Observational study

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Cognitive behavioral therapy for irritable bowel syndrome: the effects on state and trait anxiety and the autonomic nervous system during induced rectal distensions – An uncontrolled trial

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Abstract

Background and aims: Irritable bowel syndrome (IBS), is a common multifactorial gastrointestinal disorder linked to disturbances in the microbe gut-brain axis. Cognitive behavioral therapy (CBT), in face-to-face format has showed promising results on IBS and its associated psychological symptoms. The present study explored for the first time if CBT for IBS affects the autonomic nervous system (ANS) during experimentally induced visceral pain and cognitive stress, respectively. The levels of state and trait anxiety, current and perceived stress were also evaluated.

Methods: In this uncontrolled trial, individual CBT was performed in face-to-face format for 12 weeks in 18 subjects with IBS. Heart rate variability and skin conductance were measured during experimentally induced visceral pain and during a cognitive task (Stroop color-word test), before and after intervention. The levels of state and trait anxiety as well as self-rated current and perceived stress were also measured before and after the intervention.

Results: CBT did not affect ANS activity during experimentally induced visceral pain and cognitive stress. The sympathetic activity was high, typical for IBS and triggered during both visceral pain and cognitive stress. The levels of state and trait anxiety significantly decreased after the intervention. No significant changes in self-rated current or perceived stress were found.

Conclusions: Results suggest that face-to-face CBT for IBS improved anxiety- a key psychological mechanism for the IBS pathophysiology, rather than the autonomic stress response to experimentally induced visceral pain and cognitive stress, respectively.

Implications: This study indicates that IBS patients present high levels of stress and difficulties coping with anxiety and ANS activity during visceral pain and a cognitive stress test, respectively. These manifestations of IBS are however not targeted by CBT, and do not seem to be central for the study participants IBS symptoms according to the current and our previous study. Face-to-face CBT for IBS, it does not seem to affect modulation of ANS activity in response to induced visceral pain or cognitive stress. Instead, face-to-face CBT decreased levels of state and trait anxiety. Implications for further studies include that anxiety seems to be important in the IBS pathophysiology, and needs further scientific attention. This is in line with the fear-avoidance model which suggests that anxious responses to pain and discomfort drive hypervigilance to, and (behavioral) avoidance of, symptom provoking stimuli and vice versa. Catastrophic cognitions, hypervigilance and avoidant behavioral responses are proposed to produce vicious circles that withhold and exacerbate pain-related symptoms and disability, and lead to lower quality of life. Larger scale studies of potential autonomic changes are needed in order to elucidate which mechanisms elicit its effects in face-to-face CBT for IBS, and provide new avenues in understanding the pathophysiology of IBS.

Keywords: irritable bowel syndrome; cognitive behavioral therapy; state anxiety; trait anxiety; stress; autonomic nervous system; visceral hypersensitivity.

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1 Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic abdominal symptoms, such as pain, discomfort, and altered bowel habits. In Europe and North-America IBS has a prevalence of 10–15% [1]. Its pathophysiology is not fully understood, but a multicomponent conceptual model involving physiological, affective, cognitive and behavioral factors has been postulated [2]. The "Microbe-Gut-Brain Axis" (MGB-axis) is the theoretical model describing the bidirectional interaction between cognitive and emotional centers in the brain, neuroendocrine centers, metabolic organs, the enteric nervous system, the immune system, intestinal mucosa and the intestinal luminal contents. Aberrations in the regulation and interactions of this axis play a central role in IBS [3]. Examples of this in IBS are altered peripheral regulation of GI function (including sensory and secretory mechanisms), altered brain-gut signaling (including visceral hypersensitivity) as well as psychological distress [4].

Abdominal pain and visceral hypersensitivity are core symptoms of IBS. It has been reported that induced abdominal pain in IBS patients (using balloon inflation according to the barostat method), is associated with higher sympathetic responsiveness and lower parasympathetic activity, respectively, compared to controls without IBS. Furthermore, when IBS-like central processing of pain was induced in healthy subjects (rectal stimulation after acute tryptophan depletion) this resulted in altered hormonal responses and decreased negative amygdaloid feed-back to anterior cingulate cortex, hypervigilance as well as amplified pain scores [5–7].

The autonomic nervous system (ANS) has been suggested to play a key role in IBS since it provides a physiologic connection between the gut and the brain, within the MGB-axis concept. Studies in IBS report ANS dysregulation, abnormal physiological response patterns during stress- and painful IBS-like conditions including greater sympathetic responsiveness, lower parasympathetic activity, altered heart rate variability (HRV) and excessive electrodermal activity (EDA) in terms of skin conductance (SC) [8–10]. Recently, it has been demonstrated that increased ability to cope with IBS symptoms and associated stress, as a result of cognitive behavioral therapy (CBT), improves gastrointestinal and psychological symptoms in IBS [11].

