The etiology of functional somatic symptoms in adolescents

Janssens, Karin Anne Maria

Chapter 8

Symptom-specific associations between physiological and psychological arousal and functional somatic symptoms in adolescents

KAM Janssens, AJ Oldehinkel, JAM Hunfeld, AM Van Roon AM, JGM Rosmalen

(submitted)

ABSTRACT

We examined whether psychological and physiological hyperarousal were differentially related to two clusters of functional somatic symptoms in a subsample of 715 adolescents (mean age: 16.1 years, 51.3% girls). Linear regression analyses revealed that a cluster of headache and gastrointestinal symptoms was related to high psychological arousal during the stress test (β=0.09, p=0.04), and high HR in supine position before the test (β = 0.11, p = 0.01). A symptom cluster of overtiredness, dizziness and musculoskeletal pain was related to high psychological arousal before (β = 0.12, p = 0.01) and after (β = 0.12, p = 0.008) the stress test, and to high HRV in supine position before the test (β = 0.11, p = 0.03). None of the symptom clusters was related to HR or HRV assessed in sitting position. This study suggests that two clusters of functional somatic symptoms are differentially related to physiological and psychological arousal.

INTRODUCTION

Functional somatic symptoms (FSS), such as fatigue and chronic pain, are symptoms for which no organic pathological basis can be found. They are common during adolescence and can have a large impact on adolescents' lives (Hunfeld et al., 2002;Janssens et al., 2009). More insight into the etiology of this important health problem might aid the development of effective prevention and intervention strategies. FSS have often found to be the result of stressors (Gini and Pozzoli, 2009;Paras et al., 2009). However, how stressors come under the skin and lead to FSS remains unclear.

High physiological arousal, which is commonly defined as high sympathetic and low parasympathetic nervous system activity, has been thought to mediate the association between stressors and FSS (Tak et al., 2010). The association between physiological arousal and FSS has repeatedly been investigated in adults, but research in adolescents is scarce. Findings in both adolescents and adults are equivocal, since some studies did not find high, but low physiological arousal to be related to FSS, and others did not find an association between the two (Dietrich et al., 2011;Ebinger et al., 2006;Olafsdottir et al., 2001;Puzanovova et al., 2009;Tak et al., 2009;Tak et al., 2010;Wyller et al., 2008). Two large population based studies from our own group indicated an association between high physiological arousal and FSS in adolescents and young adults (Dietrich et al., 2011;Tak et al., 2010). Most previous studies on the association between physiological arousal and FSS examined physiological arousal during rest.

However, FSS might be stronger related to physiological arousal during stress and recovery, since FSS are often assumed to be the result of inadequate stress responses (Tak and Rosmalen, 2010).

The association between stressors and FSS might not only be the result of physiological arousal, but also of psychological arousal. Unlike the association between FSS and physiological arousal, the association between FSS and psychological arousal has been more established, since FSS have repeatedly been associated with psychological hyperarousal in adolescents (Alfven et al., 2008;Bjorling, 2009;Varni et al., 1996).

We previously found that two clusters of FSS were differentially related to the stress hormone cortisol. A cluster of headache and gastrointestinal symptoms was related to low cortisol levels during stress, and a cluster of overtiredness, dizziness and musculoskeletal pain was related to low cortisol levels after awakening (Janssens et al, in press). We hypothesized that the first cluster is related to inadequate stress responses, whereas the second cluster to difficulty in recovering from stressful situations (Janssens et al, in press). The current study was conducted to examine whether the cluster of headache and gastrointestinal symptoms was related to high physiological and psychological arousal during a stressful situation and the cluster of overtiredness, dizziness and musculoskeletal pain to high physiological and psychological arousal during recovery from that stressful situation and in rest. We studied our hypotheses in a large population sample (N =715) of adolescents, in which physiological and psychological arousal were assessed before, during and after a social stress test.

