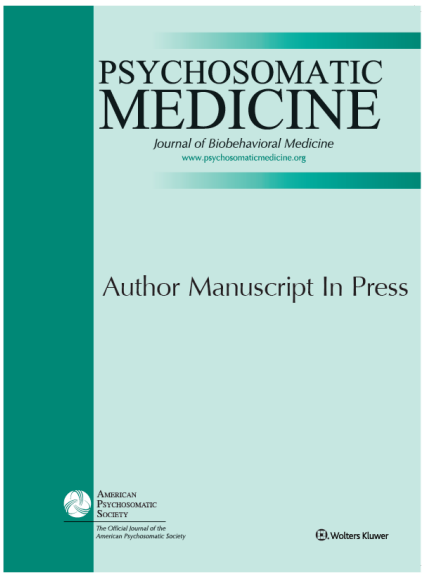
Inducing somatic symptoms in functional syndrome patients: Effects of manipulating state negative affect

Peer-reviewed author version

VAN DEN HOUTE, Maaike; BOGAERTS, Katleen; Van Diest, Ilse; De Bie, Jozef; Persoons, Philippe; Van Oudenhove, Lukas & Van den Bergh, Omer (2017) Inducing somatic symptoms in functional syndrome patients: Effects of manipulating state negative affect. In: PSYCHOSOMATIC MEDICINE, 79(9), p. 1000-1007 (Art N° 4).

DOI: 10.1097/PSY.0000000000000527
Handle: http://hdl.handle.net/1942/25306



Psychosomatic Medicine
Author's Accepted Manuscript

Article Title: Inducing somatic symptoms in functional syndrome patients: Effects of manipulating state negative affect

Authors: Maaike Van Den Houte, Katleen Bogaerts, Ilse Van Diest, Jozef De Bie, Philippe Persoons, Lukas Van Oudenhove, and Omer Van den Bergh

DOI: 10.1097/PSY.0000000000000527

Received Date: June 4, 2017

Revised Date: July 30, 2017

Psychosomatic Medicine Publish Ahead of Print
DOI: 10.1097/PSY.0000000000000527

Inducing somatic symptoms in functional syndrome patients: Effects of manipulating state negative affect

Maaike Van Den Houte, MSc[a], Katleen Bogaerts, PhD[a,b], Ilse Van Diest, PhD[a], Jozef De Bie, MD[c], Philippe Persoons, MD, PhD[d], Lukas Van Oudenhove, MD, PhD[e], & Omer Van den Bergh, PhD[a]

[a] Health Psychology, Department of Psychology and Educational Sciences, University of Leuven, Belgium

[b] REVAL - Rehabilitation Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

[c] Centre for Translational Psychological Research (TRACE), Hospital ZOL Limburg, Genk, Belgium

[d] Department of Psychiatry, University Hospital Gasthuisberg, Leuven, Belgium

[e] Laboratory for Brain-Gut Axis Studies (LaBGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Belgium.

Running head: affective modulation of symptoms in FSS

Corresponding author:

Omer Van den Bergh, PhD

KU Leuven – University of Leuven

Tiensestraat 102 – 3000 Leuven, Belgium

e-mail: omer.vandenbergh@ppw.kuleuven.be

Disclosure information: The authors report no conflict of interest.

Support: This research was supported by the Center for Excellence on Generalization Research (GRIP*TT; University of Leuven grant PF/10/005) and by Asthenes, a long-term structural funding–Methusalem grant by the FWO-Vlaanderen, Flemish Government, Belgium.

Abstract:

Objective: Induction of negative affective states can enhance bodily symptoms in high habitual symptom reporters among healthy persons, and in patients with irritable bowel syndrome. The aim of this study was to replicate this effect in patients with fibromyalgia and chronic fatigue syndrome and to investigate the role of moderators, focusing on alexithymia, negative affectivity (NA) and absorption.

Methods: Patients with fibromyalgia and/or chronic fatigue syndrome (N=81) and healthy controls (HC, N=41) viewed series of neutral, positive and negative affective pictures. After every picture series, participants filled out a somatic symptom checklist and rated emotions experienced during the picture series on valence, arousal and perceived control.

Results: Patients reported more somatic symptoms after viewing negative pictures (least square mean (LSM) = 19.40, standard error (SE) = 0.50) compared to neutral (LSM = 17.59, SE = 0.42; $p < 0.001$) or positive (LSM = 17.04, SE = 0.41; $p < 0.001$) pictures, while somatic symptom ratings of HC after viewing negative picture series (LSM = 12.07, SE = 0.71) did not differ from ratings after viewing neutral (LSM = 11.07; SE = 0.59; $p = 0.065$) or positive (LSM = 11.10, SE = 0.58; $p = 0.93$) pictures. NA did not moderate the symptom-enhancing effect of negative affective pictures, whereas the alexithymia factor 'difficulty identifying feelings (DIF)' and absorption did ($p = 0.016$ and $p = 0.006$, respectively).

Conclusion: Negative affective states elicit elevated somatic symptom reports in patients suffering from fibromyalgia and/or chronic fatigue syndrome. This symptom-enhancing effect is greater in patients having higher difficulty to identify feelings and higher absorption scores. The results are discussed in a predictive coding framework of symptom perception.

Key words: Fibromyalgia, Chronic Fatigue Syndrome, negative affect, alexithymia, absorption, somatic symptom reporting

List of abbreviations

CFS = Chronic Fatigue Syndrome

DIF = difficulty identifying feelings

$FetCO_2$ = fractional end-tidal CO_2

FMS = Fibromyalgia Syndrome

FSS = functional somatic syndromes

HC = healthy controls

IAPS = International Affective Picture System

NA = negative affectivity

SAM = Self-Assessment Manikin

SCL = skin conductance levels

Introduction

Functional somatic syndromes (FSS), like fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS), are characterized by chronic and debilitating somatic symptoms insufficiently explained by physiological dysfunction. Although the complex and multifactorial nature of FSS is not completely understood, one clue is the higher prevalence of mood and anxiety disorders in FSS (1). FSS patients score higher, on average, on personality traits associated with disturbed emotional processing such as negative affectivity (NA) and alexithymia, compared to healthy controls and patients with comparable symptoms originating from diseases with clear physiological dysfunction (1–3). NA can be defined as the tendency to experience negative emotional states (4). Alexithymia refers to a general deficit in emotion processing and regulation (5), comprising difficulty identifying feelings (DIF), difficulty describing feelings and externally-oriented thinking (6). Particularly the DIF-scale is associated with FSS (2).