CBT for IBS emphasizes cognitive, emotional and behavioral strategies to better cope with physiological and psychological stressors. Previous studies report on the effectiveness of CBT for IBS and the role of stress as a key mechanism in IBS pathophysiologys [12–18]. CBT, delivered over the internet, showed promising results regarding gastrointestinal and psychological symptoms associated with IBS as well as quality of life [12–18]. The first study of CBT for IBS in a face-to-face format [11] reported improved gastrointestinal and psychological function, as well as improved quality of life in the majority of subjects. A systematic review and meta-analysis of trials in which face-to-face CBT was directly compared to guided internet CBT reported that equivalent overall effects were produced by these modalities [19]. However, there are still few studies published regarding face-to-face versus internet delivered CBT and specific psychiatric and somatic conditions, including IBS. Previous data suggest that the components of the therapy, i.e. exposure exercises specifically tailored for IBS, affects the outcome of the therapy more than the type of modality, expectancy of improvement, therapeutic alliance or attention [15, 17].

The present study explored for the first time whether face-to-face CBT in IBS altered ANS activity in terms of HRV and SC during experimentally induced visceral pain and cognitive stress, respectively. The levels of state and trait anxiety and perceived stress were also evaluated by means of questionnaires. The research questions were:

1. Does CBT alter ANS activity in terms of HRV and SC during experimentally induced visceral pain in subjects with IBS?
2. Does CBT alter ANS activity in terms of HRV and SC during cognitive stress in IBS or not?
3. Does CBT alter self-rated state and trait anxiety and/or perceived stress in subjects with IBS?

2 Methods

2.1 Design

The study included 18 subjects with IBS whose ANS activity was assessed before and after the CBT intervention during experimentally induced visceral pain and cognitive stress, respectively. Self-ratings of state and trait anxiety, current stress and perceived stress were also assessed before and after CBT. ANS activity was assessed 4 weeks before the CBT intervention (t1, $n=13$) and/or directly before (t2, $n=18$) and after the intervention (t3, $n=18$). Dependent variables were HRV (sympathetic, vagal and sympathetic/vagal response) and SC (mean and standard deviation of the SC responses as well as the skin conductance level). For an overview of the study design, see Fig. 1.

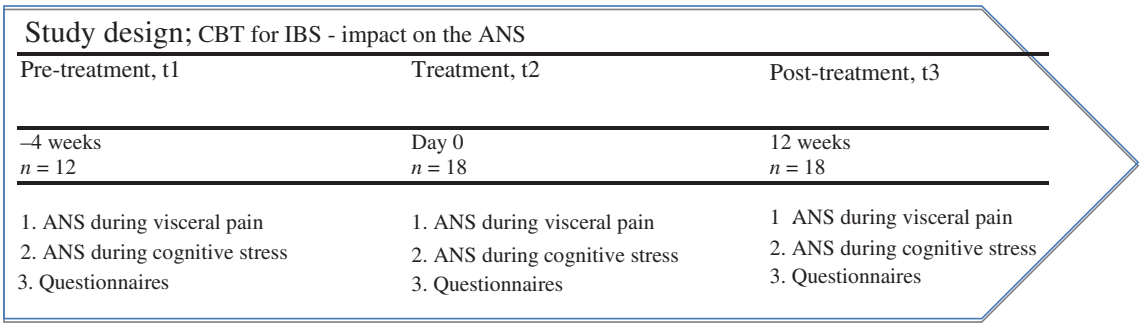

Fig. 1: Overview of the study design regarding cognitive behavioral therapy (CBT) in 18 subjects with irritable bowel syndrome (IBS) and the impact on the autonomic nervous system (ANS) activity during experimentally induced visceral pain and cognitive stress, respectively. CBT was performed for 12 weeks and questionnaire data were collected on three occasions, 4 weeks before CBT (–4 weeks), just before CBT (day 0) and after CBT (12 weeks). ANS activity was assessed during two conditions: (1) during induction of visceral pain with a barostat protocol (ANS during visceral pain), and (2) during a cognitive stress test (stroop color-word interference test and the affective memory test) (ANS during cognitive stress).

2.2 Subjects

Eighteen subjects (14 females and four men) completed the study with a mean age of 35 years (SD = 13.31; range = 17–56) suffering from IBS symptoms for 1–5 ($n = 6$) or more than five ($n = 12$) years prior inclusion and having been diagnosed with constipation ($n = 5$), diarrhea ($n = 9$), unsubtyped ($n = 3$) or mixed ($n = 1$) type IBS at a gastroenterological clinic according to ROME III criterias [20]. All subjects were eligible for an IBS diagnosis according to ROME-III self-ratings at the time of inclusion, none had other gastroenterological or psychiatric disorders, but chronic medical disorders included polycystic ovary syndrome ($n = 1$) and asthma ($n = 1$). Current medications for IBS included imodium, inolaxol and/or dimor ($n = 7$) and alternative treatments included probiotics anytime of life ($n = 9$) and/or probiotics regularly ($n = 6$). Social status was either married ($n = 3$), shared household ($n = 6$) or single-household ($n = 9$). Ten participants had completed high school only and the rest had graduated from college. Three persons were on sick-leave because of IBS.

