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Comparing Autonomic Nervous System Function in Patients with Functional Somatic Syndromes, Stress-related Syndromes and Healthy Controls

Maaike VAN DEN HOUTE[1,2,3], PhD* maaike.vandenhoute@kuleuven.be, ORCID: 0000-0002-9432-0333
Indra RAMAKERS[1], MSc* indra.ramakers@uhasselt.be, ORCID: 0000-0003-3588-9594
Lukas VAN OUDENHOVE[2,3,4], MD, PhD lukas.vanoudenhove@kuleuven.be, ORCID: 0000-0002-6540-3113
Omer VAN DEN BERGH[5], PhD omer.vandenbergh@kuleuven.be, ORCID: 0000-0001-6394-7363
Katleen BOGAERTS[1,5], PhD Katleen.bogaerts@uhasselt.be, ORCID: 0000-0002-0247-0941

*Shared first authorship

[1]REVAL – Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium
[2]Laboratory for Brain-Gut Axis Studies (LABGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium
[3]Leuven Brain Institute, KU Leuven, Leuven, Belgium
[4]Cognitive & Affective Neuroscience Lab (CANLab), Department of Psychological and Brain Sciences, Dartmouth College; Hanover, New Hampshire, USA.
[5]Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium

Corresponding author:
Maaike Van Den Houte, maaike.vandenhoute@uhasselt.be
REVAL, Wetenschapspark 7, B-3590 Diepenbeek, Belgium

Abstract

Background: The goal of this study was to examine autonomic nervous system function by measuring heart rate (HR), heart rate variability (HRV), skin conductance levels (SCL), and peripheral skin temperature (ST) in response to and during recovery from psychosocial stressors in patients with functional somatic syndromes (FSS; fibromyalgia and/or chronic fatigue syndrome), stress-related syndromes (SRS; overstrain or burn-out), and healthy controls (HC).

Methods: Patients with FSS (n=26), patients with SRS (n=59), and HC (n=30) went through a standardized psychosocial stress test consisting of a resting phase (120s), the STROOP color word task (120s), a mental arithmetic task (120s) and a stress talk (120s), each followed by a 120s recovery period. HR, HRV, SCL, and ST were monitored continuously.

Results: Average HR and SCL were higher, and HRV was lower, in both patient groups compared to HC during rest ($0.50 < \text{Cohen's } d < 0.97$). A larger SC response to psychosocial stress was found in FSS compared to HC ($d = 0.71$). However, HR increased less during psychosocial stress and showed a smaller reduction during recovery in both patient groups compared to HC ($0.68 < d < 0.98$). HRV was lower in both patient groups compared to HC during recovery ($0.91 < d < 0.98$). There were no differences in ST levels or responses between groups.

Conclusions: Our results indicate a dominance of the sympathetic nervous system in both patient groups compared to controls, suggesting that autonomic nervous system dysfunction is a transdiagnostic feature for stress-related and functional somatic syndromes.

Key words: Burn-out; Fibromyalgia; Chronic Fatigue Syndrome; Autonomic nervous system; psychosocial stressor

List of abbreviations

ANS: autonomic nervous system

FDR: False discovery rate

FSS: Functional somatic syndromes

HC: Healthy controls

HR: Heart rate

HRV: Heart rate variability

NVAB: Netherlands Society of Occupational Medicine

RMSSD: root mean square of successive differences between heartbeats

pNN50: percentage of consecutive heartbeat intervals with a difference of duration > 50ms

SCL: Skin conductance levels

SRS: Stress-related syndromes

ST: Skin temperature

1. Introduction

About 40-49% of primary health care patients and up to 76% of high health care users report at least one somatic symptom like headaches, dizziness, shortness of breath, fatigue, muscle aches, nausea, and gastrointestinal symptoms which cannot be (fully) explained by well-known organic diseases [1,2]. These bodily symptoms are often transient and benign, but can also occur in the context of stress-related syndromes (SRS) or as clusters of persistent somatic symptoms in a more chronic and debilitating form, in the literature often referred to as functional somatic syndromes (FSS) [3]. SRS can be defined as physical and psychological symptom clusters as a consequence of experiencing chronic stress / strain, and they are often studied in a work place setting [4]. Prime examples are overstrain and burnout. Overstrain can be seen as a precursor for burnout and is characterized by symptoms of disturbed or restless sleep, irritability, emotional lability, not being able to relax, and cognitive problems persisting for more than 3 months. When symptoms persist for more than 6 months and fatigue and exhaustion become dominant, the term burnout is appropriate [5]. SRS are conceptually related to the DSM-5 diagnosis *adjustment disorder* but can be differentiated from this disorder by the lack of specific and identifiable stressor that is required for the diagnosis of adjustment disorder.

