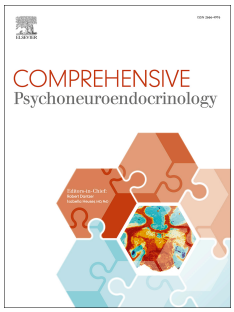

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Justify your disability! A simulated medical evaluation as a novel stress induction model in chronic pain

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Abstract

Maladaptive stress responses may exacerbate chronic widespread pain (CWP) and deserve further investigations. Yet, existing stress induction paradigms lack relevance for individuals with CWP. Patients often report intense stress in response to medical appointments due to the experience of stigma, distrust, and a lack of common understanding about their condition and level of disability. Hence, we developed the Social Benefits Stress Test (SBST), based on the Trier Social Stress Test, replacing the mock job interview, by a fake medical examination where the participant needed to justify their work incapacity.

Forty women with CWP due to hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorders were included. They underwent a 30-minutes baseline, the SBST and a recovery period. The psychophysiological stress response was captured using self-reported stress ratings, continuous heart rate and electrodermal activity (EDA) monitoring, salivary cortisol and α-amylase levels.

Compared to baseline, a significant increase in stress ratings was observed during the SBST, associated with a peak in salivary biomarkers. Heart rate variability analysis showed significant decreases in high frequency power (HF), increases in heart rate, low frequency power (LF) and in LF/HF ratio. EDA analysis revealed significant increases in skin conductance response (SCR). Subjective stress ratings correlated with physiological changes in α-amylase and LF/HF ratio.

The SBST induced a reproducible stress response across subjective and physiological measures, validating this task as a relevant experimental model of social stress in chronic pain and a valuable tool for quantitative testing of clinically relevant stress responses in patients with persistent symptoms.

Keywords: stress response ; HRV ; EDA ; α-amylase ; cortisol ; hypermobile Ehlers-Danlos Syndrome ; hypermobility spectrum disorders

1. Introduction

Chronic pain affects around 20% people worldwide, representing a physical and socioeconomic burden [1], where one of the main issues is an inability to work [2]. However, functional impairment is often met by disbelief in medico-social systems [3] due to the invisible nature of the disease [4,5]. These issues are key to the livelihood and sense of identity of patients with chronic pain, and represent major stressors [3].

The stress inflicted on patients by the denial of support or by disbelief of the veracity of the illness and the associated suffering is under-investigated [4]. Yet there is evidence that stigma, social support (or lack thereof), and interactions with healthcare and social services are key factors shaping well-being in chronic pain [3]. Socioeconomic struggles could also contribute to the vicious cycle of chronic pain. In fact, prolonged exposure to stressors can result in long-term maladaptive stress responses, which are associated with maintenance of chronic pain [6,7]. Chronic stress involves a dysregulation of the neuro-endocrine cascade of the hypothalamo-pituitary-adrenal (HPA) axis and the autonomous nervous system (ANS) balance [8]. It appears these interactions are specifically relevant for the pathophysiology of chronic widespread pain (CWP) [9].

Stress responses in CWP have been mostly studied in fibromyalgia [10–13]. Nevertheless, patients suffering from hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorders (HSD), i.e. incapacitating generalized connective tissue disorders with joint hypermobility, often present with CWP, as well as musculoskeletal complications and evidence of small fiber neuropathy [14,15]. Many suffer from fatigue, sleep disorders, anxiety, and depression [16]. The disease load is often incompatible with full-time employment [17].

Stress response mechanisms in hEDS/HSD are not yet fully understood, and in particular direct evidence of HPA axis dysregulation remains limited. However, research in chronic pain, especially in fibromyalgia, suggests altered cortisol dynamics, including flattened diurnal cortisol slopes and blunted stress reactivity, consistent with impaired adaptive stress responding [18,19]. Importantly, stress-related mechanisms identified in fibromyalgia are likely to be relevant to hEDS/HSD as well, given the substantial overlap in clinical features such as CWP, fatigue, and heightened subjective stress sensitivity.

While physiological stress response has not yet been characterized in hEDS/HSD, accumulating evidence indicates alterations in autonomic nervous system functioning in hEDS/HSD, including an increased prevalence of dysautonomia, that can manifest as orthostatic intolerance or most extremely as postural tachycardia syndrome (POTS) [20,20,21]. Studies using formal autonomic testing have demonstrated prevalent, generally mild autonomic dysfunction in hEDS, including abnormal heart rate responses and impaired orthostatic tolerance, consistent with altered sympathetic–parasympathetic balance and cerebrovascular dysregulation [22,23]. In addition, clinical cohorts report a strong association between generalized joint hypermobility and POTS, further supporting a link between connective tissue disorders and autonomic dysfunction [21,24]. These autonomic alterations might reflect a reduced capacity to maintain cardiovascular homeostasis during postural or emotionally salient stressors, thereby contributing to fatigue, dizziness, exercise intolerance, and stress-induced exacerbation of symptoms.