Criteria for participation included (1) fulfilling Rome III diagnostic criteria for IBS and pain/discomfort frequency at least 2 days a week in the last 12 weeks, (2) VAS score of global assessment of abdominal pain and discomfort equals to or >35 mm, (3) age between 18–65 years, (4) signed informed consent. Criteria for exclusion were (1) concurrent or recent treatment with drugs affecting intestinal function or mood, e.g. antidepressants, (2) concurrent or recent (<2 weeks) use of nutritional supplements or herb products affecting intestinal function or mood (e.g. aloe vera, St. John's Wort), (3) depression or suicide tendencies according to Montgomery Åsberg Depression Rating Scale-Short (MADRS-S) screen [21] and/or clinical judgment, (4) abuse of alcohol or drugs according to alcohol use disorder identification test-screen [22] and/or clinical judgment, (5) ongoing titration of psychopharmacological treatment.

2.3 The CBT intervention

After a baseline period of 4 weeks, participants were introduced to their CBT-therapist and the intervention was performed individually with 12 weekly 1-h sessions. Twelve participants performed a 4 weeks baseline and six participants started treatment directly within a week from the first assessment. During the whole study period, participants filled out weekly ratings about their gastrointestinal and psychological health using the online dedicated web portal. Participants also filled out paper- and pencil diaries consisting of five questions about their gut health using a five-point response scale [11].

Six clinical psychologists and two last-term psychology students at the Center for Health and Medical Psychology, CHAMP, at Örebro University, familiar with conducting CBT, were trained to conduct the CBT intervention. Supervision was provided by psychologists (co-authors) Author C and Author E who have considerable experience with CBT. The intervention was based on techniques and a manual developed and tested previously [14–16]. The main modules of the manual consisted of exposure mindfulness components. The total treatment entailed 12 sessions of therapy provided on an individual basis and guided by the manual. Thirteen participants participated in one session per week and the remaining five participants participated in the same therapy distributed

over 6 weeks because of time constraints. All participants completed all sessions.

2.4 Visceral pain induction

To reduce the influence of a dispose tissue mass and abdominal wall tone during the barostat assessment, subjects fasted 12 h prior assessment and was placed in the left lateral decubitus position, the rectal probe was luminated and placed 10–15 cm into the rectum. Rectal distensions were applied by a barostat (Electronic barostat, distender series II; G & J Electronic Inc., Toronto, Ontario, Canada) according to our previous study [5]. The barostat protocol consists of intermittent semi-random staircase distensions of 60 s duration (15, 10, 25, 20 mmHg, etc) separated by an interval of 30 s of baseline pressure. The end point to stop the series of distensions is the perceptual threshold for maximal tolerable pain, discomfort and/or urge or if the safety value of the maximal volume of 600 mL is exceeded. During each distension (after 13 s of distensions) subjects are asked to report their perception of pain, discomfort and urge, respectively using 100 mm VAS-scales (no pain/urge/discomfort – maximal tolerable pain/urge/discomfort). Rectal volumes are measured at the end of each distension (after 60 s of distension). Volume is corrected for air compressibility. Rectal compliance ($\wedge\vee/\wedge$P; P = 10–45 mmHg) is estimated for each subject. The barostat protocol have previously been approved by the Ethical board, EPN (www.epn.se, Drn 2010-261, 2010-08-11, Dnr 2010-282, 2010-08-25) and described in detail [23].

2.5 Measurement of autonomic nervous system activity

Autonomic measures were taken during the whole 30–40 min of the barostat program, during the last 8 min of high intensity visceral pain and during the measurement of stress (see below). The segments were compared with regard to before and after the CBT intervention. Electrodes for ECG was placed in a bipolar precordial lead and electrodes for SC was placed on the first and second finger of the left hand and continuously sampled at 500 Hz using the Biopac system and software (BioPac Inc., Santa Barbara, CA, USA). ECG and SC signals were recorded at a sample rate of 1000 Hz using a Biopac MP150 system and a Biopac module (GSR100C) and transducer (TSD203, BioPac INC., Santa Barbara, CA, USA) with electrodes placed in a bipolar precordial lead. A custom designed peak detection algorithm was used to determine the interbeat intervals of assessment of both average HR and as raw data for the analysis of HRV. SC was recorded from the first and second fingers of the left hand using a constant current method and averaged over the entire period. HRV measures included spectral analysis measures of the vagal response, sympathetic response and the ratio of the high to low frequency peak power using the modified Pan-Tompkins algorithm of real time QRS complex detection in Acqknowledge 4.3.1 [24]. The analyses were done for the data generated from the total barostat program, for the data from the last 8 min of the barostat program with the highest level of visceral pain, as well as on 8 min segments from the ECG and SC recordings made during cognitive stress and self-ratings. After visual inspection of the recordings and editing to exclude artifacts in Acknowledge 4.3.1 (BioPac INC., Santa Barbara, CA, USA), the recordings were analyzed in Excel 14.3.4 to estimate R-R intervals, HF and LF powers by analyzing the ECG segments in the time and frequency domains. The ratio of LF/HF powers were also calculated. SC amplitude was analyzed in Acknowledge 4.3.1 using the procedure by Dawson et al. [25].