FSS, on the other hand, is an overarching term for chronic and debilitating medical conditions that cannot be fully explained by organic or structural abnormalities. Prime examples are fibromyalgia and chronic fatigue syndrome. Fibromyalgia is a chronic widespread pain condition characterized by generalized pain, fatigue, sleep disturbance, cognitive problems, and increasing somatic complaints [6]. Chronic fatigue syndrome is characterized by severe fatigue and post-exertional malaise as well as impairments in concentration and short-term memory, sleep disturbance, pain, headaches, and sore throat or tender lymph nodes [7]. Both are multi-faceted and challenging conditions with considerable overlap in clinical symptoms, causes and treatments, and comorbidity is high [8,9]. While the exact underlying mechanisms of FSS

remain unclear, most researchers agree that FSS are the result of complex biopsychosocial interactions [10].

Apart from being a requirement for SRS, it is believed that chronic stress also plays an important role in the development and maintenance of FSS. Chronic stress seems to be a risk factor for the development of FSS [11-14], and ecological momentary assessment studies show that more stress leads to more symptoms in daily life in FSS [15,16]. One aspect that is thought to mediate this relationship is chronic dysregulation of the body's autonomic nervous system (ANS). The ANS prepares the body to cope with stressors, causing for instance elevated heart rate (HR), blood pressure or skin conductance levels (SCL). The ANS consists of the sympathetic nervous system – activating an individual for perceived threat – and parasympathetic nervous system – facilitating homeostasis of the body by energy conservation – working complementary with each other [17]. Parasympathetic activity is often assessed by measures of heart rate variability (HRV). Although results are inconsistent, sympathetic predominance (i.e., low HRV, high HR) is reported in the majority of studies investigating ANS dysfunction in FSS (see [18-21] for reviews). Because psychosocial stress seems to exacerbate symptoms in daily life in FSS [15,16], experimental studies investigating ANS reactivity to and recovery from a psychosocial stressor are of particular interest. These studies generally found less responsivity to stress in FSS compared to HC, demonstrated by a weaker increase of HR in response to stress and a smaller drop in HR upon recovery [22,23]. Moreover, a greater increase in the low-frequency to high-frequency in heart rate fluctuations ratio— a marker of the balance between sympathetic and parasympathetic activity—in response to a stressor, with limited recovery, was observed in FSS, indicating sympathetic predominance. [24]. However, another study found no differences in RMSSD and SDNN between patients with fibromyalgia and HC during or after cognitive stress [25]. While most studies only focused on HR(V), two studies additionally investigated SCL during stress. For instance, a significantly larger increase

in SCL in response to stress in fibromyalgia [26] and a continued increase of SCL upon recovery in chronic fatigue syndrome [23] have been reported.

Despite these important findings, ANS activity in FSS has never been compared to ANS activity in stress-related mental health syndromes such as burnout and overstrain. There is a growing interest in the role of ANS function in chronic work stress and burnout, yet the literature remains limited and inconclusive. Two systematic reviews on biological correlates of clinical burnout found inconsistent results for measures of sympathetic activity [27,28] although two recent studies did report higher HR in daily life [29] and smaller increases in plasma levels of epinephrine following a psychosocial stressor [30] in clinical burnout. Similarly, results on parasympathetic activity vary, with some studies showing lower resting HRV in burnout patients compared to HC [31-33], while others reported no differences [34]. However, these variable results can very likely be attributed to methodological issues, such as variability in the definition of burnout that is used [27,28].

In sum, while the interest in ANS (dys)function in both FSS and SRS is rising, its exact role is unclear and studies report varying results. Moreover, existing studies in both patient groups suffer from some limitations. First, most studies are limited to measuring only one single parameter of ANS function. Second, most studies measure ANS function either in uncontrolled naturalistic settings or in response to a standardized stressor in the lab, but rarely include recovery from a stressor as a main outcome variable. This is in contrast with the fact that delayed recovery from exertion is a prime symptom of chronic fatigue [35]. Finally, while ANS dysfunction has been proposed as an underlying mechanism of both FSS and SRS, ANS function has not been compared between the two groups. In the current study, we used a multiparameter procedure and focused on both responses to and recovery from psychosocial stress to investigate ANS reactivity in a FSS and SRS sample. This method was also used in Smets et al. [36] to assess ANS activity in individuals with acute (less than 3 months) stress-

related bodily symptoms. We measured HR, HRV, SCL, and skin temperature (ST) – four commonly investigated, well-accepted measures of physiological stress responses [37] - at rest, during, and after stress inducing tasks in patients diagnosed with FSS, SRS, and HC. We aimed to investigate 1) differences between the 3 groups in average HR(V), SCL, and ST during rest (baseline), 2) differences in reactivity between the 3 groups (how HR(V), SCL, and ST change from baseline to stress), and 3) differences in recovery between the 3 groups (how HR(V), SCL, and ST change from stress to recovery).