Together, these findings provide a biologically plausible framework linking stress responses to a part of the multisystem symptom burden observed in hEDS/HSD and support the relevance of further investigating stress-related mechanisms in this population.

Induced acute stress responses in chronic pain have mainly been studied using the gold standard social stress induction task, the Trier Social Stress Test (TSST) [25]. However, due to its reliance on a mock job interview,

the TSST may not be effective in this population: the disconnect between the test scenario and their real-life experiences could result in disengagement or overwhelming distress. Results may be further muddled by an elevated baseline stress level and an increased vulnerability to social stress [10]. The TSST has previously been adapted in other contexts where a job interview seemed irrelevant [26–29].

Therefore, we propose to validate the Social Benefits Stress Test (SBST), a TSST adaptation tailored to people suffering from disabling chronic pain. It was created as a research tool for future work in the interconnecting fields of chronic pain and stress, in line with established guidelines for stress research involving vulnerable and at-risk populations [30]. The job interview was replaced by a simulated interview with a confederate medical expert deciding on patients' work incapacity for social benefits allocation. The main outcome measures were subjective stress rated on visual analogue scales (VAS), heart rate variability (HRV), electrodermal activity (EDA), as well as salivary cortisol and α-amylase.

We hypothesized that the SBST would successfully induce a significant and transient stress response in patients with hEDS/HSD, reflected by increases in subjective stress levels, associated with congruent increases in EDA, salivary cortisol and α-amylase, alongside a decreased HRV, reflecting a valid stress induction task.

2. Methods

2.1 Design

This prospective single-center observational study took place at the Centre for integrative and complementary medicine (CEMIC) at the Lausanne University Hospital, Switzerland. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee for research in humans (CER Vaud - 2021-01750). Participants were compensated for their participation with a 50 CHF voucher for a local store and their travel expenses were reimbursed.

2.2 Participants

Eligible participants were adult females, suffering from hEDS or HSD according to Malfait criteria [14] reporting chronic pain (more than 6 months), willing and able to give informed consent, recruited from the CEMIC and Pain Centre. As 89% of the patients suffering from hEDS/HSD are women [31], including men in a representative way would then have resulted in sample with about 36 women and 4 men, or in a very long and demanding recruitment process to find 20 male participants with hEDS/HSD, that would not have reflected the clinical reality. Furthermore, the pain experience is more frequently disbelieved in women than in men [32]. For all these reasons, only women were included. Exclusion criteria were: insufficient French language skills to communicate without a translator (i.e. below B2 level), severe hearing impairment, active substance use disorder, somatic co-morbidity that could interfere with interpretation of HRV recordings (including cardiac malformation, recent myocardial dysfunction, cardiac transplantation, or cardiac treatment i.e. pacemaker, antiarrhythmic drugs, muscarinic receptor blockers, angiotensin-converting enzyme inhibitors or any that would induce a modification in heart rate) or contraindication to sensor positioning (i.e. local skin damage or allergies). Participants were also excluded if they presented with unstable psychiatric comorbidities, including acute episodes of major depressive disorder, generalized anxiety, psychotic or bipolar disorder. Participants with stable, treated psychiatric conditions were not excluded. Eligibility criteria were verified in two steps: medical and diagnostic criteria were confirmed through the participants' medical records accessed with their consent; remaining inclusion and exclusion criteria were assessed via a screening phone call prior to participation.

2.3 The Social Benefits Stress Test (SBST)

2.3.1 Task development

Two patient-advocates, suffering from chronic pain for more than five years, who had multiple medical encounters for their pain and with previous experiences of the social benefits system in Switzerland, were involved in the task design through semi-structured interviews. They provided advice on the confederate medical expert's attitude and specific questions.

The task was an adaptation of the TSST [25], maintaining the global timeline and procedures, including filming the test and the surprise arithmetic task (Figure 1). The fake job interview was replaced by a simulated interview with a confederate medical expert. Unlike the standard TSST protocol which involves two to three judges, a single confederate was used to reflect the real-world format of medical expertise encounters, where individual meetings with a single doctor is the norm. This design choice was deliberately made to avoid inducing an overly severe stress response and are in line with recent recommendations regarding stress induction tasks [30]. The realism of the single-expert format was confirmed both by patient-advocates based on their lived experience of the Swiss social benefits system, and by participants themselves, who reported that the simulation closely resembled actual medical encounters they had experienced. The confederate medical expert was played by a female confederate, a research collaborator (S.P.W.), in her forties, looking formal, severe, and sharp, dressed in a medical white coat. Her attitude was a "poker face", imitating in the cold neutrality of the panel in the TSST, as well as attitudes of real medical experts described by patients advocates.

2.3.3 Procedure

Participants were asked to fill standardized trait questionnaires (all French versions) online at home within the 15 days preceding the testing day. Eligibility criteria were verified by telephone screening and, with the participants' consent, through review of their electronic medical records.