METHODS

Participants

The data were collected in a subsample of TRAILS (Tracking Adolescents' Individual Lives Survey), a large prospective population study of Dutch adolescents with bi- or triennial measurements from age 11 to at least age 25. Thus far, four assessment waves of TRAILS have been completed, running from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), September 2005 to December 2007 (T3), and September 2009 to October 2010 (T4). During T1, 2230 children were enrolled in the study (for more details about the sample selection, see (de Winter et al., 2005), of whom 1816 (81.4%) participated in T3. During T3, 744 adolescents were invited to perform a series of laboratory tasks (hereafter referred to as the experimental session) on top of the usual assessments, of whom 715 (96.1%) agreed to do so. The costly and labor-intensive nature of the laboratory tasks precluded assessing the whole sample. To increase the power to detect mental health-related differences in stress responses, adolescents with a high risk of mental health problems had a greater chance of being selected for the experimental session. High risk was defined based on three criteria: temperament (i.e., high frustration and fearfulness and low effortful control) assessed by the revised parental version of the Early Adolescent Temperament Questionnaire at baseline (Ellis, 2002); lifetime parental psychopathology assessed by a parental interview at baseline; and living in a single-parent family also assessed by the parental interview at baseline (for more information see Bouma et al., 2009). In total, 66.0% of the focus sample had at least one of the above-described risk factors; the remaining 34.0% were selected randomly from the low-risk TRAILS participants. Please note that the focus sample still represented the whole range of problems seen in a normal population of adolescents, which made it possible to reproduce the distribution in the total TRAILS sample by means of sampling weights.

Procedure

The experimental session consisted of a number of different challenges, listed here in chronological order: a spatial orienting task, a gambling task, a startle reflex task, and a social stress test. The session was preceded and followed by a 40-minute period of rest. The participants filled out a number of questionnaires at the start and end of the session. Before, during, and after the experimental session, extensively trained test assistants assessed cardiovascular measures, cortisol, and perceived stress. Measures that were used in the present study are described more extensively below. The experimental sessions took place in sound-proof rooms with blinded windows at selected locations in the participants' towns of residence. The total session lasted about three-and-a-half hours, and started between 8:00 and 9:30 am (morning sessions, 50%) or between 1:00 and 2:30 pm (afternoon sessions, 50%). The protocol was approved by the Central Committee on Research Involving Human Subjects (CCMO). All participating adolescents gave informed consent.

The social stress test

The social stress test was the last challenge of the experimental session. It involved a standardized protocol, inspired by (but not identical to) the Trier Social Stress Task (Kirschbaum et al., 1993), for the induction of mild performance-related social stress. Socio-evaluative threats are highly salient challenges for adolescents and known to be effective activators of various physiological stress systems, particularly in combination with uncontrollability; that is, in situations when negative consequences cannot be avoided (Dickerson and Kemeny, 2004). The participants were instructed to prepare a 6-minute speech about themselves and their lives and deliver this speech in front of a video camera. They were told that their videotaped performance would be judged on content of speech as well as on use of voice and posture, and ranked by a panel of peers after the experiment. The participants had to speak continuously for the whole period of 6 minutes. The test assistant watched the performance critically, and showed no empathy or encouragement. The speech was followed by a 3-minute interlude in which the participants were not allowed to speak. During this interval, which was included to assess cardiac autonomic measures that were not affected by speech, the participants were told that they had to wait for a moment because of computer problems, but that the task would continue as soon as these problems were solved. Subsequently, they were asked to perform mental arithmetic. The participants were instructed to repeatedly subtract the number 17 from a larger sum, starting with 13278. A sense of uncontrollability was induced by repeated negative feedback from the test assistant (e.g., ‘‘No, wrong again, begin at 13278’’; ‘‘Stop wiggling your hands’’; ‘‘You are too slow, we are running behind schedule’’). The mental arithmetic challenge lasted for 6 minutes, again followed by a 3-minute period of silence, after which the participants were debriefed about the experiment.