2. Methods

2.1.Study setting and sampling

Participants with FSS (chronic fatigue syndrome or fibromyalgia) or SRS were outpatients at Tumi Therapeutics, a multidisciplinary diagnostic and treatment center that specializes in stress-related and functional somatic syndromes (Heusden-Zolder, Belgium). All individuals with chronic fatigue syndrome were diagnosed at the Multidisciplinary Diagnostic Center for chronic fatigue syndrome at University Hospitals Leuven using the 1994 Center for Disease Control and Prevention criteria [7] after thorough medical and psychiatric evaluation. Patients with fibromyalgia were diagnosed by a licensed rheumatologist and fulfilled the 2010 American College of Rheumatology criteria [38]. Individuals with SRS were diagnosed by a clinical psychologist at Tumi Therapeutics. This group included patients with overstrain and patients with burnout, both diagnosed according to the multidisciplinary guidelines for overstrain and burn-out for first line professionals of the Netherlands Society of Occupational Medicine [5,39,40]. According to these guidelines, overstrain is characterized by the following symptoms: disturbed or restless sleep, irritability, not being able to stand commotion/ noise, emotional lability, feeling stressed or rushed, not being able to relax, and difficulty concentrating and/or forgetfulness with a duration of more than 3 months. Burnout is defined as symptoms of overstrain persisting for more than 6 months, with prominent feelings of fatigue

and exhaustion. The patient experiences significant limitations in professional and/or social functioning [5]. The same criteria for overstrain and burnout were used in recent studies by our group [14,41]. For all patient groups, patients with comorbid psychiatric disorders – other than somatization, somatoform disorder following the DSM-IV criteria for the FSS group – were excluded from participation. The presence of psychiatric disorders was assessed through clinical observation by a trained clinician during the intake procedure as well as with the Simplified Mini International Neuropsychiatric Interview (MINI-s [42]). It was ensured that patients with comorbid depression, anxiety disorders, and post-traumatic or acute stress disorders were not included in the study sample. However, given the conceptual and diagnostic overlap between adjustment disorder and overstrain/burnout, and the fact that the criteria for adjustment disorder are not administered in the MINI-S, included patients may have fulfilled the criteria for adjustment disorder. Patients with concurrent organic diseases were excluded based on doctor's reports, physical examination, and medical tests.

Since there is overlap between the diagnostic criteria for burnout and chronic fatigue syndrome, we cannot exclude the possibility that some FSS patients also fulfilled the criteria for SRS. However, none of the patients received both diagnoses, as the CFS diagnosis takes precedence over burnout when its more stringent criteria are met.

HC were recruited through flyers and social media and were recruited by means of frequency sampling, a technique that promotes comparability between patient and healthy control groups by selecting healthy control participants in such a way that the frequency distribution of certain characteristics (age, gender, BMI) matches that of the patient sample. Specifically, HC were only recruited if sufficient patients from the same age range (18–20, 21–25, 26–30 years, and so on), educational level, BMI (+-3), and of the same gender had participated. To ensure that the HC group consisted of physically and mentally well individuals, HC were selected based on their scores on the Checklist for Symptoms in Daily life (CSD [43])

and the Dutch trait version of the Positive and Negative Affect Schedule (PANAS-trait [44]). Only participants with a score equal or lower than 75 on the CDS and equal or lower than 21 on trait negative affect were included in the study. These cut-off scores represent the upper quartiles in a large healthy sample and show favorable discriminative power [45-47]. Other exclusion criteria for all participants were any self-reported medical conditions, such as cardiovascular, gastrointestinal, neuromuscular, pulmonary, or psychiatric conditions, and pregnancy. Data collection took place between January 2017 and July 2019. The study design was not pre-registered.

2.2.Procedure

As part of their intake procedure at Tumi Therapeutics, all patients filled out questionnaires and completed an examination assessing physiological parameters. All included patients provided written informed consent for the use of their data for research purposes during the intake session with their psychotherapist. The next session, typically 1-2 weeks after the intake session, consisted of the physiological assessment including a standardized stress test. Healthy controls provided informed consent, filled out questionnaires, and participated in the standardized stress test in a single test session. All participants were instructed to refrain from drinking caffeinated drinks the day of, and alcoholic beverages from the evening before, the physiological assessment. Participants were asked not to smoke in the hours before the physiological assessment, but were instructed to take medication as usual. In case of acute illness, the assessment was postponed. The standardized stress test consisted of a resting phase (120s), a Stroop Color Word task (120s), a recovery phase (120s), a Mental Arithmetic Task (120s), a recovery phase(120s), a Stress talk (120s), and a recovery phase (120s) (Figure 1). This test is built in the BioTrace+ software. All tasks were given in the same order for all participants. During the entire psychophysiological examination, patients were instructed to sit on a chair with their feet on the ground, back against the backrest and hands placed on their lap.