Recent theoretical accounts that rely on a predictive coding framework suggest that symptoms experienced by FSS patients can be understood within a general account of symptom perception (7). In this framework, the experience of symptoms is seen as the end-result of an inferential process in which the brain interprets and modulates interoceptive input in the light of "predictions" (priors) about the cause of this input. Depending on their relative precision (statistical confidence), the eventual percept may be more determined by priors or by prediction errors related to somatosensory input (7). Contextual cues (such as affective state), characteristics of the person (such as personality traits or past experiences) and their interactions may influence the relative contribution of priors and prediction errors in the symptom experience (8,9), see Figure 1. Consequently, the relationship between physiological dysfunction and the conscious experience of symptoms may vary between and within persons.

In this sense, FSS may represent one extreme end of this continuum: somatic symptom experiences seem to be determined largely by priors predicting symptoms and only to a small extent by somatosensory input. Several experimental studies have shown that persons with

high habitual symptom levels and patients with FSS show a reduced within-person correspondence between induced physiological changes and self-reported symptoms (10–11). In addition, brain imaging studies have revealed that FSS patients show stronger activation of affective networks after symptom induction (12,13). This pattern of results suggests that elevated symptom reports in FSS patients reflect stronger affective responding to interoceptive information, possibly at the expense of detailed sensory-perceptual processing.

In this framework, interoceptive information resulting from negative affective states might be interpreted by the brain as symptoms indicative of physical dysfunction when confidence in symptom-related priors is high, and when prediction errors related to somatosensory input are imprecise (low signal-to-noise ratio). A number of studies showed that the mere induction of negative affective states through picture viewing while assessing symptom reports leads to elevated physical symptom reports, particularly in healthy high habitual symptom reporters (14–16) and in patients with irritable bowel syndrome (IBS; 17), while no group differences were found in physiological arousal while viewing the pictures. In addition, it appeared that this effect was more pronounced in persons who also had difficulty to identify feelings (DIF), and who were more easily absorbed and immersed in sensory and emotional experiences (absorption; 15,18).

The first goal of this study was to replicate these results in a new group of FSS patients, namely FMS/CFS patients. We expected that patients, more so than healthy controls, would report more physical symptoms after viewing negative compared to positive or neutral pictures. The second goal of this study was to investigate the role of potential moderators in this patient group. For instance, patients may vary regarding NA, which may affect the intensity of the affective states as induced by the pictures and, consequently, the degree of overlap between negative affective states and aversive somatic sensations. Furthermore, we wanted to investigate if this effect would be more pronounced in patients with difficulty identifying feelings (DIF) and absorption, as has been found in healthy high habitual symptom reporters (15).

Methods

Participants

Patients with a doctor-based diagnosis of CFS and/or FMS were recruited through the Psychiatry Departments of University Hospital Gasthuisberg (Leuven) and East Limburg Hospital (Genk) and through the Rheumatology Center in Genk. After inclusion, participants also filled out a questionnaire checking for the 1994 CDC criteria of CFS (19) and the 2010 ACR criteria for FMS (20). Exclusion criteria for patients were a body mass index > 35, pregnancy, an electronic implant, uncorrected hearing problems, alcohol- or drug dependence, anorexia or bulimia nervosa, a history of psychosis and a chronic cardiovascular, respiratory or neurological disorder. Patients were first informed about the study by their physician, who brought them in contact with the researcher if they were interested in participating. After recruiting about half of the patient sample, recruitment of healthy controls (HC) started through local advertisement. An additional exclusion criterion for HC was any history of psychiatric disorders. To have sufficient power for the analyses concerning possible moderators *within* the patient group, we decided to recruit double the number of patients to HC. In order to have a similar distribution of age and sex in patients and HC, HC were recruited by means of frequency sampling: HC could only participate if sufficient patients from the same age range (18-20; 21-25; 26-30; and so on) and of the same sex had participated. This was accomplished by advertising for specific age ranges. For the sake of simplicity, sampling based on age and sex was carried out independently from each other. Taking into account the 2:1 ratio between patients and HC, the minimal required total sample size was 102 (34 controls, 68 patients) for a power of 0.95 in detecting medium sized effects at $\alpha = 0.05$. All participants provided written informed consent at the start of the study. Participants were asked to abstain from smoking, caffeine and sports for four hours prior to the test session, and from alcohol 24 hours prior to the test session. The study was approved by the Medical Ethical Committees of the University Hospital Gasthuisberg, Leuven and East

Limburg Hospital, Genk. All participants received financial compensation of 75 euros and travel costs.

Design

This study was part of a larger study involving four experimental paradigms administered to the same participants, aiming to investigate symptom perception in FMS and CFS patients. Participants went through the MINI Neuropsychiatric Interview (21), filled out an online questionnaire battery at home and participated in a test session in the hospital. Only the results of the picture viewing paradigm are reported here. Data collection took place between October 2014 and December 2016.

Affective stimuli

Two hundred and sixteen pictures were selected from the International Affective Picture System (IAPS) and were grouped into three categories (positive, negative, neutral; 72 pictures per category) based on normative data (22). Pictures within one picture category had similar valence and arousal ratings in the normative data. Only low disgust pictures were included.

Materials and apparatuses

Dependent variables

Affective evaluation of each picture series was assessed with the digital Self-Assessment Manikin system (SAM; 23). Participants rated their affective state during picture viewing on the dimensions valence (very sad – very happy), arousal (very calm – very excited) and perceived control (very low – very high perceived control) on a continuous scale (range 0-18). This method is a widely used and valid way to assess affective responses (23).

Physical symptoms experienced during picture viewing were measured with a symptom checklist rating ten physical symptoms on a 5-point (1: not at all – 5: very strong) Likert scale. The following symptoms were assessed: tight feeling in the chest, heart pounding,

stomachache, headache, fatigue, difficulty breathing, faster heart rate, nausea, dizziness, muscle ache. This resulted in a symptom score ranging from 10-50. This checklist has previously been used in similar paradigms (15,16).

Trait Questionnaires

Negative affectivity (NA) was measured with the NA scale of the trait version of the Positive and Negative Affect Schedule (PANAS; 24). The respondent has to indicate on a 5-point Likert scale how often they experience ten negative emotions in daily life. The NA scale has been shown to have adequate construct validity and internal consistency (Chronbach's α = 0.89; 25), and high stability (test-retest reliability, r = 0.81; 24).