3 Induction and measurement of stress

3.1 Stroop color-word interference task

A computerized version (Inquisit 4.1.1, Millisecond) of the classical Stroop color-word interference task ([26]; for a review, see [27]) was employed as a cognitive stressor. Color words (red, green, blue or black; in English) were presented one after the other on a computer screen, with an interstimulus interval of 200 ms. Participants were asked to indicate for each word its print color (red, green, blue or black, respectively) by pressing the corresponding response key on a qwerty keyboard (D, F, J or K, respectively). The color word was either printed in the congruent color (e.g. the word “red” printed in red; 28 trials), or in an incongruent color (e.g. the word “red” printed in green, blue or black; 28 trials). In addition to these critical word trials, 28 neutral trials were included during which a color patch instead or a word was presented. The task consisted of a single block of eight trials that were randomly intermixed.

3.1.1 State-trait anxiety inventory for adults (STAI)

This 40-item two-scale instrument ([28], Swedish version available from Jan Bergdahl, institution of psychology,

Umeå University) was used to evaluate the level of anxious feelings in terms of state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening). The Y form, which is the most common, was used and consist of 20 items for state anxiety and 20 items for trait anxiety, all scored on a 4-point likert-scale ranging from 1 = almost never to 4 = almost always. The psychometric properties include Cronbachs' alpha of >0.89, test-retest reliability of 0.88 [29] as well as acceptable concordant and discriminative validity [30].

3.1.2 Perceived stress scale (PSS)

This scale [31] was used as a measure of the degree to which situations in one's life are appraised as stressful, i.e. perceived stress. Items are designed to tap how unpredictable, uncontrollable and overloaded the respondents find their lives. The scale also includes a number of items about current levels of experienced stress.

3.1.3 Stress symptom rating questionnaire (SSRQ)

This scale consists of 12 visual analog rating scales anchored by mood-related adjective pairs [32]. The subjects place a mark along a 100 mm line connecting two antonyms of a pair to indicate how they are currently feeling. The 12 scales are grouped into six subscales including arousal (lively/unmotivated and awake/drowsy), stress (tense/relaxed and stressed/at ease), anxiety (nervous/calm and jittery/tranquil), anger (irritable/agreeable and annoyed/patient), fatigue (tired/energetic and focused/forceful), and attention (focused/distracted and attentive/scattered). Four of the scales are reversed and the outcome is mm of each subscale as well as the mean total score in mm.

3.1.4 The affective memory test

This test [33] included 30 highly emotionally loaded words unrelated to IBS (12 positive, 12 negative and six neutral; In Swedish) that were presented inter-randomly on a computer screen using the Microsoft Powerpoint software (version 14.3.4). After the presentation session, the subject was asked to recall as many words as possible in no particular order, i.e. immediate recall. After 30 min, the subject was instructed to recall as many words as possible from the trial, i.e. delayed recall. The free recalls were recorded with a smartphone and summarized. A previous study indicates that subjects with IBS have decreased total immediate memory recall scores compared to controls [6].

3.2 Statistical analyses

The main comparison made is between t2 and t3 (before and after CBT; $n = 18$), with paired samples *t*-tests for all dependent variables separately and skewed data (according to the Shapiro-Wilk test of normality) was analyzed with the non-parametric Wilcoxon signed rank test. Because several *t*-tests were made, significance levels were adjusted with a Bonferroni correction. Effect sizes are reported in terms of Cohen's *d* for paired comparisons.

In case of a significant difference between t1 and t2 (4 weeks before and directly before CBT; $n = 12$) for a certain dependent variable, as assessed with paired samples *t*-tests, the difference between t2 and t3 for that dependent variable was examined with an ANCOVA ($n = 12$), controlling for the (centered) difference between t1 and t2.

3.3 Ethics

The study was approved by the ethical board, EPN, in Uppsala (www.epn.se, Drn 2013/275) and conducted according to good clinical practice and the ethics of the Helsinki Declaration [34]. Informed consent was obtained from all participants included in the study.