During the Stroop Color Word task, color words (“red”, “yellow”, “blue” or “green”) were written in an incongruent ink color. Participants were instructed to name the print color of each word while ignoring the meaning of the printed word as quickly and accurately as possible. Mistakes were pointed out to the participant. Although speed and accuracy were not measured, the experimenter instructed them to go as fast and accurate as possible with the intention to induce psychosocial stress. For the second and third stressor, participants were instructed to close their eyes. The mental arithmetic task consisted of backwards counting in steps of 7 starting from 1081. Participants were instructed to say each answer out loud. When a mistake was made, participants were instructed to start over. They were instructed to perform the task as quickly and accurately as possible. The final stressor was a stress talk. During this task, participants talked about a stressful life experience and were prompted to describe their thoughts and feelings during this event. Each stressor was followed by a 2-minute recovery period, in which participants were instructed to close their eyes whilst relaxing music was being played.

2.3.Instruments

HR, HRV, SCL, and ST were continuously measured during the standardized stress test using the NeXus 10 MK II hardware (MindMedia, Herten, The Netherlands). HR was measured at a sampling frequency of 128 Hz using a blood volume pulse sensor based on photoplethysmography, attached to the ring-finger. This sensor measures blood flow changes induced by heartbeats using light-based technology. Average RMSSD (root mean square of successive differences between heartbeats) and pNN50 (percentage of consecutive heartbeat intervals with a difference of duration more than 50ms), both reflecting parasympathetic activity and valid to use for short recordings [48-51], were extracted per phase from the HR data as time-domain measures of HRV. Only time-domain measures of HRV were extracted due to the relatively short measurement periods. SCL was measured with electrodes attached

to the distal phalanx of the middle and index fingers at 32 Hz. Lastly, ST was measured at 32 Hz by attaching a thermistor to the distal phalanx of the little finger. The thermistor was a small point probe protected by tape to avoid interference by breathing-related air flow. All sensors were attached to fingers of the nondominant hand and secured at least 15 minutes before the onset of the experiment, so that participants could habituate to the equipment and adjust their position accordingly. Since motion artifacts may occur, all participants were instructed to keep their hands still. Physiological data was streamed to a PC monitor during the experiment. The data was visually inspected offline afterwards using BioTrace+ software (MindMedia, Herten, The Netherlands), and motion artifacts were removed.

Patients filled out a questionnaire battery at the onset of their trajectory at the treatment center. Scores on a selected number of questionnaires are reported here as to better characterize the patient sample:

- The Quality of Life in Depression Scale is a quality of life measure for individuals with mental health problems [52]. The scale consists of 34 yes / no items (coded 0 -1) with higher values indicating a higher quality of life.
- The Symptom Checklist – 90 consists of 90 items (scored 1-5 on a Likert scale) measuring a broad range of symptoms of psychopathology [53]. Here, we report scores on the depression, anxiety, and somatic symptoms subscales, as well as the total score, which is considered a measure of general psychopathology.
- The Traumatic Experiences Checklist evaluates the occurrence and impact of different types of traumatic experiences [54]. In this study, the total number of encountered experiences (number of items coded “yes” out of the 29 listed experiences) was used as a measure of adverse experiences.

2.4. Statistical analysis

Average HR, HRV, SC, and ST levels were calculated for the 7 phases (resting phase, the Stroop task, recovery 1, the math task, recovery 2, stress talk, and recovery 3). If more than 1/3rd of the data within a phase were missing due to motion artifacts, the whole phase was considered missing. See supplementary table 1 for an overview of missing data. HR, HRV (pNN50, RMSSD), SCL, and ST were not normally distributed and consequently BoxCox transformed before analysis. Five different covariance pattern models (i.e. marginal linear mixed models, repeated measure models in which the covariance structure of the correlated residuals for the within-subject factor is modeled instead of using random effects as is the case in typical linear mixed models) were performed on HR, SCL, and ST as dependent variables in separate models and the different groups (FSS, SRS, and HC) and phase (rest, Stroop, Stroop recovery, Mental Arithmetic Task, Mental Arithmetic Task recovery, Stress talk, Stress Talk recovery) as independent variables. In order to investigate the research questions, average HR/SCL/ST during the different phases were compared to each other in planned contrasts: 1) rest in FSS vs. HC, FSS vs. SRS, and SRS vs. HC, 2) the difference between stress (average of the three stress phases) and rest in FSS vs. HC, FSS vs. SRS, and SRS vs. HC, 3) the difference between recovery (average of the three recovery phases) and stress (average of the three stress phases) in FSS vs. HC, FSS vs. SRS, and SRS vs. HC. Because of the large effects of verbal activities on HRV [55], we selected only data from the silent periods for the HRV parameters (baseline and the recovery phases). The following planned contrasts were calculated for pNN50 and RMSSD: 1) rest in FSS vs. HC, FSS vs. SRS, and SRS vs. HC, and 2) recovery in FSS vs. HC, FSS vs. SRS, and SRS vs. HC. A false discovery rate (FDR) correction was applied on the p-values of the planned contrasts to correct for multiple testing within each outcome measure – reported p-values are FDR-corrected. An FDR correction is a statistical adjustment method used to decrease the number of false positives in case of multiple statistical tests, by controlling