Patients were invited for a unique study visit about stress (without further information regarding the task) lasting about 2h30, starting at 2PM for each participant. After collecting informed consent, patients received instructions for the saliva collection and sensors were positioned for ECG recording.

The task started with a 30-minutes "**baseline**" with the participants siting on a comfortable chair and invited to relax while watching a marine life documentary (Océans, Jacques Perrin, 2009) (Figure 1).

After this baseline, they received the following instructions: "*Imagine* that you are not able to work full-time due to your pain, and you have asked for financial social support from an insurance company or the state. You will face a medical expert who will evaluate your work capacity. You now have 10 minutes to prepare for this interview." Participants were also told that nonverbal behaviour and global performance would be analysed based on a video-recording.

This initiated the 10-minute "**anticipation**" phase, where patients were provided with a paper and pencil to prepare. The "**stress task**" followed: They were guided to a conference room, where they were introduced to the confederate medical expert and were seated, as usual medical encounters are done in a seated setting. She explained in a cold and distant way "You now have 5 minutes to justify your inability to work". The interactions followed a protocol with scripted questions: If the subject spoke for less than 3 minutes, she said

'You still have some time left. Please continue.' If the subjects finished a second time before the 3 minutes were over, the expert stayed quiet for 20 seconds. In any case, after 3 minutes, the expert asked prepared questions (see supplementary methods) during 2 minutes until the end of the 5 minutes. Following this "i**nterview**", participants were asked to undergo a mental "**arithmetic task**" for 5 minutes, i.e. sequentially subtracting 13 from the number 2033 (as in the TSST). Affects were assessed before anticipation and at the end of the stress task to measure changes in subjective affective state associated with the stress procedure.

Then the "**recovery**" phase followed: participants were guided back to the first room. They were invited to sit and relax while watching another 30 minutes of the marine documentary. After 30 minutes, the sensors were removed, and the patients were fully debriefed about the purpose of the task ("**debriefing**"). The research collaborator made it a point of honour to emphasize the recognition of their condition and provided a detailed clarification of the expected impacts of the study. To ensure the SBST did not induce long term effects, the patients were called by phone for further task-related debriefing the day after and the week after their participation in the study and asked about their recovery.

Figure 1

2.4 Measures

2.4.1 Trait questionnaires

Traits questionnaires filled online were the Brief Pain Inventory (BPI), assessing the pain severity and its impact on daily functions [33,34]; the Perceived Stress Scale (PSS), evaluating how much their life was overwhelming and unpredictable over the past month [35,36]; the Pain Catastrophizing Scale (PCS) quantifying rumination, magnification and helplessness regarding pain [37,38] and the Hospital Anxiety and Depression Scale (HADS) to measure anxiety and depression tendencies [39,40].

2.4.1 Subjective stress and pain

Ratings on VAS were used to repeatedly assess subjective stress and levels of pain with two 10 cm-lines anchored "no <stress // pain>" on the left (=0/10) and "worst <stress // pain> imaginable" on the right (=10/10). Ratings were collected upon arrival and after each phase of the SBST (see Figure 1).

2.4.2 Physiological recordings

Continuous physiological monitoring was performed using a 3-electrodes electrocardiogram (at a sampling rate of 1024 SPS) (NeXus-10 MKII, Mindmedia, Herten, the Netherlands): the skin was cleaned with alcohol and electrodes were placed on the right and left clavicle and left lower ribcage (lead II configuration). The physiological signals were recorded using the BioTrace+ software (Mind Media BV, Netherland) and analysed using the Neurokit2 Python library (v.0.2.3) [41]. Power spectral density was estimated using the Welch method with a Fast Fourier Transform (FFT). The following frequency bands were used: Very Low Frequency (VLF: 0–0.04 Hz), Low Frequency (LF: 0.04–0.15 Hz), and High Frequency (HF: 0.15–0.40 Hz). Raw data were exported, visually inspected, and corrected for artifacts and peak detection. Then HRV (root mean square successive differences (RMSSD), LF power and HF power components) and EDA outcomes (*skin conductance response* (SCR) i.e. the number of peaks for the phasic component were calculated during designated 5-minute periods. SCR peaks with a minimum amplitude of 0.1 µS were identified as events [42].

As the interview and arithmetic periods were 5 minutes sharp; they were fully analysed. For the phases lasting more than 5 minutes, the extracted time-series were selected as a 5-minutes block outside of events of interference (e.g., sneezing, moving, talking, which had been noted with their timing during the testing) (see Figure 1).

A typical stress response is characterized by a decreased HRV (with a decrease in RMSSD, an increase in LF, a decrease in HF, or an increase in the LF/HF ratio) [43] and by an increased number of EDA peaks during the stress task compared to baseline recordings.

2.4.3 Salivary cortisol and α-amylase

Saliva samples were collected using Salivettes (Sarstedt, Germany) to analyse the levels of salivary free cortisol and salivary α-amylase at the 7 specified time points (Figure 1).