4 Results

4.1 Sample characteristics

Two of the original 20 subjects included in the study terminated their participation because of personal reasons and because of a lack of motivation for performing the exposure therapy, respectively. This left a total of 12 participants at t1, and 18 participants at t2 and t3 for the analyses. Three subjects were deleted from ANS analysis because of technical obstacles during the barostat assessment and because of not being able to guarantee the induction of visceral pain.

Research question 1: Does CBT improve ANSs activity in terms of higher levels of HRV and lower levels of SC as measured during in subjects with IBS or not?

4.2 Heart rate variability and skin conductance during the barostat assessment

The last 8 min of the barostat program with highest pain was used to compare the parameters of HRV and SC before and after CBT (t2, t3) and the baseline measurements, respectively (t1, t2). None of the comparisons were significant and there were no trends. For descriptive data see Table 1. For statistical data see Table 2.

Research question 2: Does CBT improve ANS activity in terms of increased HRV and decreased SC during cognitive stress in IBS or not?

4.3 Heart rate variability and skin conductance during cognitive stress

Parameters of HRV and SC were assessed during cognitive stress including the stroop color-word interference test and the affective memory test and compared in terms of before and after CBT (t2, t3) and in terms of the baseline measurements, respectively (t1, t2). None of the comparisons were significant and there were no trends. For descriptive data see Table 3. For statistical data see Table 4.

Table 1: Descriptive data for dependent variables collected during experimentally induced visceral pain 4 weeks before (–4 weeks), just before (day 0) and after CBT (12 weeks).

	M	Mdn	SD	95% CI	*n*
–4 weeks					
HRV	1.75	1.36	1.18	0.76, 2.74	8
Vagal	0.41	0.43	0.15	0.28, 0.54	8
Symp	0.59	0.57	0.15	0.46, 0.72	8
SCL	4.10	7.88	1.45	4.75, 12.67	8
SCR-M	0.15	0.13	0.09	0.05, 0.24	8
SCR-SD	0.07	0.07	0.05	0.01, 0.13	10
Day 0					
HRV	1.51	1.12	1.30	0.43, 2.60	14
Vagal	0.48	0.47	0.20	0.32, 0.65	15
Symp	0.52	0.53	0.20	0.35, 0.68	15
SCL	9.87	5.77	3.0	5.77, 10.42	15
SCR-M	0.27	0.23	0.21	0.13, 0.40	12
SCR-SD	0.12	0.10	0.13	0.04, 0.20	12
Week 12					
HRV	1.57	0.80	1.90	–0.02, 3.16	15
Vagal	0.51	0.56	0.21	0.34, 0.68	15
Symp	0.49	0.44	0.21	0.32, 0.66	15
SCL	7.6	5.32	4.87	5.14, 11.17	15
SCR-M	0.27	0.14	0.33	0.06, 0.49	12
SCR-SD	0.09	0.06	0.12	0.01, 0.17	12

Means (*M*), medians (Mdn), standard deviations (SD) and 95% confidence intervals (CI) for dependent variables. HRV = heart rate variability; vagal = vagal response; symp = sympathetic response; SCL = skin conductance level; SCR-M = skin conductance mean; SCR-SD = standard deviation, respectively (SCR-SD). The variables were collected during induction of visceral pain (ANS during visceral pain).

Research question 3: Does CBT improve self-rated state and trait anxiety, current stress and/or perceived stress in subjects with IBS or not?

The stress symptom rating questionnaire (SSRQ) was not significantly lower after CBT [$t(17) = -1.547$, $p = 0.140$, 95% CI [57.96, 71.40], Cohen's $d = 0.30$]. The two baseline measures for SSRQ (t1 and t2) did not differ significantly [$t(12) = 1.544$, $p = 0.149$, 95% CI [–1.50, 8.81], Cohen's $d = 0.31$]. For means and standard deviations see Table 5.

The perceived stress scale (PSS) was not significantly lower after CBT [$t(16) = 1.308$, $p = 0.209$, 95% CI [20.00, 22.34], Cohen's $d = 0.35$]. The two baseline measures for PSS (t1 and t2) differed significantly [$t(11) = 3.12$, $p = 0.010$, 95% CI [0.64, 3.70], Cohen's $d = 1.37$], with lower values at t2. For means and standard deviations see Table 5.

The trait anxiety inventory (STAI-Trait) was significantly lower after CBT [$t(16) = 3.113$, $p = 0.007$, 95% CI [41.48, 51.36], Cohen's $d = 0.83$]. The two baseline measures for STAI-trait was not significantly different [$t(11) = -0.74$, $p = 0.474$, 95% CI [–6.00, 2.96], Cohen's $d = 0.16$]. For means and standard deviations see Table 5.