the expected proportion of false positives among all rejected null hypotheses. All analyses were carried out with SAS 9.4 (SAS Institute, Cary, NC, USA). Prism 9 was used to create the figures.

2.5. Ethical considerations

The study was approved by the Social and Societal Ethics Committee of KU Leuven, Belgium (S5890) and all participants provided written informed consent. All patients gave consent to the use of their pseudonymized data for research purposes.

3. Results

3.1. Sample characteristics

Our total sample consisted of a total of 115 white participants of Belgian nationality (70.4% women) with an age range of 20-59 years and a mean age of 41.67 years (SD = 9.31). We included 26 patients with FSS (92.3% women), 59 patients with SRS (61% women), and 30 HC (70% women). The FSS sample consisted of 12 individuals with chronic fatigue syndrome and 14 individuals with fibromyalgia. While patients may have fulfilled criteria for both disorders, patients received the diagnosis most relevant to their rehabilitation process. As can be seen in table 1, there was no significant difference in age between the groups. There was, however, a difference in gender distribution between FSS and SRS patients ($\chi^2 = 8.51$, $p = 0.004$) and between patients with FSS and HC ($\chi^2 = 4.39$, $p = 0.036$). Consequently, we controlled for gender in the analyses. No a priori power analysis was performed. Therefore, we performed a post-hoc sensitivity analysis that determines the minimum effect size that could be detected given the sample size of the study and the desired level of statistical power. Sensitivity power analysis indicated an effect size of Cohen's D = 0.93 can be detected with 80% power for each of the planned contrasts. The alpha level for the sensitivity analysis was set at 0.011, as the lowest critical value after FDR correction for 9 tests using a desired FDR level (q) of 0.10.

3.2.Heart rate.

Overall, average HR levels changed across phases (main effect of phase: $F_{6,105} = 83.67$, $p < 0.001$) and there was a significant difference between groups (main effect of group: $F_{3,105} = 4.04$, $p = 0.009$). There was a significant phase*group interaction effect ($F_{18,105} = 2.11$, $p = 0.010$) (Figure 2A). Planned pairwise comparisons revealed a significantly higher average HR during rest in patients with FSS ($t_{105} = 3.53$, $p = 0.003$, Cohen's $D = 0.97$) and with SRS ($t_{105} = 2.17$, $p = 0.048$, Cohen's $D = 0.50$) compared to HC. Patients with FSS and patients with SRS did not differ in average HR during rest ($t_{105} = 1.93$, $p = 0.073$, Cohen's $D = 0.47$) (Figure 3.A.). Next, we found a greater increase in average HR during the stress phases compared to rest in HC compared to FSS ($t_{105} = -2.46$, $p = 0.028$, Cohen's $D = 0.68$) and SRS ($t_{105} = -3.29$, $p = 0.003$, Cohen's $D = 0.75$) (Figure 3.B.), and a greater decrease in HR during the recovery phases compared to the stress phases in HC compared to patients with FSS ($t_{105} = -3.30$, $p = 0.003$, Cohen's $D = 0.91$) and SRS ($t_{105} = -4.28$, $p < 0.001$, Cohen's $D = 0.98$) (Figure 3.C.).

3.3.Heart rate variability

Because of the large effects of verbal activities on HRV [55], only the rest and recovery phases of pNN50 and RMSSD were investigated.