Alexithymia was measured with the Toronto Alexithymia Scale (TAS-20; 6), which consists of 20 statements measured on a five-point scale (completely disagree – completely agree). Only the difficulty identifying feelings (DIF) subscale (range 7-35) was used in this study. The DIF scale has been shown to have acceptable internal consistency (Chronbach's α = 0.78) and good construct validity (26), and the TAS-20 has been shown to have adequate stability (test-retest reliability, r = 0.77; 6).

Absorption was measured with the Tellegen Absorption Scale (27). Participants indicate whether each of 39 statements apply to them (true/not true). Total scores range from 0-39, with higher scores indicating higher levels of absorption. The scale has been shown to have high internal consistency (Chronbach's α = 0.88) and stability (test-retest reliability, r = 0.91; 27).

Physiological recordings

Heart rate, skin conductance levels and fractional-end tidal CO_2 ($FetCO_2$) levels were recorded continuously in order to assess physiological arousal during picture viewing.

Three disposable ECG electrodes (diameter 24mm, Kendall™) were placed under the left and right clavicle and at height of the left lower ribs to measure heart rate. The signal was sampled

at 1000 Hz and fed into a Couldbourn V75-04 Bioamplifier (Allentown, PA). The ECG recording was visually inspected and processed offline with Artiifact (28). Average heart rate during each picture series was derived from the R-R intervals.

Skin conductance levels (SCL) were recorded with two reusable 8-mm electrodes filled with K-Y jelly placed on the palm of the non-dominant hand. The signal was sampled at 10Hz and fed into a Couldbourn V75-04 Bioamplifier (Allentown, PA). SCL recordings were visually inspected and processed offline in MatLab R2015a (Mathworks inc, Massachusetts, USA). Average SCL in the ten seconds prior to the start of a picture series were subtracted from average SCL during that picture series. The difference scores were logarithmically transformed (log10(difference score + 3.10)); the constant was added to handle negative scores.

$FetCo_2$, an index of breathing in excess of metabolic needs, was measured with a nose cannula connected to an infrared capnograph (Poet RC, Criticare, Milwaukee, USA in East-Limburg Hospital; Capnogard, Novametrix, Wallingford, USA in the University Hospital of Leuven). $FetCO_2$ data was recorded at 50H. The signal was visually inspected and processed offline with PSPHA (29). Average $FetCO_2$ was calculated for each picture series.

Procedure

During the picture viewing experiment, participants viewed three series of pictures (neutral, positive, negative). For every participant, 60 pictures (20 for each series) were randomly selected from the IAPS picture pool. Each series consisted of 1) a 40-second baseline, in which "The picture series will start in a few moments" was presented on the screen, and 2) a 160-second picture series (20 pictures viewed for eight seconds each). The order of the pictures within one series was randomized, the order of the series was counterbalanced across participants. Heart rate, SCL and $FetCO_2$ levels were measured continuously during picture viewing

After every picture series, participants rated the picture series on valence, arousal and perceived control using the SAM ratings scale, and filled out the symptom checklist. There was a one-minute break in between the ratings and the start of the new picture series.

Statistical analysis

To investigate differences between patients and HC in symptom reporting after picture viewing, separate mixed model analyses with picture category as within-subject factor and group as between-subject factor were carried out on different dependent variables: valence ratings, arousal ratings, perceived control ratings, symptom checklist scores, heart rate, SCL and FetCO2. We expected that more symptoms would be reported after negative vs. neutral and positive pictures, and that this effect would be more pronounced in patients than in HC. We expected no differences in physiological measures. Because of the unbalanced design, follow-up comparisons (t-tests with stepdown Bonferroni correction) were made both in the case of a significant main effect of group and in the case of a significant group*picture series interaction effect.

To investigate moderation effects of individual difference variables on symptom reporting after picture viewing *within* the patient group, similar analyses were carried out on the patient group alone, with picture category as within-subject factor and each of the trait variables (NA, absorption and DIF) as between-subject variables in separate analyses. When appropriate, follow-up comparisons were made with post-hoc t-tests with Tukey-Kramer correction for multiple comparisons. We expected that particularly patients scoring high in NA, absorption, or DIF, would report more symptoms after negative compared to positive/neutral picture viewing. When one of the trait variables appeared a significant moderator of this effect, we investigated the mediator role of that trait in the association between patient status (patients vs. HC) and the effect of affective state on symptom reporting with a simple mediation analysis using ordinary least squares path analysis (30). The effect of affective state on symptom reporting was quantified as ‘symptoms after negative series – (symptoms after

neutral series + symptoms after positive series)/2)' and this newly created variable was used as the dependent variable in the mediation analysis.

All analyses were carried out with SAS 9.4. The mediation analyses were performed with the PROCESS procedure for SAS (30).

Results

Sample characteristics

Eighty-one patients (mean age: 42.11, SD = 40.62; 71 women) and 41 HC (mean age: 42.37, SD = 11.38; 36 women) participated in the experiment. All participants were white. Thirty-nine patients (49.4%) met the criteria for both CFS and fibromyalgia as determined by the 1994 CDC criteria for CFS (19) and the 2010 ACR criteria for fibromyalgia (20). Thirty-four patients (43.0%) met the criteria for fibromyalgia, but not for CFS. Two patients met the criteria for CFS alone, and four patients did not meet the criteria for CFS or fibromyalgia (Table 2). Because these four patients had a recent doctor-based diagnosis, they were not excluded from the study. Patients fulfilling the criteria for fibromyalgia alone did not differ from patients fulfilling the criteria for both fibromyalgia and CFS with regards to NA, DIF or absorption. Moreover, there was no main or interaction effect of diagnosis on symptom, valence, arousal or control ratings. Therefore, in the remainder of the analyses, the patient group was treated as a whole.

Descriptive sample statistics are displayed in Table 1. Briefly, patients scored higher on NA and DIF compared to HC, whereas no difference was found for absorption. Prevalence of psychiatric comorbidities and medication use in the patient group are displayed in Table 2. Heart rate data of 11 subjects (3 HC, 7 patients), $FetCO_2$ data of 14 subjects (1 HC, 13 patients) and skin conductance data of 9 subjects (5 HC, 4 patients) could not be used due to technical problems. Two patients did not fill out the online questionnaire battery.