The participants were given instructions to abstain from eating, drinking, brushing their teeth, or smoking for 1 hour prior to the study visit. On the sampling day, they were also required to fill out a form, providing information about any medications or specific events that could potentially affect the analysis of collected biomarkers and none of them lead to data exclusion. Then, samples were centrifuged at +4°C (3'500 rpm, 15 minutes) and stored at −80°C until the analysis. Cortisol and α-amylase levels assessments were performed at the Psychological Institute laboratory of the University of Zürich. Cortisol levels (nmol/L) were assessed using a commercial luminescence immunoassay kit (ELISA; IBL International, RE62111/RE62119). For α-amylase analysis, saliva samples were incubated with a substrate reagent, α-Amylase CC FS from Diasys, at 37°C. The increase in absorbance was transformed into α-amylase concentrations (U/ml) using a standard curve. Each sample was run in triplicate. Intra- and inter-assay coefficients of variation were reported to be below 10%.

2.4.5 Intervention questionnaires

Affects were assessed using the Positive and Negative Affect Schedule (PANAS) [44] comprising two 10-item subscales measuring positive affect (e.g., "enthusiastic," "attentive") and negative affect (e.g., "scared," "irritable").

At the end of the stress task, participants also rated its characteristics on five separate 100-point Likert scales (0=not at all, 50=moderately, 100=extremely), covering novelty, difficulty, stressfulness, controllability, and predictability, in line with methodological recommendations from the acute stress literature [45] and a previously validated stress paradigm [46].

2.4.6 Debriefing interview

A script based qualitative interview was delivered by phone at + 1 and +7 days, Based on 10 items from the PTSD Checklist Civilian for DSM-5 (PCL-C). Participants were questioned about any consequence the task could have induced in their daily life, their subjective stress and nervousness level since the experiment, any disturbing memories, dreams, or thoughts related to the study. They were also asked if thinking back to the study made them feel overwhelmed, if it induced increased heartbeat, sweating, pain, or difficulty breathing, if they tended to avoid talking about the study, had any new concentration or sleep difficulty, more negative emotions, and finally, their current stress and pain level on a numerical rating scale from 0 (not at all) to 10 (most intense). Previous experiences with social benefits were also investigated (either if they already faced a

real medical expert, had paper/email interactions with social benefits or were never involved in social benefits procedures) and are described in Table 1. These results will be described in details in further work.

2.5 Statistical analyses

2.5.1 Data analyses

Given that the SBST is a new stress paradigm, no prior data existed for an a priori power calculation. Therefore, a sample size of N=40 was estimated based on a meta-analysis on the TSST [47]. Statistical analyses were performed using python v3.8.10 and R v4.3 under RStudio v2021.09.1-372. Results were considered significant at $p<0.05$. Linear mixed-effects models were used to evaluate time effect on subjective stress and pain ratings, HRV and EDA components. Time was entered as a fixed effect, and a random intercept for each participant was included to account for individual differences in baseline stress levels and the non-independence of repeated measurements. Degrees of freedom were estimated using the Kenward-Roger approximation. If the time effect was significant, post-hoc pairwise t-tests were performed with a Tukey correction for multiple comparisons. All the results are reported corrected. To test the validity of the new stress task, the post-hoc analysis focused on the following comparisons: baseline vs stress task and stress task vs recovery. The entire set of post-hoc comparisons is presented in supplementary results.

Repeated measures correlations [48] were conducted to test associations between paired measures repeatedly assessed during the task, i.e. stress VAS, LF/HF ratio, EDA components and salivary α-amylase. As cortisol is produced with a variable delay, the correlations were not assessed. Two tailed paired t-tests were conducted to compare PANAS scores before and after the SBST completion. Positive Affect (PA) and Negative Affect (NA) scores were computed as the sum of their respective 10 items, following the original scoring procedure [44] and preserved in the French-Canadian validation of the PANAS [49]. Scores on each subscale could therefore range from 10 to 50, with higher scores reflecting greater intensity of the corresponding affective state.

Prior to all inferential analyses, distributional assumptions were systematically verified. Normality was assessed using Shapiro-Wilk tests and visual inspection of Q-Q plots, applied to raw variables for paired t-tests and repeated measures correlations, to difference scores for paired comparisons, and to model residuals for all regression and mixed-effects models. Homoscedasticity was examined through visual inspection of residual-versus-fitted plots for all models and additionally tested using a Breusch-Pagan test for the multiple linear regression. For the Box-Cox transformed cortisol data, normality of the transformed distribution was verified prior to modeling.