Overall, average pNN50 levels changed across phases (main effect of phase: $F_{6,105} = 4.47$, $p < 0.001$) and there was a significant difference between groups (main effect of group: $F_{3,105} = 5.02$, $p = 0.003$). The phase*group interaction effect did not reach significance ($F_{18,104} = 1.58$, $p = .080$). Planned pairwise comparisons revealed a significantly lower average pNN50 during rest in patients with FSS ($t_{105} = 3.47$, $p = 0.002$, Cohen's $D = 0.95$) and SRS ($t_{105} = 3.19$, $p = 0.004$, Cohen's $D = 0.73$) compared to HC. There was no significant difference in pNN50 between patients with FSS and patients with SRS during rest ($t_{105} = 0.90$, $p = 0.37$, Cohen's $D = 0.22$) (Figure 4A). HC had higher levels of pNN50 during the recovery phases than patients

with FSS ($t_{105=}$ 3.87, p = 0.001, Cohen's D = 1.07) and SRS ($t_{105=}$ 2.72, p = 0.011, Cohen's D = 0.62), while there were no differences between the two patient groups ($t_{105=}$ 1.78, p = 0.092, Cohen's D = 0.43) (Figure 4B)

For RMSSD, there was a significant main effect of phase ($F_{6,105}$ = 10.58, p < 0.001) and group ($F_{3,105}$) = 3.41, p = 0.020, but no significant phase*group interaction effect ($F_{18,105}$ = 0.85, p = 0.64). Planned pairwise comparisons indicated that individuals with FSS had lower RMSSD during baseline ($t_{105=}$ 2.43, p = 0.040, Cohen's D = 0.67) and recovery ($t_{105=}$ 2.95, p = 0.023, Cohen's D = 0.81) compared to HC (Figure 5). Additionally, SRS patients had lower RMSSD compared to FSS during recovery ($t_{105=}$ 2.37, p = 0.040, Cohen's D = 0.58).

3.4. Skin conductance levels

Overall, average SC levels changed across phases (main effect of phase: $F_{6,109}$ = 47.31, p < 0.001), and there was a significant difference between groups (main effect of group: $F_{3,109}$ = 9.13, p < 0.001) (Figure 2.B.). Moreover, although we found no significant phase*group interaction effect ($F_{18,109}$ = 1.39, p = 0.15), planned pairwise comparisons revealed a higher average SC in rest in FSS (t_{109} = 3.39, p = 0.004, Cohen's D = 0.94) and SRS (t_{109} = 3.55, p = 0.004, Cohen's D = 0.81) compared to HC (Figure 6.A.). Furthermore, there was a greater increase in SC during the stress phases compared to rest in FSS compared to HC (t_{109} = 2.59, p = 0.032, Cohen's D = 0.71) (Figure 6.B.). There were no significant differences between the groups regarding the other phases (Figure 6.C.).

3.5. Skin temperature

Overall, average ST levels changed across phases (main effect of phase: $F_{6,108}$ = 4.16, p < 0.001), but there were no significant differences among the groups (main effect of group: $F_{3,108}$

= 0.54, p = 0.66) and there was no significant phase*group interaction effect ($F_{18,108}$ = 0.98, p = 0.49).

4. Discussion

The present study aimed to investigate ANS activity at rest, and during and after psychosocial stress by measuring HR, HRV, SCL, and peripheral ST in patients with FSS (i.e. fibromyalgia, chronic fatigue syndrome), patients with SRS (i.e. overstrain, burnout), and HC. By implementing a multiparameter paradigm, focusing on both the stress response and recovery from stress, and by comparing patients with SRS and FSS, this study fills an important gap in the literature.

As hypothesized, results showed that both patient groups had significantly higher resting HR and lower resting HRV compared to the HC group, in keeping with previous research [19,21,24-26,28,55], and consistent with findings that HR and HRV are negatively correlated [56]. Additionally, both patient groups showed a weaker increase in HR in response to psychosocial stress and a smaller HR decrease during recovery compared to HC, consistent with earlier findings [22,25,26]. HRV in response to psychosocial stress was not available due to the influence of verbal tasks during the stress test [55]. However, lower levels of HRV were found during recovery from the stressor in both patient groups compared to HC. These findings on HR and HRV are indicative of lower parasympathetic and higher sympathetic activity in rest and reduced cardiac stress *reactivity* in FSS and SRS. While reduced cardiac stress reactivity might seem surprising given the sympathetic predominance in FSS, two plausible explanations for this finding can be derived from existing literature. First, these results could be due to the high HR and low HRV levels during rest, diminishing the response range during the exposure to a psychosocial stressor. Second, the reduced cardiac stress reactivity can be seen as a blunted response as a consequence of "wear and tear" due to chronic sympathetic activation, similar to the blunted hypothalamic-pituitary-adrenal (HPA) axis reactivity often reported in FSS: there

is evidence for both hypocortisolism during the day [57-60] and a blunted cortisol responses to psychosocial stress [61-64] in fibromyalgia and chronic fatigue syndrome. The results of our study may be interpreted as a blunted cardiovascular response to psychosocial stress in chronic stress conditions, possibly as a consequence of "exhaustion" of the stress response system. A blunted HRV response to stress has been previously found in FSS [21] and in fibromyalgia specifically [19], and this ANS hypo-responsivity has been hypothesized to underlie burnout symptoms as well [65]. This interpretation is also in line with findings that (childhood) adverse experiences are a risk factor for bodily symptoms and illness in general, partly due to their effects on functioning of the ANS and the neuroendocrine stress response system [66,67]. As can be seen in Table 1, individuals with FSS, and to a more limited extent, SRS, reported higher levels of adverse experiences than HC, which may have contributed to the blunted stress response found in both patient samples.