Patients vs. HC: SAM-ratings (Table 3)

SAM-ratings for arousal and control were moderately correlated across the different picture categories ($0.25 < r < 0.53$ for arousal ratings, $0.49 < r < 0.76$ for control ratings). Valence ratings for the positive and neutral condition were significantly correlated to each other ($r = 0.37$), but were not correlated to valence ratings in the negative condition. A main effect of group (patients vs. HC) was found for valence ratings ($F_{1,120} = 7.73$, $p = 0.006$) and control ratings ($F_{1,119} = 10.84$, $p = 0.001$), but not for arousal ratings ($F_{1,120} = 1.14$, $p = 0.29$). Patients overall rated the picture series as more unpleasant and had lower feelings of control in all picture series. No significant group x picture type interaction effects were found for the SAM-ratings. However, follow-up analyses showed that the effect of group on valence ratings was significant in the positive ($t_{120} = 1.52$, $p = 0.042$) but not in the neutral ($t_{120} = 2.58$, $p = 0.22$) or negative ($t_{120} = 2.49$, $p = 0.22$) picture category.

Patients vs. HC: symptoms (Table 3)

Symptom ratings were highly correlated across the different picture categories ($0.81 < r < 0.93$). There was a main effect of picture category ($F_{2,120} = 15.67$, $p < 0.001$) and group ($F_{1,120} = 85.92$, $p < 0.001$) on symptom ratings, and a trend for a group x picture category interaction effect ($F_{2,120} = 2.66$, $p = 0.074$). Follow-up tests indicated that patients reported significantly more symptoms in the negative compared to the neutral ($t_{120} = 5.89$, $p < 0.001$) and positive ($t_{120} = 6.57$, $p < 0.001$) picture category, and reported less symptoms in the positive compared to the neutral ($t_{120} = 2.74$, $p = 0.029$) picture category. However, there were no significant differences between picture categories in the control group ($t_{120} = 1.93$, $p = 0.11$ for negative vs positive, $t_{120} = 2.32$, $p = 0.065$ for negative vs neutral, $t_{120} = 0.09$, $p = 0.93$ for neutral vs positive).

Patients vs HC: physiological data

No main or interaction effects were found for heart rate or $FetCO_2$. Patients had overall higher SCL (main effect of group: $F_{1,111} = 4.70$, $p = 0.032$) while watching the picture series, but SCL did not differ between picture categories (picture category: $F_{2,111} = 0.99$, $p = 0.37$; picture category x group: $F_{2,111} = 2.33$, $p = 0.10$).

Within patients: effect of negative affectivity

Patients scoring higher on NA reported more symptoms after watching all picture series (main effect of NA: $F_{1,78} = 7.02$, $p = 0.010$). However, this effect did not differ by picture series (picture category x NA interaction effect: $F_{2,78} = 0.24$, $p = 0.79$). Patients scoring high on NA also found the picture series overall more unpleasant ($F_{1,78} = 5.29$, $p = 0.024$) and more arousing ($F_{1,78} = 6.88$, $p = 0.010$), and felt overall less in control while watching the picture series ($F_{1,78} = 9.16$, $p = 0.003$). The picture category x NA interaction effects were not significant for valence, arousal and control ratings. NA was unrelated to physiological measures during picture viewing.

Within patients: effect of absorption

A significant absorption x picture category effect on symptom ratings ($F_{2,77} = 5.39$, $p = 0.006$) and a trend for a main effect of absorption on symptom ratings ($F_{1,77} = 3.90$, $p = 0.052$) was found. Follow-up analyses indicated that while symptom ratings were significantly higher in the negative versus neutral or positive picture series for patients with higher absorption scores (all p-values < .001 when absorption = average or 1 SD above average), symptom ratings didn't differ between picture categories for patients with lower absorption scores ($p = 0.16$ for negative vs. positive and $p = 0.17$ for negative vs neutral for patients with absorption scores 1 SD below average), see Figure 2. Absorption scores were unrelated to valence and arousal ratings and to physiological measures during picture viewing.

Within patients: effect of difficulty identifying feelings

A significant DIF x picture category effect on symptom ratings ($F_{2,78} = 4.33$, $p = 0.016$) was found. The main effect of DIF on symptom ratings was not significant ($F_{1,78} = 0.87$, $p = 0.35$). Follow-up analyses indicated that while symptom ratings were significantly higher in the negative versus neutral or positive picture series for patients with higher DIF scores (all p-values < 0.001 when DIF = average or 1 SD above average), symptom ratings did not differ significantly between different picture categories for patients with lower DIF scores ($p = 0.052$ for negative vs. positive and $p = 0.20$ for negative vs neutral for patients with DIF scores 1 SD below average), see Figure 3. Patients scoring higher on DIF rated all picture series as more unpleasant (main effect of DIF on valence ratings: $F_{1,78} = 5.78$, $p = 0.019$) and felt less in control during the picture viewing (main effect of DIF on control ratings: $F_{2,78} = 5.35$, $p = 0.023$). No significant interaction effects were found. DIF was unrelated to arousal ratings and physiological measures.

Mediation analyses

The total effect of patient status on the symptom difference score was significant ($c = 1.14$, $p = 0.039$), indicating that patient status was associated with the symptom difference score when DIF or absorption were not taken into account.

Patient status was significantly associated with DIF ($a = 5.551$, $p < .0001$) and DIF was significantly associated with the symptom difference score ($b= 0.147$, $p = 0.004$). Most importantly a bias-corrected bootstrap confidence interval for the indirect effect ($ab = 0.817$) based on 10 000 bootstrap samples did not include zero (0.0942 – 2.391), supporting the hypothesis of DIF as a mediator. The direct effect of patient status on the symptom difference score was not significant ($c' = 0.327$, $p = 0.59$), indicating that patient status was not significantly associated with the symptom difference score when DIF was taken into account, supporting the hypothesis that the relationship between patient status and affective modulation of symptom reporting is fully mediated by DIF (Figure 4).

Patient status was not associated with absorption (a = -1.292, p = 0.36). Therefore, we did not perform the mediation analysis on absorption.

Discussion

Eighty-one patients diagnosed with FMS and/or CFS and 41 HC viewed a negative, positive and neutral picture series. After each picture series, participants rated their emotional state on valence, arousal and perceived control, and filled out a symptom checklist. We expected that 1) participants would report more somatic symptoms after watching negative compared to neutral and positive pictures, 2) this effect would be larger in FSS patients compared to HC, and 3) this effect would be more pronounced in patients with higher NA, DIF and absorption.

Overall, participants reported more somatic symptoms after viewing negative compared to neutral and positive pictures. In contrast to our expectations, the group x picture category interaction effect did not reach significance, suggesting an equal effect of negative mood on symptom reporting for patients and HC. However, the interpretation of this interaction effect is complicated by the unbalanced design. Follow-up analyses indicated that the effect of picture category on symptom reporting was significant in the patient group but not in the healthy control group, confirming our first two hypotheses. These results corroborate earlier findings from our group obtained in non-clinical high habitual symptom reporters (14–16). Like in these previous studies, this difference could not be explained by group differences in state NA, arousal or physiological activity in the negative picture series.