2.5.2 Salivary cortisol

A linear mixed model (LMM) was fitted on raw salivary cortisol values with timepoint as a fixed effect and a random intercept per participant to account for the repeated-measures structure of the data. Salivary cortisol concentrations were then transformed using the Box-Cox power transformation procedure with a λ of 0.26 recommended by Miller and Plessow [50]. We first fitted a linear mixed model with timepoint (seven levels, raw chronological order) as a categorical fixed effect and a random intercept per participant to test for an overall effect of time on cortisol across the session. Data were then analyzed using a two-piece multilevel

growth curve model with landmark registration, following the approach of Lopez-Duran et al [51]. This method was chosen because it allows cortisol reactivity and recovery to be modeled separately while accounting for individual differences in peak latency. Two spline terms were then created to estimate separate slopes before and after the peak. Baseline cortisol was included as a covariate, and all available cortisol observations were retained in the mixed-effects models. The main models estimated peak cortisol level as well as activation and recovery slopes. Further details are provided in the supplementary methods.

2.5.2 Salivary α-amylase

Raw salivary α-amylase values were log-transformed prior to analysis to address the positive skew characteristic of salivary biomarkers. A linear mixed model (LMM) was fitted with timepoint as a fixed effect and a random intercept per participant to account for the repeated-measures structure of the data. Further details are provided in the supplementary methods.

2.5.4 Exploratory outcomes

To identify personal-level confounders of stress induction, a LASSO regression was conducted with the differential stress VAS (post- minus pre-SBST maximum) as the continuous outcome. The following potential personal-level confounders were entered simultaneously as predictors: age, education level (6-level ordinal scale, modelled as an ordered factor with polynomial contrasts), diagnosis group, maximum pain VAS during the task, pain VAS increase, and baseline questionnaires: BPI, HADS, PCS, PSS, BRS, degree of work incapacity (continuous, 0-100%), BMI and physical activity per week. All 15 variables were entered simultaneously into a LASSO regression with leave-one-out cross-validation. Bootstrap stability selection (1000 resamples) was used to assess the robustness of variable selection.

We also evaluated stress induction tasks responders, which are typically determined by cortisol increases. It can be defined as a cortisol increase from baseline to peak of ≥ 1.5 nmol/l or using a percentage baseline-to-peak increase of 15.5% [52]. Given the very low cortisol concentrations in our population, cortisol stress reactivity was defined as the latter.

To examine the correspondence between expert and participant stress ratings after the interview and arithmetic task, we used a LMM with participant self-reported stress at these timepoints as the outcome, expert ratings as a fixed effect, and a random intercept for each participant to account for the non-independence of repeated measures across the two timepoints (interview and arithmetic task).

3. Results

3.1 Demographic data and psychological traits

The study sample consisted in 40 female subjects with an average age of 42 (±11.2 years). hEDS diagnostic criteria were fulfilled in 25, whereas 15 were categorized as suffering from HSD. Their demographic characteristics are described in Table 1.

Patients characteristics (N=40)	
Age: years mean ± SD (min-max)	42 ± 11.2 (22 - 63)
Diagnosis N (%)	
Ehlers-Danlos syndrome	25 (62.5%)
Hypermobility spectrum disorder	15 (37.5%)
Social benefits experience N (%)	
Faced a medical expert	26 (65%)
Involved in procedures without facing a medical expert	6 (15%)
No previous experience	8 (20%)
BMI (kg/m²)	
Mean ± SD (min-max)	28.8 ± 8 (17 - 45.9)
Activity involving movement (h/week)	
Mean ± SD (v)	9.3 ± 8.3 (1 - 40)
Smoking N (%)	
Yes: (mean ± SD)	21 (52.5%): (6.2 packs year ± 11.2)
No	19 (47.5%)
Education level N (%)	
Compulsory education	2 (5%)
Apprenticeship	17 (42.5%)
Highschool	2 (5%)
University	16 (40%)
Others	2 (5%)
Civil status N (%)	
In a relationship or married	20 (50%)
Single or divorced	19 (47.5%)
Widow	1 (2.5%)
Work incapacity	
Yes	18 (45%)
No	22 (55%)
If yes, percentage of incapacity (mean ± SD, min-max)	93.2 ± 14.1 (50-100)
Questionnaires: mean ± SD (min-max)	
BPI-severity	5.47 ± 1.49 (2.5 - 9)
BPI-interference	5.51 ± 1.87 (1 - 8.57)
HADS-anxiety [% above cutoff ≥ 8]	10.53 ± 3.36 (4 - 18) [77.5%]
HADS-depression [% above cutoff ≥ 8]	8.88 ± 3.30 (2 - 15) [67.5%]
PCS [% above cutoff ≥ 30]	25.43 ± 9.84 (6 – 42) [40%]
PSS [% of high PSS ≥ 27]	22.40 ± 5.97 (8 - 35) [30%]

Table 1: Demographic characteristics of the study population. BPI: Brief pain inventory, HADS: Hospital anxiety and depression scale, PCS: Pain catastrophizing scale, PSS: Perceived stress scale

On average, the group reported daily pain with a moderate intensity that considerably interfered with their daily life. A tendency to catastrophize about pain was also frequently observed. Anxiety and depression were likely co-morbidities, with 55% scoring above clinical detection criteria for both conditions. All patients but one displayed moderate to high subjective stress scores.