Measures

Heart rate recordings

HR was recorded at the start of the experimental session (after 40 min of rest). A three-lead electrocardiogram was registered using 3M/RedDot Ag/AgCl electrodes (type 2255, 3M Health Care, Neuss, Germany), while the participant was subsequently sitting (300 s), lying (300 s), and standing (300 s), while breathing spontaneously. With the same procedure, heart rate was recorded in sitting position during and after the social stress test, in seven blocks: pretest (300 s), speech preparation (420 s), speech (360 s), silent interlude after speech (180 s), mental arithmetic (360 s), silent interlude after mental arithmetic (180 s), and posttest (300 s). The HR signals were amplified with a BIOPAC Amplifier-System (MP100, Goleta, CA), and filtered before digitization at 250 samples/second. Dedicated software (i.e. PreCARSPAN, for more details see (Dietrich et al., 2007)) was used to check signal stationarity, to correct for artifacts, to detect R-peaks, and to calculate the interbeat-interval (IBI) between two heartbeats. Blocks were considered invalid if they contained artifacts with a duration of more than 5 s, if the total artifact duration was more than 10% of the registration, or if the block length was less than 100 s (invalid blocks before test sitting: $N = 38$; before test supine: n = 39, before test standing $N = 41$; pretest: $N = 15$, preparation: $N = 28$, speech: $N = 27$, interlude after speech: $N = 35$, mental arithmetic: $N = 29$, interlude after mental arithmetic: $N = 31$, posttest: $N = 32$). HR is inversely related to IBI by the equation HR = 60000/IBI. HR was defined as the number of beats per minute (bpm). Calculation of the heart rate variability (HRV) was performed by power spectral analysis in the CARSPAN software program (Mulder, 1988) using estimation techniques based on Fourier transformations of IBI series (Robbe et al., 1987). HRV-HF was defined as the power in the high-frequency (0.15–0.40 Hz) band, which is associated with the respiratory cycle, and expressed in ms^2. HRV-HF is mainly determined by parasympathetic nervous system activity, whereas HR is determined by a combination of parasympathetic and sympathetic nervous system activity (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Since we defined hyperarousal as high sympathetic and low parasympathetic nervous system activity in this study, low HRV-HF reflects hypoarousal, and high HR hyperarousal. HR recordings in sitting and supine position at the start of the experiment were used to indicate HR and HRV-HF during rest. It is good to note that these measures might have been influenced by anticipatory stress. The calculation of HR and HRV-HF during stress was based on HR recordings during the 3-minute interludes directly following the speech and mental arithmetic tasks, when the participants were not allowed to speak. HR recordings during the speech and arithmetic performance itself were not used, since adolescents spoke during those moments, and speech is known to interfere with analysis of HRV-HF (e.g. Bernardi et al., 2000;Sloan et al., 1991). The stress level remained relatively high during the interludes, because the participants expected that they had to continue any moment. Nevertheless, it was probably lower than during speech and mental arithmetic performance and might not reflect the maximum response. For the HR and HRV-HF during recovery, the HR recordings assessed during the posttest were used.

Psychological arousal

Psychological arousal was assessed by means of the Self-Assessment Manikin (SAM), a non-verbal pictorial assessment technique to measure person's affective reactions to a stimulus (Bradley and Lang, 1994). The subjective intensity of the feelings of arousal and unpleasantness could be indicated by choosing one out of nine ordered pictures. The pictures were translated into a nine-point scale (range 1-9) in such a way that high scores represented high levels of arousal and unpleasantness. Feelings of arousal and unpleasantness in rest were assessed when the adolescents moved from supine to standing position at the beginning of the experiment. Feelings of arousal and unpleasantness during the social stress test were assessed directly after this test, with a reference to the test ("How did you feel during this test?"). Posttest feelings of arousal and unpleasantness were measured at the end of the experimental session (40 minutes after the social stress test). A mean item score of perceived arousal and unpleasantness was computed for each assessment point to reflect psychological arousal.

Functional somatic symptoms

FSS were measured by the Somatic Complaints scale of the Youth Self-Report (Achenbach et al., 2003). This scale contains items referring to somatic complaints without a known medical cause or without obvious reason. The adolescents could indicate whether they experienced these complaints on a three point scale with 0 = never, 1 = sometimes or a little bit, or 2 = often or a lot. We used the single items overtiredness, dizziness and headache from this scale. Furthermore, a mean gastrointestinal symptom item score was computed out of the items stomach pain, vomiting and nausea. Since the Youth Self-Report did not include musculoskeletal symptoms, those symptoms were assessed by asking participants questions about how often they experienced pain in their neck, back, shoulders, arms and legs during the past three months. Questions were rated on a 7-point measurement scale with response categories: 'Not at all', 'Less than once a month', 'Once a month', 'Two to three times a month', 'Once a week', 'Two to six times a week', and 'Almost every day'. A mean item score of musculoskeletal pain was created out of the five items and divided by three-and-a-half to rescale to the YSR. Based upon a previously performed factor analysis (Janssens et al, in press), symptoms were divided into two symptom clusters, one consisting of headache and gastrointestinal symptoms and the other consisting of overtiredness, dizziness and musculoskeletal pain. Mean item scores, which could range from 0-2, were computed for each cluster.