The state anxiety inventory (STAI-State) was significantly lower after CBT [$M = 43.89$, SD = 9.54, $t(17) = 2.226$, $p = 0.040$, 95% CI [38.07, 50.60], Cohen's $d = 0.57$]. The two baseline measures for STAI-state did not differ between t1 and t2 [$t(11) = -1.80$, $p = 0.099$, 95% CI [–10.73, 1.06], Cohen's $d = 0.46$]. For means and standard deviations see Table 5.

5 Discussion

5.1 Summary of the results

This study explored for the first time if face-to-face CBT for IBS [11] affected ANS activity during experimentally induced visceral pain and a cognitive stress test, respectively, and self-rated state and trait anxiety, current stress and perceived stress. The study results are as follows, (i) the CBT intervention did not alter HRV, sympathetic and parasympathetic activity, nor SC during the induced visceral pain, (ii) or during cognitive stress, (iii) the CBT

Table 2: Statistical data for analysis of dependent variables during experimentally induced visceral pain.

	t1–t2				t2–t3			
	t/Z	*df*	*p*-Value	Cohens' *d*	*t/Z*	*df*	*p*-Value	Cohens' *d*
HRV	1.23	7	0.258	0.27	−0.35	–	0.730	–
Vagal	−1.31	7	0.231	0.27	−0.49	14	0.631	0.16
Sympathetic	1.31	7	0.231	0.40	1.48	14	0.160	0.39
SCL	−0.76	7	0.474	2.45	−0.22	–	0.826	–
SCR-M	0.56	7	0.575		−0.267	–	0.790	–
SCR-SD	−0.14	5	0.173		−1.156	–	248	–

t/Z statistics, degrees of freedom (*df*), *p*-values (*p*) and Cohens' *d* for dependent variables regarding autonomic nervous system (ANS) activity during visceral pain with the barostat method; heart rate variability (HRV), vagal response (vagal), sympathetic response (sympathetic), skin conductance level (SCL), skin conductance mean (SCR-M) and standard deviation, respectively (SCR-SD). The variables were collected during induction of visceral pain 4 weeks before (−4 weeks), just before (day 0) and after CBT (12 weeks).

Table 3: Descriptive data for dependent variables collected during cognitive stress 4 weeks before (−4 weeks), just before (day 0) and after CBT (12 weeks).

	M	Mdn	SD	95% CI	*n*
−4 weeks					
HRV	2.45	2.36	1.51	1.36, 3.53	10
Vagal	0.35	0.30	0.17	0.23, 0.47	10
Symp	0.65	0.70	0.17	0.53, 0.77	10
SCL	9.55	8.65	3.45	7.58, 12.55	10
SCR-M	0.26	0.23	0.15	0.15, 0.39	10
SCR-SD	0.12	0.09	0.10	0.05, 0.21	10
Day 0					
HRV	2.32	1.24	2.25	0.71, 3.92	15
Vagal	0.41	0.45	0.20	0.27, 0.56	15
Symp	0.59	0.55	0.20	0.44, 0.73	15
SCL	7.69	7.68	3.29	5.48, 9.44	15
SCR-M	0.31	0.22	0.39	0.13, 0.34	15
SCR-SD	0.13	0.09	0.11	0.07, 0.20	14
Week 12					
HRV	2.50	1.96	1.79	1.21, 3.78	15
Vagal	0.36	0.34	0.17	0.23, 0.48	15
Symp	0.64	0.66	0.17	0.52, 0.77	15
SCL	6.60	6.89	3.66	4.00, 8.34	15
SCR-M	0.22	0.12	0.27	0.09, 0.42	15
SCR-SD	0.12	0.07	0.13	0.05, 0.21	14

Means (*M*), medians (Mdn), standard deviations (SD) and 95% confidence intervals (CI) for dependent variables. HRV = heart rate variability; vagal = vagal response; symp = sympathetic response; SCL = skin conductance level; SCR-M = skin conductance mean; SCR-SD = standard deviation, respectively (SCR-SD). The variables were collected during induction of visceral pain (ANS during visceral pain).

intervention did not alter self-rated current and perceived stress, (iv) state and trait anxiety were reduced after the CBT intervention, (v) IBS patients ANS activity were high, typical for IBS and equally triggered during visceral pain and during cognitive stress.

5.2 Chronic and high ANS response during visceral pain and cognitive stress

The participants had deficiencies in ANS regulation during both visceral pain and cognitive stress that was not altered by face-to-face CBT for IBS. Participants' ANS activity was high, typical for IBS [8, 9] and triggered equally during both the induced visceral pain and during cognitive stress. This finding is consistent with earlier studies suggesting that IBS patients present high levels of stress and difficulties coping with anxiety and ANS activity in general [9] and during physically and psychologically stressful situations in particular [8–10]. Regarding current models of the importance of anxiety, stress and ANS activity for IBS pathophysiological mechanisms [35], the present study confirms that ANS activity seems to be of importance for the IBS pathophysiology during visceral pain as well as during psychologically challenging situations.

