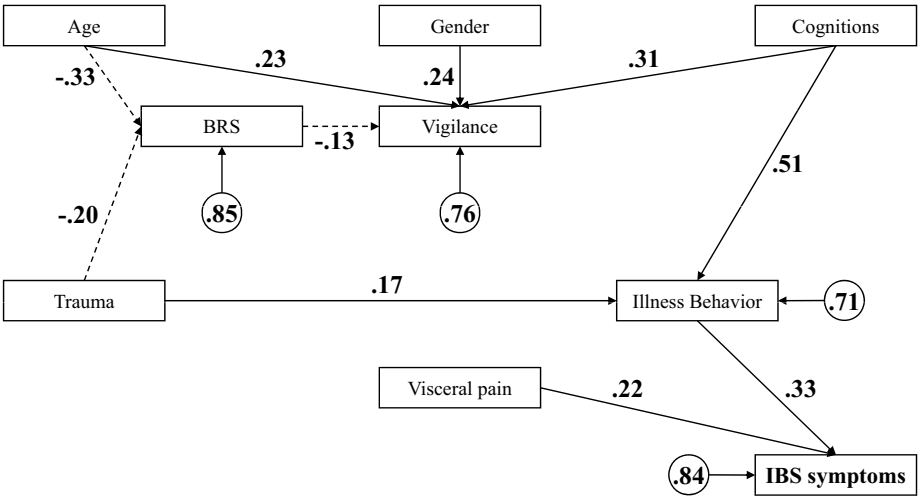

Figure 3. Alternative model to Figure 1 after paths were added between trauma and illness behavior, trauma and IBS symptoms and illness behavior and IBS symptoms and non-significant paths were deleted. Reversal of the path direction from cognitions to illness behavior yielded a significantly better fit than the fit of the non-trimmed model of Figure 2.

DISCUSSION

The biobehavioral model proposed by Naliboff et al. was one of the first attempts to improve our understanding of the pathophysiology and clinical expression of irritable bowel syndrome (IBS). In the present study, this model was operationalized to be able to determine the effect of 1) Autonomic Nerve System (ANS) function, 2) local (visceral) factors, and 3) cognitive-behavioral aspects on IBS symptom severity, as well as the interaction between these domains. Our data do not support the operationalized version of the biobehavioral model presented in Figure 1. In particular, we found no association between ANS functioning (represented by baroreceptor reflex sensitivity) and IBS symptom severity. While the working model indicates that autonomic dysfunction modulates IBS symptoms by increasing visceral sensitivity and/or inducing hypervigilance, these path coefficients were not significant. This leads to rejection of hypotheses 1 and 2 (see Introduction), and raises the question whether ANS-stress responses are involved in symptom generation. However, a growing body of literature highlights ANS alterations in IBS patients[10,11,16,17,49], with most studies suggesting sympathetic predominance or reduced parasympathetic activity. It is likely that altered autonomic functioning is involved in the pathophysiology of IBS, but this probably takes place through different mechanisms than those proposed in the model, for example by modifying intestinal motility[50]. Our finding that ANS functioning was significantly correlated to (hyper)vigilance without affecting IBS symptom severity is supported by a recent study showing that repeated

exposure to aversive visceral stimuli in IBS patients leads to habituation of visceral perception, while central processing of anticipation of visceral pain (i.e., vigilance) remains activated[51].

The relationship between visceral pain during rectal balloon distension and IBS symptoms has been established in the last decades and was confirmed by our model. Hypothesis 6 can thus be accepted. The model also predicts that visceral pain or hypersensitivity would be defined by a history of 'abdominal trauma' (sexual or physical abuse, inflammatory processes), autonomic dysfunction, and vigilance. Yet, none of these path coefficients were significant, thereby rejecting hypotheses 1, 2 and 3. One explanation may be that the level of visceral sensitivity is determined by other factors that are currently unknown, or were not the subject of investigation. A possible candidate is the presence of psychiatric comorbidity, for example depression[52]. Alternatively, it is possible that 1) other measures for assessment of abdominal trauma, ANS function and vigilance, are required, or 2) these domains interact in a different way than proposed in the model.