Other variables

The covariates gender, depression, body mass index (BMI), smoking, physical activity level, medication use (i.e. psychopharmaca and sympathicomimetic drugs), which are known to be potential confounders in the relationship between HR, HRV-HF and FSS (Tak et al., 2009), were used in this study. Depression was measured using the mean item score of 13 depression items from the Youth Self-Report (Cronbach's alpha = .75, see Janssens et al., 2010). Physical activity level and smoking frequency were assessed as part of the regular T3 measurements, the questionnaire was filled out at school, on average 3.1 month (*SD* = 5.1) before the experimental session. Smoking was defined as being a daily smoker (yes or no). Physical activity level was operationalized as the number of days of a week an adolescent was physically active for at least one hour. The use of medication (i.e. psychopharmaca and sympathicomimetic drugs) was assessed by means of a checklist on current medication use administered at the beginning of the stress experiment. During the school assessments, height and weight were measured by trained test assistants. BMI is defined as the weight in kilograms divided by the height in meters squared.

Statistical analyses

Linear regression analyses were used to examine whether the two clusters of FSS were related to psychological arousal before, during or after the stress test. These analyses were adjusted for gender. Moreover, the clusters of FSS were simultaneously included as predictors in the model, so effects were adjusted for each other. Linear regression analyses were also performed to examine whether particular FSS were related to HRV-HF or HR before, during or after the social stress test. These analyses were adjusted for the potential confounders gender, medication use (i.e. psychopharmaca and sympathicomimetic drugs), smoking, BMI, physical activity level, depression and the other cluster of FSS. We examined whether the results found in our subsample deviated from the results that would be found in the general population by repeating the analyses while using sampling weights to correct for the oversampling on adolescents with a high risk of mental health problems.

RESULTS

Descriptive statistics

Characteristics of the sample, clusters of FSS, perceived stress, physiological measures and confounders are shown in Table 1. Of all adolescents, 54.9% reported having experienced headache or gastrointestinal symptoms, and 74.4% overtiredness, musculoskeletal pain or dizziness at least once during the past six months. Mean item scores of the clusters were comparable (Table 1). The HRV-HF was highest and HR lowest when assessed in supine position before the stress test, and HRV-HF was lowest and HR highest when assessed in sitting position before the stress test. Pearson correlations between the HRV-HF measures and between HR measures are shown in Table 2. None of the psychological arousal measures was significantly related to HR or HRV-HF.

Table 1. Sample characteristics

	Valid *N*	Mean (*SD*) or percentages
Female	715	49.1%
Age	715	16.1 (0.60)
LN HRV-HF rest (supine)[a]	676	7.9 (1.3)
LN HRV-HF rest (sitting)[a]	677	6.7 (1.2)
LN HRV-HF stress (sitting)[a]	648	7.1 (1.1)
LN HRV-HF recovery (sitting)[a]	687	7.0 (1.1)
HR rest (supine)[b]	684	64 (10)
HR rest (sitting)[b]	685	76 (11)
HR stress (sitting)[b]	651	72 (10)
HR recovery (sitting)[b]	694	71 (10)
Psychological arousal (rest)	705	2.9 (1.2)
Psychological arousal (stress)	714	4.5 (1.6)
Psychological arousal (recovery)	699	2.6 (1.3)
Cluster of gastrointestinal symptoms and headache[c]	680	0.39 (0.43)
Cluster of overtiredness, dizziness and musculoskeletal pain[d]	679	0.35 (0.36)
BMI	696	21.3 (3.29)
Depression[e]	695	0.25 (0.24)
Medication use[f]	715	4.3%
Smoking (daily)	699	17.3%
Physical activity level[g]	696	3.3 (2.1)

[a]ln(ms²); [b]beats per minute; [c]mean item score of the cluster of headache and gastrointestinal symptoms which could range from 0-2; [d]mean item score of the cluster of overtiredness, dizziness and musculoskeletal symptoms, which could range from 0-2; [e]mean item score of depression which could range from 0-2; [f]use of psychopharmaca and sympathicomimetics drugs; [g]mean number of days a week on which at least one hour physical active; LN= natural logarithmic transformed

Table 2. Correlation between HRV-HF and HR during rest, stress, and recovery

	LN HRV-HF rest (supine)	LN HRV-HF rest (sitting)	LN HRV-HF stress (sitting)	LN HRV-HF recovery (sitting)	HR rest (supine)	HR rest (sitting)	HR stress (sitting)	HR recovery (sitting)
LN HRV-HF rest (supine)	X							
LN HRV-HF rest (sitting)	0.57*	X						
LN HRV-HF stress (sitting)	0.68*	0.77*	X					
LN HRV-HF recovery (sitting)	0.64*	0.79*	0.85*	X				
HR rest (supine)	-0.53*	-0.52*	-0.54*	-0.49*	X			
HR rest (sitting)	-0.33*	-0.68*	-0.57*	-0.55*	0.80*	X		
HR stress (sitting)	-0.37*	-0.56*	-0.65*	-0.59*	0.79*	0.83*	X	
HR recovery (sitting)	-0.35*	-0.57*	-0.62*	-0.65*	0.75*	0.82*	0.89*	X