3.2 Visual analog scales for subjective stress and subjective pain during the SBST

A significant time effect was reported for subjective stress ($F(8, 312)=39.82$, $p < .001$) (see Figure 2, a). Compared to baseline ($M=1.56$, $SD=1.72$), subjective stress was significantly higher during the interview ($M=4.84$, $SD=2.54$; $p<.001$) and the arithmetic task ($M=5.36$; $SD=2.69$; $p<.001$). Compared to the end of the arithmetic task, subjective stress was significantly lower at the end of the recovery phase ($M=1.46$; $SD=1.77$; $p<.001$).

A significant time effect was also reported for the pain ratings (F(8, 312)=4.15, p<.001) (see Figure 2, b). Compared to arrival (M=4.32, SD=2.43), subjective pain was significantly higher during the arithmetic task (M=5.08, SD=2.69, p=.009). All comparisons are presented in supplementary results.

Figure 2

3.3 Heart rate variability

Due to technical issues during the recordings, 6 participants with missing data were excluded from the these analyses (N=34). RMSSD outliers were defined using age-specific 2nd–98th recommended percentile reference values [53] corresponding to our sample, excluding values below 5.5 ms and above 205.5 ms (N=8 signals excluded). For LF/HF, no values were excluded on the basis of extreme ratios, as these could reflect the autonomic dysregulation characteristic of hEDS/HSD and POTS [20,54].

A significant time effect was reported for heart rate (F(4, 130.94)=27.27, p<.001) (Figure3, a). Compared to the baseline (M=78.34, SD=10.87), the heart rate was significantly higher during the interview (M=84.1, SD=13.3; p<.01) and arithmetic task (M=83.37, SD=12.36; p<.001). Heart rate was also significantly lower during the recovery phase (M=73.51, SD=10.1; p<.0001,) compared to arithmetic.

We observed significant time effects for LF (F(4, 131.55)=9.29, p < .001). Compared to the baseline (M=.016, SD=.01), LF was significantly higher during the arithmetic task (M=.031, SD=.014; p<.001) and then decreased significantly at the end of the recovery phase (M=.016, SD=.014; p=.001) (Figure 3, b).

There was a significant time effect for HF (F(4, 123.4)=3.23, p=.015). HF increased significantly during recovery (M=.016, SD=.018; p=.026 vs interview) (Figure3, c).

Prior to analysis, LF/HF was log-transformed. A significant time effect was also observed for LF/HF ratio (F(4, 131.29)=9.87, p < .001). LF/HF ratio was significantly higher during both the interview (M= 2.84, SD= 0.87; p < .0001) and the arithmetic parts (M= 2.78, SD= 0.84; p < .001) compared to the baseline (M= 1.25, SD= 0.84, Figure 3, d).

For RMSSD, a significant time effect was observed (F(4, 129.74)=6.22, p<.001). RMSSD was significantly higher during recovery compared to all task phases (all p ≤ .006) (Figure 3, e). All comparisons are presented in supplementary results. HRV data required a mean manual correction of M=5.8, SD=9.2 peaks per signal.

Figure 3

3.4 Electrodermal activity

Due to technical issues, N=11 datasets were excluded from the EDA analyses (final sample N=29): 6 participants had no recorded EDA data due to device failure, and 5 datasets were excluded due to corrupted files and/or heavy artefacts, including exceeding a 100-peak threshold within our 5-minutes recording session based on Braithwaite et al. (2013) guidelines [55].

We observed significant time effects for SCR (F(4, 109.02)=6.55, p < .001). Compared to the baseline (M=9.31, SD=12.32), the number of SCR peaks was significantly higher during the interview (M=17.48, SD=9.68; p=.015) and arithmetic (M=16.5, SD=13.9; p=.048), and decreased significantly during the recovery phase (M=8.76, SD=8.34) compared to the arithmetic task (M=16.54, SD=13.88; p=.027) (Figure 3, f). All comparisons are presented in supplementary results.

3.5 Salivary α-amylase and cortisol

Two participants were excluded from all salivary analyses due to insufficient saliva volume (analysis for α-amylase n=38), and 2 more from the cortisol analyses because the concentrations were under detection levels (n=36).

A linear mixed model testing for an overall effect of raw timepoint on cortisol revealed a significant effect of time ($F(6, 217.0) = 7.45$, $p < .001$; Figure 4, b). Post-hoc comparisons showed a significant decrease in cortisol levels, with values at 30- and 40-minutes recovery significantly lower than at 10-min post-SBST (ps ≤ .0104).

At the individual level, salivary cortisol levels increased significantly from the start of the SBST task (Activation Slope $b=0.004$, $SE=0.002$, $t(214)=1.96$, $p < .05$), and then declined significantly after reaching peak, (Recovery Slope $b=-0.008$, $SE=0.002$, $t(214)=-3.70$, $p < .001$), after controlling for pre-task baseline cortisol ($b=0.80$, $SE=0.08$, $t(34)=9.73$, $p < .001$), indicating a rise-and-fall pattern relative to each participant's own baseline and peak (Figure 4, c).