The results suggest that CBT for IBS improved the participants' psychological wellbeing rather than their autonomic stress response to experimentally induced visceral pain. The lack of impact on the autonomic stress response during visceral pain is supported by the previous report on the barostat pressure data and pain ratings [36] in which the intervention did not have an effect on the participants' level of perceived visceral pain or the induced pressure against the abdominal wall that participants could tolerate.

All measures indicating improvements in the current and its associated studies [11, 36] are self-reported measures, justified by the fact that CBT for IBS seems to work primarily via psychological pathways. For example, GI-related anxiety is actively reflected upon and behaviorally targeted, and thus self-reported measures are considered the most important measures in terms of reflecting both effects and mechanisms of the treatment. Physiological

Table 4: Statistical data for analysis of dependent variables during cognitive stress.

	t1–t2				t2–t3			
	t/Z	*df*	*p*-Value	Cohens' *d*	*t/Z*	*df*	*p*-Value	Cohens' *d*
HRV	0.15	–	0.88	–	−0.31	–	0.753	–
Vagal	0.92	9	0.38	–	−0.66	–	0.510	–
Sympathetic	−0.92	9	0.38	–	−0.66	–	0.510	–
SCL	1.67	9	0.129	0.53	1.41	14	0.181	0.31
SCR-M	−1.17	–	0.241	–	−0.87	–	0.382	–
SCR-SD	0.036	8	0.972	0	−0.63	–	0.530	–

t/Z statistics, degrees of freedom (*df*), *p*-values (*p*) and Cohens' *d* for dependent variables regarding autonomic nervous system (ANS) activity during cognitive stress; heart rate variability (HRV), vagal response (vagal), sympathetic response (sympathetic), skin conductance level (SCL), skin conductance mean (SCR-M) and standard deviation, respectively (SCR-SD). The variables were collected during cognitive stress with the Stroop color-word interference test and the affective memory test 4 weeks before (–4 weeks), just before (day 0) and after CBT (12 weeks).

Table 5: Descriptive statistics for questionnaire data.

	–4 weeks			Day 0			Week 12		
	M	SD	95% CI	*M*	SD	95% CI	*M*	SD	95% CI
SSRQ	67.15	11.44	59.01, 71.98	61.68	11.52	54.63, 69.51	65.00	10.30	57.96, 71.40
PSS	24.17	2.72	22.44, 25.90	22.00[a]	2.09	20.73, 23.27	21.12	2.83	20.00, 22.34
STAI-T	44.92	10.85	38.02, 51.81	45.73	7.19	41.48, 51.36	39.00[b]	8.95	33.04, 43.46
STAI-S	39.50	11.06	32.47, 46.53	43.89	9.54	38.07, 50.60	38.28[a]	10.21	31.45, 45.05

Means (*M*), standard deviations (SD) and 95% confidence intervals (CI) for the questionnaire data. SSRQ = stress symptom rating questionnaire; PSS = perceived stress scale; STAI-T = state and trait anxiety trait questionnaire; STAI-S = state and trait anxiety state questionnaire. The questionnaires were collected 4 weeks before (–4 weeks), just before (day 0) and after CBT (12 weeks). [a]$p < 0.05$, [b]$p < 0.01$.

stress during rectal assessments, on the other hand, was both induced and assessed by means of biomedical equipment and therefore, it could be tentatively suggested that physiological stress during visceral pain, as well as visceral pain, is not at the core mode of action in CBT for IBS. However, even though the present uncontrolled trial suggests that CBT for IBS does not affect these pathways, larger scale studies of potential autonomic changes are needed in order to elucidate the mechanisms by which face-to-face CBT for IBS works and not.

5.3 Decreased anxiety after face-to-face CBT

The present study suggests that the levels of state and trait anxiety are being lowered by the intervention. These findings confirm earlier studies with comparable measures including, e.g. the hospital anxiety and depression subscales [18], IBS quality of life [11, 16, 18], and the Gastrointestinal Symptom-specific Anxiety (GSA) [17]. To understand these mechanisms, the "fear-avoidance" model [37, 38] can be used. It suggests that anxious responses to pain and discomfort drive hypervigilance to, and (behavioral) avoidance of, symptom provoking stimuli and vice versa [11]. Catastrophic cognitions, hypervigilance and avoidant behavioral responses are posed to create vicious circles that withhold and exacerbate pain-related symptoms and disability, and lead to lower quality of life [11]. Thus, the pathway involving conditioned psychological responses to pain and discomfort, as explained in the fear-avoidance model [11] seems to have been affected in the current study.