The working model suggests that illness behavior influences cognitions, which in turn modulate symptom severity. This association was indeed present, but not in the form we anticipated. A better model fit was achieved when the proposed correlation between illness behavior and cognitions was inversed and an additional path from illness behavior to IBS symptoms was added. The alternative model proposes illness behavior as a mediator between cognitions and IBS symptoms and omits the direct relationship between cognitions and symptoms that was initially assumed. This suggests that dysfunctional cognitions on IBS do not affect symptom severity by themselves but are modulated by a patient's approach to his or her symptoms (illness behavior). These findings lead to rejection of hypotheses 4 and 5. Moreover, these results present cognitions as an autonomic or exogenous variable in the model, rather than illness behavior. The final model suggests that more dysfunctional cognitions lead to altered illness behavior and, subsequently, to increased symptom severity. The hypothesized effect of illness behavior on IBS symptoms is thereby confirmed, although the model by Naliboff postulates an indirect association involving environmental response, health beliefs and vigilance.

An interesting finding of this study is that a history of 'abdominal trauma' leads to increased IBS symptoms, but in a different way than we expected. Whereas the working model predicts that a history of abdominal trauma aggravates IBS symptoms by increasing visceral pain perception, the alternative model shows that the effect of trauma on IBS symptoms is mediated by illness behavior. The effect of sexual and/or physical abuse on illness behavior has long been established[53], but the relationship with abdominal illness such as acute gastroenteritis (another form of 'trauma') is less clear. Moreover, it has been shown that long-lasting gut dysmotility and vis-

ceral hyperalgesia develop in mice after transient colonic inflammation[54], suggesting a relationship between abdominal illness (i.e., colonic inflammation) and visceral hypersensitivity. Our sample-size was too small to perform subgroup analyses in patients with post-inflammatory IBS and in those with a history of abuse. However, the relationship between any kind of abdominal trauma and symptom severity in IBS is interesting and deserves further investigation.

Age and gender were expected to affect IBS symptomatology through vigilance (higher in older female patients)[39] and ANS function (impaired in the elderly)[38]. Although the associations with ANS function and vigilance were all significant, age and gender were not related to IBS symptom severity via these paths since no significant path coefficients were found from BRS to IBS symptoms and from vigilance to IBS symptoms. Several mechanisms have been proposed regarding the female predominance in IBS patients, including gender differences in visceral sensitivity, CNS pain processing, gastrointestinal transit time, and specific effects of estrogen and progesterone on gut function[25]. The link with the observed sex differences yet remains to be clarified. Decreased prevalence of functional bowel disorders in older patients has been suggested but, again, very little research addressed this topic and the effect of age on IBS remains largely unknown.

A possible limitation of our study is the adjustment we made to the cognitive-behavioral section in the biobehavioral model proposed by Naliboff and colleagues. The original model suggests that IBS symptoms successively modify illness behavior, environmental responses, health beliefs, vigilance, and visceral motor and sensory function, eventually leading back to IBS symptoms. The model also predicts a direct effect of IBS symptoms on health beliefs and vice versa. As explained in the Introduction, we were coerced to perform a path analysis rather than a structural equation model analysis (including latent variables) due to the ratio between the number of observed variables and the number of patients. In addition, our data were from a cross-sectional design, not a longitudinal design. By eliminating the abovementioned feedback loop, we simplified the model to be able to test its validity, but at the same time denied some of the interactions that may be important in the pathophysiology of IBS. Larger patient samples and a longitudinal design are required to overcome this limitation. Another possible limitation is that 'arousal' and 'environmental responses' were not incorporated in the working model. These were omitted because no accurate measures were available to quantify these domains. Finally, visceromotor activity and viscerosensory activity were operationalized as 'visceral pain' because verification of the proposed interaction would require a much larger sample size and more complex statistical calculations that would exceed the aim of this study.

In conclusion, the biobehavioral model that was proposed by Naliboff and colleagues to improve our understanding of the pathophysiology of irritable bowel syndrome could not be validated in the present study. Although the association between visceral hypersensitivity and IBS symptom severity was undoubtedly present, a relationship between ANS function and IBS symptoms could not be confirmed. Cognitive-behavioral aspects are important in the clinical expression of IBS, with illness behavior playing an intermediate or modulating and not an autonomic role. Internal and/or external stimuli seem to affect IBS symptoms by modulating illness behavior rather than ANS function or visceral sensitivity. Future longitudinal studies in larger patient samples are required to further investigate the mechanisms involved in the pathophysiology of IBS.

Computational Note

The descriptive analyses and linear regression analyses were performed with SPSS, version 11.5. The missing imputation and the path model analyses were performed with EQS, version 6.1. For each path analysis, we used the option METHOD=ML, ROBUST.

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