Results revealed a significant effect of timepoints ($F(6, 222)=8.61$, $p < .001$), indicating that α-amylase levels varied significantly across the session (Figure 4, a) . Post-hoc pairwise comparisons (Holm-corrected) showed no significant differences among pre-task timepoints (baseline, anticipation, and SBST) but a significant descrease in α-amylase levels at the end of the SBST, with values during recovery all significantly lower than both SBST phases (ps ≤ .0002). Levels at S1, S2, and S3 did not differ from one another, indicating a sustained post-task decrease. Recovery was evidenced by S4 returning to baseline levels ($p=1.00$).
Individual peak analysis revealed a significant increase from baseline to individual peak (mean $\Delta=0.40$, 95% CI [0.26, 0.55], $t(37)=5.70$, $p < .001$), corresponding to an approximate 49% increase in raw units.

Figure 4

3.6 Correlation between physiological and subjective stress measures

Subjective stress VAS significantly correlated with: salivary α-amylase concentration ($r_{rm}(113)=.30$, $p<.01$) and LF/HF ratio ($r_{rm}(97)=.28$, $p<.005$).

3.7 Patients' perception of the task, debriefing and post-task effects

At the end of the recovery, participants rated the task as difficult (M=79.4, SD=19.46), stressful (M=76.5, SD=21.64), moderately novel (M=50.4, SD=36.67), not so controllable (M=41.75, SD=29.32) and weakly predictable (M=20.88, SD=3.17) (0–100 Likert scales).
There was a significant decrease in the PANAS Positive Affect after the task (M=24.08, SD=7.47 before the task vs M=21.63, SD=8.92 after; $t(39)=-2.89$, $p=.006$) and a significant increase in Negative Affects (M=13.06, SD=3.76 before vs M=20.68, SD=7.90 after; $t(39)=6.15$, $p<.001$).
Finally, at the one-day follow-up call, participants reported what they considered as usual levels of stress (M=3.03, SD=2.53) and pain (M=5.65, SD=1.77) in their daily lives (n=38) (0–10 numerical rating scale). Similar ratings were observed after one week (Stress: M=2.68, SD=2.01 and Pain: M=5.42, SD=2.62, n=34). Among the list of 16 potential aftereffects (adapted from the PCL-C, e.g., intrusive thoughts, avoidance, hyperarousal symptoms), participants reported only few symptoms (M=1.42 symptoms /16, SD=1.83 after one

day and M=1.06, SD=2.01 after a week), The most common symptoms were fatigue/pain (n=15), nervosity (n=11) and thoughts regarding the task (n=5).

One participant experienced an exacerbation of a past trauma (evoked by the ocean documentary) but not specifically related to the stress task of the SBST. One other participant experienced sleep disturbance that she attributed to the task and to her having no more psychiatric support at the time, and for which she received counsel from the study physician.

3.8 Exploratory results

The cross-validated LASSO model shrank all 15 predictor coefficients to zero at both λmin and λ1SE, and no predictor was selected in more than 27.8% of bootstrap resamples (below the conventional ≥70% stability threshold). No personal-level confounders on stress induction were significant, nor did it justify multilevel analyses. The statistics of these analyses are presented in supplementary results.

Among the 36 participants with sufficient saliva volume for analysis, N=11 (30.6%) were identified as responders to the SBST with at least a 15.5% baseline-to-peak salivary cortisol increase.

The linear mixed model combining both timepoints, accounting for the non-independence of repeated measures, revealed a significant positive association between expert and participant stress ratings (marginal R^2=.10, conditional R^2=.84, t(60.89)=3.93, p<.001), suggesting that higher expert-rated stress was associated with higher self-reported stress across both phases.

4. Discussion

In this study, we developed and validated the SBST, an adaptation of the Trier Social Stress Test that is relevant to patients unable to work, for example due to chronic pain. The task design was informed by people with lived experience and the clinical experiences of diverse medical personnel treating people with chronic pain conditions. We tested if a confederate medical expert interview situation could be used as a relevant and ecological stressor in patients suffering from CWP. We demonstrated that the SBST triggered a reversible stress response, measured as significant and transient increases in self-reported stress (VAS), α-amylase concentrations and changes in HRV and EDA metrics.

4.1 The SBST, a good stress induction task?

The SBST elicited a significant increase in subjective stress (mean +3.8 pts on VAS). This response was comparable or even higher than observed with the TSST in healthy volunteers, where a meta-analysis described a mean range of increase between 2.0 to 3.9 pts [56]. In patients suffering from fibromyalgia, the TSST induced smaller increases in subjective stress (mean increase: less than 1 point in n=27; and 2 points in , n=13) [10,57]. Further studies using other stress paradigms in CWP patients (fibromyalgia), did not report subjective stress increases (n=36, “Mental Arithmetic with Harassment) [11] or also reported a smaller increase (n=23, +1.7 points for the two-choice reaction-time test) [13]. The SBST also lead to a significant increase in PANAS NA and a decrease in PA, both similar to the emotional response observed in healthy subjects during the TSST [56].