In a predictive coding framework of symptom perception, the conscious experience of symptoms is the end-result of an inferential process in which somatosensory input is interpreted and modulated by the brain in the light of “priors” about the cause of the somatosensory input through a hierarchical prediction error minimization process. Prediction errors are defined as the portion of input that is not predicted by the prior. The relative contribution of the prior and the somatosensory input to the subjective experience depends on their relative precision (7,31). More confident priors and less precise prediction errors

resulting from somatosensory input (low signal-to-noise ratio) will result in a larger influence of the prior on the final percept (Figure 1). The paradigm described in this study is set up in such a way that somatosensory input is low and thus imprecise (no explicit symptom induction), while symptom-related priors might gain confidence by prompting the participants for symptoms with the symptom checklist. In negative affective states, prediction errors resulting from priors predicting somatic dysfunction and prediction errors resulting from priors predicting negative affective states may largely overlap. This might especially be the case in FSS patients, who have an augmented affective-motivational response to somatic stimuli, possibly at the cost of detailed perceptual-sensory processing (10-13). Assuming that FSS patients have more confident symptom-related priors (strengthened by regular doctor visits, high health anxiety, …), priming such priors through a symptom questionnaire while inducing negative affective states will result in FSS patients reporting more symptoms in negative compared to neutral/positive affective states.

The second aim of this study was to investigate possible moderators of this effect *within the patient group*, with a focus on NA, DIF and absorption. It is reasonable to assume that the relative contribution of priors and prediction errors to the eventual symptom experience varies within the FSS patient group. Individuals high in NA are known to have an increased motivational-affective response to both affective (32) and somatic stimuli (33). This enhanced affective processing may go at the expense of detailed sensory-perceptual processing (34), causing the prediction errors related to negative affective states and somatic symptoms to largely overlap. Therefore, we expected that patients who scored higher on NA would report more somatic symptoms after viewing negative affective pictures. While NA was associated with higher symptom checklist scores overall, this was not dependent on the affective content of the pictures. Thus, our results did not support the hypothesis that affective modulation of symptom perception in functional syndrome patients is moderated by NA. However, our results showed that the influence of negative affective states on somatic symptom reporting was larger in patients scoring high on DIF and absorption. Individuals scoring higher on DIF

have more difficulties with regulating emotions. Moreover, it has been suggested that the inability to correctly identify, classify and interpret emotions is related to an increased confusion between the changes in bodily states that accompany a negative emotional state and changes in bodily states that are a sign of disease (i.e., symptoms; 35). DIF might thus express itself in a reduced detailed sensory-perceptual processing and a larger overlap between prediction errors related to affective and somatic stimuli. Our follow-up exploratory mediation analysis further indicated that DIF was a full mediator of the relationship between patient status and the symptom difference score, suggesting that the difference in affective modulation of symptom reporting between patients and HC can be explained by a difference in DIF. The tendency to become absorbed in experiences also acted as a moderator of affective modulation of symptom reporting within the patient group. Individuals scoring high on absorption have a heightened focus towards internal sensations (18). In negative affective contexts, this might lead to a large overlap between affective and somatic prediction errors and very low precision. Increased interoceptive attention, in combination with confident priors, might cause the system to selectively sample these signals that confirm symptom-related priors (7).

Our findings have some important clinical implications. First, we showed that FSS patients are particularly vulnerable to experience and report somatic symptoms in negative affective states. Secondly, we demonstrated the importance of alexithymia, and more specifically the DIF construct, both as a moderator of this effect within the patient group and as a mediator of the difference between patients and HC in this effect. This implies that FSS patients with high DIF especially might benefit from treatments training emotion identification/recognition. Although research on treatments targeting emotional awareness and emotion regulation strategies in FSS patients is currently lacking (36), results from experimental studies are promising (37). Third, in accordance with the predictive coding account, patients sensitive to affective modulation of symptom perception might benefit from treatment reducing precision of symptom-related priors (e.g. by targeting rumination and reducing health anxiety) and

augmenting the precision of somatosensory input (e.g. with "interoceptive differentiation training" and/or by reducing the internally focused attention).

The current study with a well-validated paradigm in a large patient sample showed substantial variation in the variables of interest (NA, alexithymia and absorption). This made it possible to draw valid conclusions on possible moderators of affective modulation of symptom reporting within the patient group. However, comparing the patient group with a substantially smaller group of HC complicated the interpretation of main and interaction effects involving patient status. Another issue is that the patient and control group differed inherently on variables such as medication use, and the presence of psychiatric illnesses such as depression and anxiety disorders. This is inevitable when recruiting a patient group representative of the FMS/CFS population, but it may complicate the interpretation of the results. A last drawback of the study was that the TAS-20, a self-report questionnaire, was used as a measure of alexithymia. It can be argued that individuals with high levels of alexithymia might not be well-suited to assess their own ability to deal with emotions (38). Despite this critique the TAS-20 is still the most used method to measure alexithymia in FSS research (39). However, future studies focusing on the relationship between alexithymia, state NA and symptom reporting might benefit from using a multimodal approach to measuring alexithymia.

In sum, we demonstrated that inducing negative affective states elevated somatic symptom reports, especially in patients suffering from FMS and/or CFS. However, this difference between patients and HC disappeared when adjusting for differences in DIF. Both DIF and absorption were significant moderators of the effect *within* the patient group. These findings add to our understanding of the affective modulation of symptom perception, and can have important implications for treatments to reduce somatic symptoms in FSS patients.

Acknowledgments

The authors would like to thank the physicians and psychologists at the Psychiatry Departments of UZ Gasthuisberg, ZOL Genk, and at the Rheumatology Center in Genk for their help with the recruitment of patients; Emma Biggs for her help with data processing, and Lotte Ceuterick, Katrien Coremans and Celine Samaey for their help with data collection.

References

1. Henningsen P, Zimmerman T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: A meta-analytic review. Psychosom Med 2003;65:528–33.

2. Steinweg DL, Dallas AP, Rea WS. Fibromyalgia: unspeakable suffering, a prevalence study of alexithymia. Psychosomatics 2011;52:255–62.

3. Bucourt E, Martaillé V, Mulleman D, Goupille P, Joncker-Vannier I, Huttenberger B, Reveillere C, Courtois R. Comparison of the Big Five personality traits in fibromyalgia and other rheumatic diseases. Joint Bone Spine 2016.