Our results also showed significantly higher resting SCL in patients with FSS and SRS compared to the HC group. The existing literature on SCL in FSS reports conflicting findings. For instance, while two studies found no difference in SCL between patients with fibromyalgia and HC during rest [24,26], another study found lower mean SCL during rest in fibromyalgia patients [68]. Interestingly, as our measurements were taken on the nondominant hand, our findings are in line with the results of Mitani et al. [69], reporting higher mean SCL during rest in the dominant hand, but not in the non-dominant hand in FSS. As hypothesized, our results also showed a higher increase of SCL following psychosocial stress in FSS compared to HC, in line with Thieme and Turk [26]. Additionally, as SCL are thought to be a potential marker of chronic stress [70], this could be a possible important feature of SRS. However, to our knowledge, SCL have never been studied before in this patient group in the context of an experimentally induced psychosocial stressor. We found no significant differences in SCL responses to psychosocial stress between SRS and HC. In addition, no differences were found

regarding the recovery period in both patient groups compared to HC. However, Christopoulos et al. [71] reported that SCL may not fully recover when one is anticipating a next stimulus. Since our study design consisted of two recovery periods followed by a next psychosocial stressor and the recovery periods only lasted for 120s, this may have influenced the results.

Even though ST changed significantly across phases in our design, our results indicated that peripheral ST could not differentiate between the patient groups and HC, nor between the different patient groups. To our knowledge, ST has not yet been studied in the context of experimentally induced stress within FSS or SRS.

In general, the results found for SRS and FSS were strikingly similar. Consequently, we infer that there is sympathetic predominance in both patient groups. Since these chronic conditions and SRS have never been compared to each other regarding ANS activity, these results are indicative of sympathetic predominance and a blunted cardiac response to stress that could be transdiagnostic features for both types of conditions, and are not specific to particular bodily symptoms found in these conditions. This is in line with theories that both types of disorders may have not only shared symptomatology but also shared underlying biological mechanisms, including chronic stress and resulting stress axes dysfunction [72,73].

Some limitations of the study need to be mentioned. First, as our data was collected in a clinical setting, this resulted in no-counterbalancing of the order of the different stress tasks. That is why we opted to aggregate the different psychosocial stressors for further analyses. Further, patients were diagnosed in different settings: chronic fatigue syndrome patients received a diagnosis in the university hospital, fibromyalgia patients were diagnosed by local rheumatologists, and individuals with SRS were diagnosed by the clinicians in Tumi Therapeutics. While this guarantees that diagnoses were made following appropriate evaluations by qualified professionals, it may have introduced variability in diagnostic consistency and comparability. Second, to ensure that the healthy control group consisted of

physically and mentally well individuals, we pre-selected healthy controls on low symptom reporting and low negative affectivity. As a consequence, our healthy control sample may not have been fully representative of the healthy population, introducing potential selection bias. This could have contributed to observed case-control differences, as individuals with higher negative affectivity, who may also be at greater risk for SRS and FSS, were likely underrepresented. Third, we did not report data on HRV parameters in response to the psychosocial stressors. However, due to the large effects of talking on HRV [55], and all three stress tasks involved talking, the results would lack reliability. Fourth, the analyses were not controlled for the level of physical exercise, which may have influenced the findings. Fifth, given the female predominance in FSS, there was a difference in gender distribution between the two patient groups. However, for the sake of our patient sample being representative of the FSS and SRS population, we only matched the gender distribution of healthy controls to the entire patient sample, but not the patient samples to each other. Because of the unequal distribution of gender between the groups, we controlled for gender in all analyses. Last, because of the cross-sectional design of our study, the data does not allow us to draw conclusions about directionality or causality of the found effects.