**All p-values <0.001; HRV-HF= heart rate variability in the high frequency band; LN= natural logarithmic transformed HR= heart rate*

Psychological arousal during stress and recovery and particular FSS

Linear regression analyses revealed that the cluster of headache and gastrointestinal symptoms was positively related to psychological arousal during the stress test (Table 3). The cluster of overtiredness, dizziness and musculoskeletal pain was positively related to psychological arousal during rest and during recovery from the stress test. The association between this symptom cluster and psychological arousal during stress pointed in the same direction, but just failed to reach significance. These analyses were all adjusted for gender. When we repeated these analyses using sampling weights to correct for the oversampling on adolescents with a higher risk of mental health problems, the results remained essentially the same. In general the associations became a bit stronger and the association between the cluster of overtiredness, dizziness and musculoskeletal pain and psychological arousal during stress became statistically significant ($\beta = 0.10$, $p = 0.02$).

Table 3. Psychological arousal during rest, stress and recovery and clusters of FSS

	Rest Psychological arousal	**Stress Psychological arousal**	**Recovery Psychological arousal**
Headache and gastrointestinal symptoms	-0.02 (0.70)	**0.09 (0.04)**	-0.01 (0.80)
Overtiredness, dizziness and musculoskeletal pain	**0.12 (0.01)**	0.08 (0.06)	**0.12 (0.008)**

B (p-value); bold numbers indicate significant effects; all analyses are adjusted for gender

Physiological arousal during stress and recovery and particular FSS

The cluster of overtiredness, dizziness and musculoskeletal pain was related to high HRV-HF and marginally significant related to low HR measured in supine position prior to the stress test (Table 4). The cluster of headache and gastrointestinal symptoms showed the opposite pattern and was related to high HR, and marginally significant related to low HRV-HF in supine position prior to the stress test (Table 4). None of the clusters of FSS was related to HR or HRV-HF assessed in sitting position, neither before, nor during, nor after the stress test (Table 4). Again, when we repeated these analyses using sampling weights, the results remained essentially the same (i.e. significant result remained significant and nonsignificant results nonsignificant).

Table 4. HRV-HF and HR during stress and recovery and clusters of FSS

	LN HRV-HF rest (supine)[a]	HR rest (supine)[b]	LN HRV-HF rest (sitting)[a]	HR rest (sitting)[b]	LN HRV-HF stress (sitting)[a]	HR stress (sitting)[b]	LN HRV-HF recovery (sitting)[a]	HR recovery (sitting)[b]
Headache and gastrointestinal symptoms	-0.08 (0.08)	**0.12 (0.01)**	0.01 (0.80)	0.05 (0.24)	-0.02 (0.64)	0.05 (0.29)	0.03 (0.45)	0.04 (0.34)
Overtiredness, dizziness and musculoskeletal pain	**0.11 (0.03)**	-0.09 (0.10)	0.00 (0.97)	-0.01 (0.80)	0.04 (0.43)	-0.03 (0.63)	-0.02 (0.72)	0.02 (0.65)

B (p-value); bold numbers indicate significant effects; All analyses are adjusted for gender, medication use, smoking, exercise frequency, body mass index, and depression; LN= natural logarithmic transformed; [a]ln(ms²); [b]mean interbeat-interval in ms

DISCUSSION

This study revealed that a cluster of headache and gastrointestinal symptoms is related to psychological hyperarousal during social stress and to physiological hyperarousal (i.e. high HR) in supine position. A cluster of overtiredness, dizziness, and musculoskeletal pain was related to psychological hyperarousal before, during and after social stress and to physiological hypoarousal (i.e. high HRV-HF) in supine position. None of the symptom clusters was related to physiological arousal assessed in sitting position, neither before, nor during nor after social stress.