4. Watson D, Clark L. Negative affectiviointty: the disposition to experience aversive emotional states. Psychol Bull 1984;96:465–90.

5. Parker JDA, Taylor GJ, Bagby RM. The alexithymia construct: relationship with sociodemographic variables and intelligence. Compr Psychiatry 1989;30:434–41.

6. Bagby M, Parker JDA, Taylor GJ. The twenty-item Toronto Alexithymia Scale -I. Item selection and cross-validation of the factor structure. J Psychosom Res 1994;38:23–32.

7. Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: Taking the inferential leap. Neurosci Biobehav Rev 2017;74:185–203.

8. Brown RJ. Psychological mechanisms of medically unexplained symptoms: an integrative conceptual model. Psychol Bull 2004;130:793–812.

9. Van den Bergh O, Bogaerts K, Van Diest I. Symptom perception, awareness and interpretation. In: Wright, editor. International Encyclopedia of the Social & Behavioral Sciences. vol 23. 2nd ed. Elsevier: Oxford; 2015. p. 866–72.

10. Bogaerts K, Millen A, Li W, De Peuter S, Van Diest I, Vlemincx E, Fannes S, Van den Bergh O. High symptom reporters are less interoceptively accurate in a symptom-related context. J Psychosom Res 2008;65:417–24.

11. Bogaerts K, Van Eylen L, Li W, Bresseleers J, Van Diest I, De Peuter S, Stans L, Decramer M, Van den Bergh O. Distorted symptom perception in patients with medically unexplained symptoms. J Abnorm Psychol 2010;119:226–34.

12. Montoya P, Sitges C, Garcia-Herrera M, Izquierdo R, Truyols M, Blay N, Collado D. Abnormal affective modulation of somatosensory brain processing among patients with fibromyalgia. Psychosom Med 2005;67:957–63.

13. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology 2011;140:91–100.

14. Bogaerts K, Janssens T, De Peuter S, Van Diest I, Van den Bergh O. Negative affective pictures can elicit physical symptoms in high habitual symptom reporters. Psychol Health 2010;25:685–98.

15. Bogaerts K, Rayen L, Lavrysen A, Van Diest I, Janssens T, Schruers K, Van den Bergh O. Unraveling the relationship between trait negative affectivity and habitual symptom reporting. PLoS One 2015;10:e0115748.

16. Constantinou E, Bogaerts K, Van Diest I, Van den Bergh O. Inducing symptoms in high symptom reporters via emotional pictures: the interactive effects of valence and arousal. J Psychosom Res 2013;74:191–6.

17. Constantinou E, Bogaerts K, Van Oudenhove L, Tack J, Van Diest I, Van den Bergh O. Healing words: Using affect labeling to reduce the effects of unpleasant cues on symptom reporting in IBS patients. Int J Behav Med 2015;22:512-20.

18. Tellegen A, Atkinson G. Openness to absorbing and self-altering experiences "Absorption", a trait related to hypnotic susceptibility. J Abnorm Psychol 1974;83:268–77.

19. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1990; 121, 953–959.

20. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62, 600–610.

21. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–33.

22. Mikels JA, Fredrickson BL, Larkin GR, Lindberg CM, Maglio SJ, Reuter-Lorenz PA. Emotional category data on images from the International Affective Picture System. Behav Res Methods 2005;37:626–30.

23. Bradley M, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 1994;25:49–59.

24. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.

25. Crawford JR, Henry JD. The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. Br J Clin Psychol 2004;43:245-65.

26. Bagby RM, Taylor GJ, Parker JD. The twenty-item Toronto Alexithymia Scale—II. Convergent, discriminant, and concurrent validity. J Psychosom Res 1994;38:33-40.

27. Tellegen A. Content categories: Absorption items (Revised). Unpublished manuscript, University of Minnesota 1982.

28. Kaufmann T, Sütterlin S, Schulz SM, Vögele C. ARTiiFACT: a tool for heart rate artifact processing and heart rate variability analysis. Behav Res Methods 2011;43:1161–70.

29. De Clercq A, Verschuere B, De Vlieger P, Crombez G. Psychophysiological Analysis (PSPHA): A modular script-based program for analyzing psychophysiological data. Behav Res Methods 2006;38:504–10.

30. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. Guilford Press; 2013.

31. Edwards MJ, Adams RA, Brown H, Paree I, Friston KJ. A Bayesian account of "hysteria." Brain 2012;11:3495–512.

32. Ormel J, Bastiaansen A, Riese H, Bos EH, Servaas M, Ellenbogen M, Rosmalen JGM, Aleman, A. The biological and psychological basis of neuroticism: current status and future directions. Neurosci Biobehav Rev 2013;37:59–72.

33. Van den Bergh O, Walentynowicz M. Accuracy and bias in retrospective symptom reporting. Curr Opin Psychiatry 2016;29:302–8.

34. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3:655–66.

35. Taylor GJ, Bagby RM, Parker JD. Disorders of affect regulation: alexithymia in medical and psychiatric illness. Cambridge University Press; 1999.

36. Kleinstäuber M, Gottschalk J, Berking M, Rau J, Rief W. Enriching cognitive behavior therapy with emotion regulation training for patients with multiple medically unexplained symptoms (ENCERT): Design and implementation of a multicenter, randomized, active-controlled trial. Contemp Clin Trials 2016;47:54–63.

37. Constantinou E, Van Den Houte M, Bogaerts K, Van Diest I, Van den Bergh O. Can words heal ? Using affect labeling to reduce the effects of unpleasant cues on symptom reporting. Front Psychol 2014;5:807.

38. Suslow T, Kersting A, Orhmann P, Arolt V. A critique of the construct “alexithymia” and its measurement - the weakness of self-report and the opportunities of an objective assessment approach. Z Psychosom Med Psychother 2001;47:153–66.