The study results have theoretical and clinical implications. On a theoretical level, we demonstrated decreased cardiovascular reactivity to stress in patients compared to HC, which was most pronounced in individuals with FSS. These findings should be interpreted in light of recent literature theorizing that more chronic and debilitating forms of persistent somatic symptoms are less driven on peripheral sensory input and more on perceptual deficits (i.e. dysfunctions in interoceptive processing and symptom perception) [14, 74, 75]. Future studies could confirm this hypothesis by studying ANS function and symptom perception processes in the same sample of individuals with SRS and FSS. Clinically, since there are some indications of dysfunctional ANS activity in these chronic conditions, ANS biofeedback-assisted therapy

has previously been examined in FSS [76-78]. To date, HRV biofeedback has been the most studied form of ANS biofeedback. For instance, an integrative literature review found supporting evidence for HRV biofeedback as a promising treatment for fibromyalgia -related chronic pain [77], while HRV biofeedback was also shown to reduce general fatigue and have additional benefits for mental health, including improving mental health-related quality of life and depression in patients with chronic fatigue syndrome [78]. Research on biofeedback in SRS is scarce. However, results from a systemic review support HR(V) biofeedback as an effective intervention for healthier stress management in the work place [79]. Moreover, HRV biofeedback has also been shown to decrease school burnout symptoms in a sample of college students [80]. Other forms of ANS biofeedback are investigated to a lesser extent, but are also promising. For instance, autogenic training consisting of ST and SC feedback has been proven effective in a sample of patients with medically unexplained symptoms [81]. Given that respiratory biofeedback improves HRV [82], and respiratory dysfunction has already been shown in FSS and SRS [14], this is also a potential treatment target for these populations.

In sum, our results showed that average HR and SCL were higher and average HRV (pNN50) was lower in FSS and SRS patients compared to HC during rest. Additionally, average HR during rest was higher in FSS compared to SRS. Results showed a smaller increase in HR following a psychosocial stressor and smaller drop in HR upon recovery in both patient groups compared to HC. On average, significantly lower levels of pNN50 during recovery were found in both patient groups compared to HC. The SC response to stress in both patient groups was larger compared to HC. Last, ST could not differentiate between the different groups. Our results are indicative of a blunted cardiac response to psychosocial stress and sympathetic predominance in patients compared to HC which was most pronounced in FSS. These results suggest the possibility of ANS dysfunction as one of the underlying working mechanisms for both FSS and SRS.

5. Statements relating to the ethics and integrity policies

5.1. Data and code availability statement

The data that support the findings of this study are available from the corresponding author upon request.

5.2.Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

5.3.Conflict of interest disclosure

KB is a founding member and shareholder of Tumi Therapeutics (interdisciplinary center of expertise on the prevention, diagnostics and treatment of stress-related and persistent somatic symptoms) where the patients in this study were recruited and where data collection was performed.

5.4. Ethics approval statement

The study was approved by the local ethics committee (S5890).

5.5. Acknowledgements

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6. Tables

	FSS (N = 26)		SRS (N = 59)		HC (N = 30)		F	p
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age	41.85	9.37	42.32	9.20	40.23	9.63	0.50	0.61
Quality of life	26.52[a]	5.62	24.07[a]	7.08	33.30[b]	0.92	25.53	< 0.001
Depressive symptoms	36.29[a]	10.61	38.57[a]	10.66	17.83[b]	2.20	52.75	< 0.001
Anxiety symptoms	19.29[a]	5.51	21.70[a]	7.03	10.93[b]	1.36	35.16	< 0.001
General psychopathology	182.0[a]	42.5	188.3[a]	44.0	103.7[b]	10.6	52.89	< 0.001
Nr. of adverse experiences	3.36[a]	3.77	2.40[ab]	2.47	1.57[b]	1.38	3.24	0.043

Table 1. Descriptive statistics for the participant sample. Quality of life was measured with the Quality of Life in Depression Scale. Depressive and anxiety symptoms were measured with the depression and anxiety subscales of the Symptom-Checklist 90. General psychopathology was quantified as the total score of the Symptom-Checklist 90. The number of adverse experiences was measured using the Traumatic Experiences Checklist. Number with the same superscript on the same row are not statistically different from each other. FSS = Functional Somatic Syndromes. SRS = Stress-related Disorders.

7. Figure headings

Figure 1. Timeline of the standardized stress test. Created with Biorender.com.

Figure 2. Heart rate (A) and skin conductance levels (B) during the entire protocol. Least square means are displayed. Error bars represent standard errors.

Figure 3. A. Average heart rate at baseline. B. Average difference between heart rate during stress and heart rate at rest. C. Average difference between heart rate during recovery and heart rate during stress. Raw untransformed values are displayed. P-values reflect least square means estimates.

Figure 4. Average heart rate variability, quantified by pNN50, during baseline (A) and recovery (B). Raw untransformed values are displayed. P-values reflect least square means estimates.

Figure 5. Average heart rate variability, quantified by RMSSD, during baseline (A) and recovery (B). Raw untransformed values are displayed. P-values reflect least square means estimates.

Figure 6. A. Average skin conductance levels at baseline. B. Average difference between skin conductance levels rate during stress and at baseline. C. Average difference between kin conductance levels during recovery and during stress. Raw untransformed values are displayed. P-values reflect least square means estimates.

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