A strength of our study is that we examined the associations in a relatively large sample, which increased the robustness of our findings. Furthermore, using sampling weights enabled to demonstrate that findings could be generalized to the general population of adolescents. Moreover, the assessment of a wide range of variables enabled us to adjust for many potential confounders. One might wonder whether adjusting for depression should be considered overadjustment. We did not find evidence for that, since results remained essentially the same when we did not adjust for depression (results available upon request). A final strength is that stress measures were repeatedly assessed before, during and after a social stress test, which allowed examination of whether one cluster of FSS was closer related to stress indicators during a stressful situation, and the other cluster to stress indicators during recovery from that stressful situation.

Apart from these strengths there are also several limitations of our study. One limitation is that, despite the fact that we lumped the FSS into two symptoms clusters, many analyses were performed. This might have increased the risk of chance findings. However, since we were interested in general stress response patterns and not in specific associations, we considered false positive findings less problematic than false negative ones. Another limitation is that the pain questionnaire did not explicitly state that musculoskeletal pain symptoms had to occur without a medical cause. Some musculoskeletal pain symptoms might thus have been due to medically explained conditions, like sport injuries. However, we should be careful in distinguishing between medically unexplained and medically explained symptoms, since it perpetuates mind-body dualism and doctors often disagree about whether a particular symptom is medically unexplained or not (Dimsdale et al., 2009).

In line with previous research, this study shows that FSS are related to psychological hyperarousal (Alfven et al., 2008;Bjorling, 2009;Varni et al., 1996). In addition to previous research, it shows that the nature of this association depends on the investigated symptom cluster. The cluster of headache and gastrointestinal symptoms was positively related to high psychological arousal during the stress test only. Combined with the previously found association of this symptom cluster with low cortisol levels during the same stress test (Janssens et al, in press), this finding supports our assumption that headache and gastrointestinal symptoms are related to an inadequate stress response. The cluster of overtiredness, dizziness and musculoskeletal pain was related to high psychological arousal throughout the stress test, which suggests that this symptom cluster is associated with long lasting psychological arousal. This might be related to the finding that this cluster was associated with low cortisol levels after awakening, a daily phenomenon, but not with cortisol levels during stress (Janssens et al, in press).

Unlike psychological arousal, physiological arousal was not differentially related to the symptom clusters throughout the stress experiment. However, such differences might become apparent when heart rate would be recorded in supine instead of sitting position during the stress experiment. That FSS were associated with physiological arousal in supine but not in sitting position might be explained by the fact that the basic bodily state of arousal is more accurately assessed in supine position due to a lack of orthostatic load and (often) a lack of visual input (Sipinkova et al., 1997). It is good to note that the before-mentioned large population-based cohort studies that found associations between FSS and physiological arousal also assessed physiological arousal in supine position (Dietrich et al., 2011;Tak et al., 2010). We found indications for a distinction between symptom clusters when examining physiological arousal in supine position. The cluster of headache and gastrointestinal symptoms was associated with physiological hyperarousal (i.e. high HR, trend for low HRV-HF), whereas the cluster of overtiredness, dizziness and musculoskeletal pain was associated with physiological hypoarousal (i.e. high HRV-HF, trend for low HR).

That the association between FSS and physiological arousal assessed in supine position was symptom-specific might explain the divergence of prior findings on associations between FSS and physiological arousal. Overtiredness, dizziness and musculoskeletal pain may have been dominant in studies that found an association between FSS and hypoarousal. Headache and gastrointestinal symptoms may have been dominant in studies that found an association between

FSS and hyperarousal. However, a meta-analysis in adults did not find evidence for this assumption, since it found that neither irritable bowel syndrome, nor chronic fatigue syndrome, nor fibromyalgia was significantly related to HRV-HF (Tak et al., 2009). This might have been due to the low quality of the included studies (Tak et al., 2009). Nevertheless, the assumption does hold for a study of our own group, which found a negative association between a sum score of FSS and HRV-HF at the first assessment wave of TRAILS (Dietrich et al., 2011). This sum score of FSS was largely determined by headache and gastrointestinal symptoms, since overtiredness and dizziness were rare at this wave (Janssens et al., 2009), and musculoskeletal pain symptoms were not included. Interestingly, the association found in the first-wave of the TRAILS study was equal (β -0.09) to the current (i.e. third-wave) association of headache and gastrointestinal symptoms with HRV-HF. Contrary to the current one, the previous association was statistically significant, due to a larger sample size in the previous study.

In conclusion, this study provides evidence that FSS can be subdivided into two symptom clusters that are differentially related to psychological and physiological arousal. To gain more insight in the exact etiology of these two symptom clusters, more research is necessary to investigate whether other factors, like the activity of the immune system or the amount of stress exposure, are also differentially related to these clusters.