39. Maes F, Sabbe BGC. Alexithymie bij fibromyalgie : prevalentie. Tijdschr Psychiatr 2013;56:798–806.

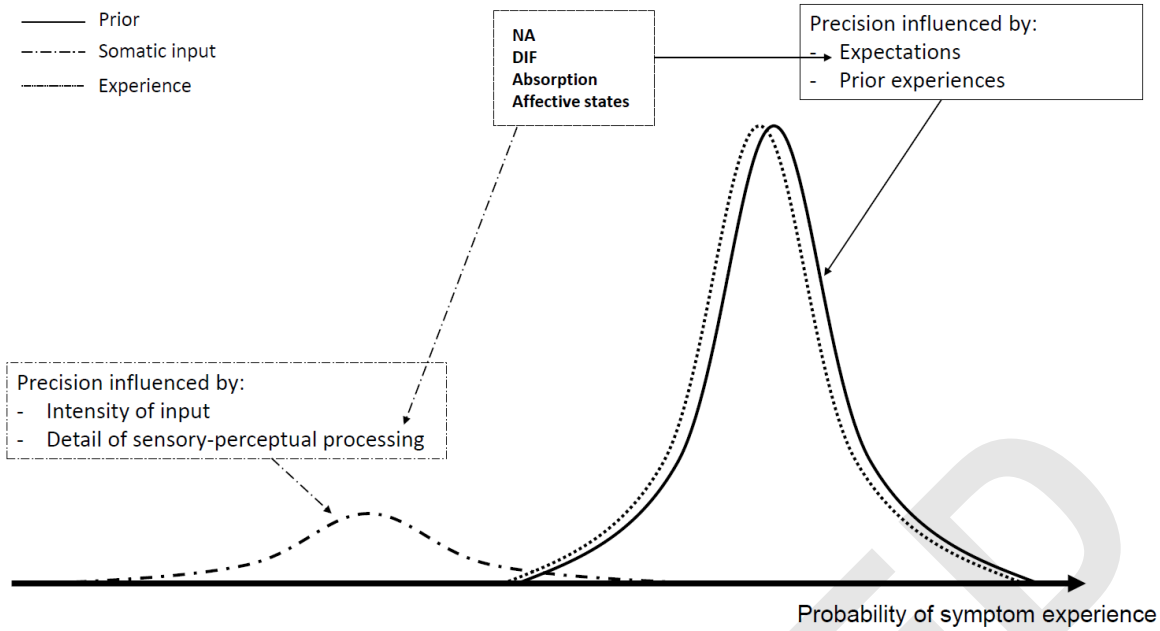
List of figures

Figure 1. Simplified visual representation of the predictive coding perspective on functional somatic symptoms (see 7 for further elaboration). In cases where a symptom-related prior (hypothesis about the cause of the somatic input; full line) is precise and the somatic input (dashed line) is imprecise, the eventual experience (dotted line) will be determined largely by the prior and to a lesser extent by the somatic input. The precision of the prior is determined by expectations and previous experiences, while the precision of the somatosensory input is influenced by the intensity of the input and the amount of detail in sensory-perceptual processing. Expectations and detail of processing can in turn be influenced by the affective context and personality traits such as negative affectivity (NA), difficulty identifying feelings (DIF) and absorption.

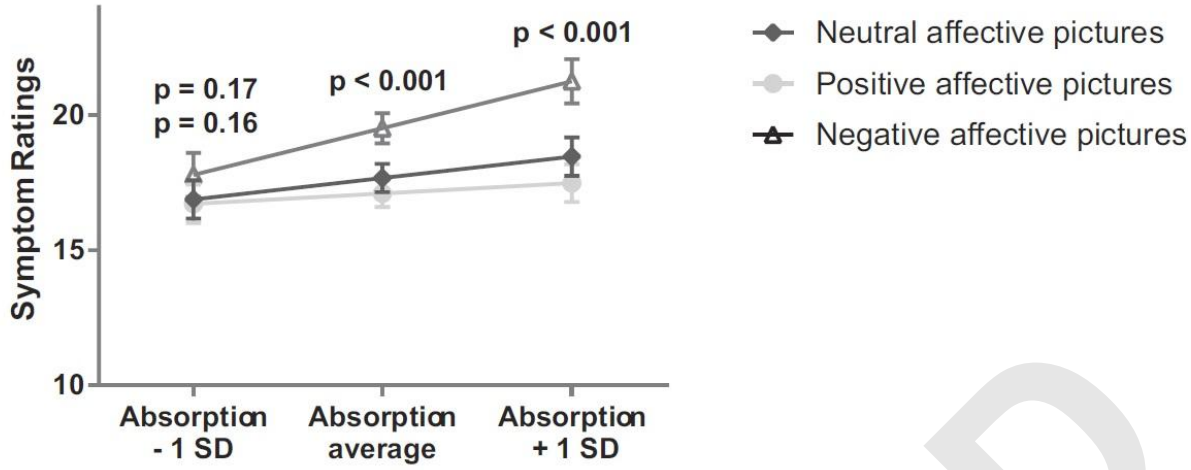
Figure 2. Interaction effect between absorption (continuous variable measured by the Tellegen Absorption Scale) and picture category (neutral vs. positive vs. negative) on symptom ratings after picture viewing. Symptom ratings were estimated by the full model for patients (n = 81) with an average, 1 standard deviation below average and 1 standard deviation above average absorption score. Error bars denote standard errors.

Figure 3. Interaction effect between difficulty identifying feelings (DIF; continuous variable measured by the Toronto alexithymia scale) and picture category (neutral vs. positive vs. negative) on symptom ratings after picture viewing. Symptom ratings were estimated by the full model for patients (n = 81) with an average, 1 standard deviation below average and 1 standard deviation above average DIF score. Error bars denote standard errors.

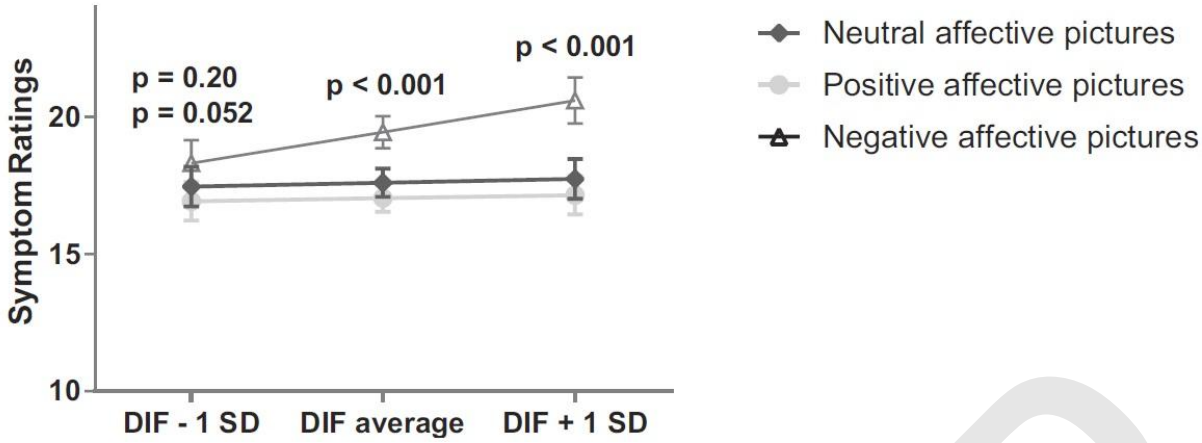
Figure 4. Simple mediation model for the direct and indirect effect of patient status (patients (n = 81) vs. healthy controls (n = 41)) on the symptom difference score, mediated by DIF (difficulty identifying feelings). The model coefficients are reported in unstandardized form. ***$p < .001$.