5.4 Anxiety seems important for relieving IBS symptoms

Interestingly though, while the levels of state and trait anxiety were lowered by the intervention, so was not the case for ANS response during the induced visceral pain. The reason for this is not clear but a recent study [39] showed that trait anxiety correlates significantly with both quality of life and GI-related anxiety among subjects with IBS. This study [39] also found that GI-specific anxiety is at

the very core of the concept of suffering according to IBS patients, and mechanistic studies [17] propose this is the core mode of action for CBT aimed for IBS. Thus, it might be on the one hand that reduced GI-related anxiety precedes improvements in IBS symptoms, quality of life [11] and state and trait anxiety while on the other hand; a physiological stress response during visceral pain is not directly related to the CBT mode of action. Thus, the present study, as well as many previous studies [12–18] indicates that anxiety, both in terms of state and trait anxiety, as well GI-specific anxiety [12–18], plays an important role in the IBS pathophysiology, and needs further attention in studies investigating these mechanisms. As was shown in another study, abdominal pain-related fear was a better predictor of disability than was the actual abdominal pain intensity [40]. Moreover, significant differences has been found between participants who perceive their IBS as small problem and those who perceive it as medium important issue, according to the illness perception measure, IPM [39]. Participants, who perceive their illness as small, represented their illness as more distant, showed lower average symptom severity, and had lower GI-specific anxiety and higher quality of life. Thus, the psychological difficulties associated with IBS seem to have foundational impact on the IBS suffering and symptoms and are at the core target of the CBT intervention.

5.5 Self-rated perceived stress

The ratings of perceived stress suggest lowered levels of stress at the end of the baseline period but not after the treatment. This might have to do with positive expectations and stress relief as a result of being included in the study and awaiting CBT for the IBS symptoms.

5.6 Limitations

The study had several shortcomings. The two conditions of physical and cognitive stress were not counterbalanced and it cannot be excluded that the effect from physical stress was transferred to the cognitive stress. The reason for not counterbalancing, however, was the need for fasting during the barostat condition which made this measurement the first one in the morning and except from the ethical reasons for this, it was also needed in order to avoid the possible spill-over effect of being fasting while performing the cognitive stress.

The statistical power was calculated *post-hoc* using the g*power software [41] based on a one-way paired samples *t*-test with a medium effect size of $d = 0.5$, an error probability of 0.05 and a total sample size of 18 and 12, respectively. The power (1-B error probability) of the study was 0.65 and 0.50, respectively, and thus the power was low but at the same time reported interesting effects despite the small sample size and limited power. A future study with the same design would need 27 participants in order to achieve a power of $d = 0.8$.

Second, as with all uncontrolled trials, the lack of a control group raises the question which changes can actually be attributed to the intervention. Finally, the sample size is small and therefore the study should be seen as a first explorative indication of whether the results obtained in previous trials of internet-delivered CBT could be extended in an individual CBT format, using the same protocol as in the internet-based trials [12–16], and with regard to the ANS activity during experimentally induced visceral pain and cognitive stress, respectively, as well as state and trait anxiety, and perceived stress.

6 Conclusions

In conclusion, the present study explored for the first time if CBT for IBS affected ANS activity during experimentally induced visceral pain and cognitive stress, respectively, as well as state and trait anxiety, and perceived stress. The CBT intervention did not alter ANS activity during visceral pain or during cognitive stress. State and trait anxiety were reduced after the CBT intervention. Results suggest that face-to-face CBT for IBS improved the level of anxiety, a key psychological mechanism of importance for the IBS pathophysiology, rather than the autonomic stress response to the experimentally induced visceral pain.

7 Implications

Regarding the IBS pathophysiology, the present study indicates that IBS patients present high levels of stress and difficulties coping with anxiety and ANS activity during visceral pain and cognitive stress, respectively. However, these manifestations of IBS are not targeted by CBT, and do not seem to be central for participants' experience of suffering and symptoms according to this as well as our previous study [11].

Regarding the mechanisms of the face-to-face CBT for IBS, it did not seem to involve modulation of ANS activity in response to induced visceral pain or cognitive stress.

Instead, face-to-face CBT decreased levels of state and trait anxiety.

Implications for further studies include that anxiety seem to play an important role in the IBS pathophysiology, and needs further attention in studies investigating these mechanisms as they are described in the fear-avoidance model. Larger scale studies of potential autonomic changes are needed to elucidate by which mechanisms face-to-face CBT for IBS elicits its valued effects, and also what mechanisms are involved in the IBS pathophysiology.

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Authors' statements

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Informed consent: Informed consent was obtained from all participants included in the study.

Ethical approval: The study was approved by the regional ethical board, Etikprövningsnämnden, (www.epn.se) in Uppsala (number of the application: 2013/275) and conducted according to good clinical practice and the ethics of the Helsinki declaration.

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