Symptom Ratings by Condition and TAS Score



Symptom Ratings by Condition and DIF Score



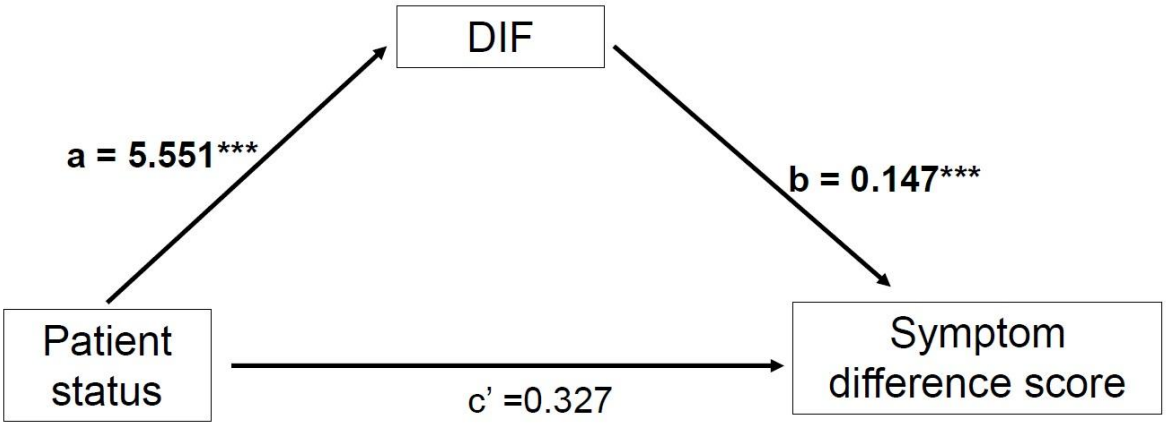


Table 1. Sample demographics and average scores and standard deviations for patients (n = 81) and healthy controls (n = 41) for the trait questionnaires used.

	Patients		HC		Statistics		
	Mean	SD	Mean	SD	t-value	df	p-value
Age	42.11	10.62	42.37	11.38	0.12	120	0.90
BMI, kg/m^2	24.85	4.93	24.41	3.69	-0.55	103.03	0.62
NA	27.40	8.98	15.98	4.67	9.204	118.95	< .001
Alexithymia - DIF	19.58	3.86	14.02	3.97	6.330	106.16	< .001
Absorption	13.68	7.05	14.98	7.74	0.920	118	.35
	%	N	%	N	X^2	df	p-value*
Sex					0.001	1	0.98
Men	12.3	10	12.2	5			
Women	87.4	71	87.8	36			
Smoking status					2.61	2	0.27
Non-smoker	49.4	39	56.1	23			
Smoker	30.4	24	17.1	7			
Former smoker	20.2	16	26.8	11			
Highest educational level					7.49	3	0.058
Primary education	5.2	4	4.9	2			
High school	58.4	45	36.6	15			
Higher education	36.4	28	58.5	24			

HC = Healthy Controls, BMI = Body Mass Index, NA = Negative Affectivity, DIF = Difficulty Identifying feelings, X^2 = Chi-Square test. Higher education comprises both college and university.

Table 2. Psychiatric comorbidities and medication use in the patient group (n = 81).

Psychiatric comorbidity	N	%
Depressive episode	37	45.7
Panic disorder	8	9.9
Agoraphobia	18	22.2
Social phobia	9	11.1
Obsessive-compulsive disorder	10	12.3
Post-traumatic stress disorder	5	6.2
Generalized anxiety disorder	44	54.3
Somatization disorder	25	30.9
Any of the above	**68**	**84.0**
Medication use	N	%
Anti-depressants	38	46.9
Benzodiazepines	18	22.2
Opioids	26	32.1
Paracetamol	24	29.6
NSAID	16	19.8
Any of the above	**61**	**75.3**
Fulfillment of diagnostic criteria*	N	%
Fibromyalgia alone	34	43.0
CFS alone	2	2.5
Fibromyalgia + CFS	39	49.4
Not meeting criteria	4	5.1

Psychiatric comorbidities were determined by means of the MINI International Neuropsychiatric Interview, which is based on the DSM-IV criteria for psychiatric disorders.

Table 3. Least square means (LSM) and standard errors (SE) for SAM-ratings and the symptom checklist after the three different picture categories, for patients (n = 81) and healthy controls (HC; n = 41).

	Group		Positive	Neutral	Negative
Valence ratings	HC	LSM	15.46[a]	11.98[b]	5.85[c]
		SE	0.42	0.58	0.51
	P	LSM	14.18[a]	10.83[b]	4.90[c]
		SE	0.30	0.41	0.36
Patients vs. HC			*p = 0.042*	*p = 0.22*	*p = 0.22*
Arousal ratings	HC	LSM	4.39[a]	3.95[a]	7.71[b]
		SE	0.55	0.54	0.60
	P	LSM	4.26[a]	4.90[a]	8.57[b]
		SE	0.39	0.38	0.43
Patients vs. HC			*p = 0.85*	*p = 0.45*	*p = 0.49*
Control ratings	HC	LSM	14.38[a]	13.58[a]	11.20[b]
		SE	0.67	0.72	0.77
	P	LSM	12.06[a]	11.41[a]	8.40[b]
		SE	0.47	0.50	0.54
Patients vs. HC			*p = 0.012*	*p = 0.015*	*p = 0.010*
Symptom checklist	HC	LSM	11.10[a]	11.07[a]	12.07[a]
		SE	0.58	0.59	0.71
	P	LSM	17.04[a]	17.59[b]	19.40[c]
		SE	0.41	0.42	0.50
Patients vs. HC			*p < 0.001*	*p < 0.001*	*p < 0.001*

Numbers with the same superscript on one row are not statistically different from each other, after correction for multiple testing (Bonferroni stepdown method).