Moreover, the SBST successfully induced physiological stress responses. Heart rate temporarily increased during the stress task, akin to observations in patients with fibromyalgia in TSST settings [12], and mental arithmetic exercises [58]. Phasic EDA components were higher during the stress task, similarly to a prior

observation in fibromyalgia during an arithmetic task and social conflict [59]. We also observed a transient significant increase from baseline to individual peak in α-amylase, consistent with the group-average pattern reported above. A comparable individual-level increase was observed in cortisol among responders, mirroring the responses seen in individuals with rheumatoid arthritis, psoriasis or multiple sclerosis during the TSST [60,61] . The SBST responder rate was 30.6% , i.e. higher than observed in patients with fibromyalgia or chronic musculoskeletal pain in response to the TSST settings (almost all participants qualified as non-responders) [62,63]. Importantly, we also observed that stress VAS positively correlated with LF/HF ratio and α-amylase. Such correlations between subjective and physiological outcomes were not reported in chronic pain patients in most prior stress induction studies. The fact that VAS correlated with autonomic responses and α-amylase suggests that participants' self-reports accurately reflected their physiological state and supports the strength of the SBST paradigm.

Furthermore, the SBST's impact was transient, inducing an acute stress response without 1-week posttest effects except in two psychologically vulnerable patients (undisclosed PTSD n=1; lack of necessary psychological support n=1). While this suggest caution must be applied in the inclusion of patients in future studies with the SBST, the task aligns with current ethical considerations regarding the intensity of experimental stress inductions [30].

Previous studies have also adapted the TSST to choose an ecological stressor, more relevant and specific for a targeted population: recognizing their crying baby for new mothers, expressing how good a friend they are for adolescents or defending themselves against shoplifting accusations in adult men [26–28]. In our study, the SBST demonstrates relevance for a chronic widespread pain population by considering their possible work impairment [17], ensuring adequate stress induction while maintaining acceptable levels of intensity as recommended for stress studies in vulnerable and at-risk populations [30]. Our manipulation check confirmed the task's effectiveness in eliciting a challenging experience, which they rated as difficult, stressful, unpredictable, and uncontrollable. Yet, the novelty was rated as moderate, possibly indicating that the SBST's realism resonated with participants who had undergone or heard about similar real medical expertise, or other medical encounters where they felt disbelief or judgment [64].

Positive association between expert and participant stress ratings suggests that the experimenter was able to partially capture the participants' subjective stress experience. However, the modest effect size (β=0.41) indicates that expert and participant ratings did not fully converge, which is consistent with the broader literature showing that external observers tend to underestimate subjective stress [65].

Finally, relying only on one confederate, the SBST presents a logistical advantage, compared to the panel of three confederates used in the original TSST.

4.2 The stress response in chronic widespread pain

Compared to prior published samples, hEDS/HSD patients exhibited very low salivary cortisol concentrations (i.e. M=2.06±1.36 nmol/L, vs normative afternoon levels in healthy controls above 7 nmol/L [66]), and elevated levels of α-amylase (i.e. M=168.54±117.19 U/mL, vs mean afternoon levels under in healthy controls 140U/mL [67]), suggesting an alteration of the neuroendocrine stress response system. To our knowledge there is little research describing the stress response in the hEDS/HSD population. The only identified publication on cortisol production in hEDS/HSD patients employed a small sample (n=10) without a unified collection time

(9h-17h), hence not allowing a comparison with our data [68]. We also observed low HRV, which reflects reduced vagal (parasympathetic) modulation of cardiac activity [69], congruent with the existing literature describing higher LF/HF ratio in a sample of fibromyalgia patients (n=39) compared to controls [54]. This is compatible with an autonomic dysfunction in hEDS/HSD [70]. Further work with appropriate controls and the combination of biological and physiological markers will be needed to better characterize the specificities of the stress response in hEDS/HSD.

Baseline alterations in the stress response have been better studied in other patient populations with chronic widespread pain. In fibromyalgia, reduced cortisol awakening response [71], elevated levels of salivary α-amylase [72], altered autonomic regulation of electrodermal activity [73], and sympathetic mediated HRV at baseline have been described [69]. In the light of these baseline alterations, the stress response induction by a relevant task is of specific interest. Individuals with fibromyalgia compared to healthy controls exhibited a blunted cortisol response and higher subjective stress levels when exposed to the TSST [10]. The absence of a control population in our study, whether of healthy volunteers or patients with another painful condition, does not allow to qualify the observed stress response, and this should be examined in further work. Future investigations should assess the feasibility and suitability of the SBST in other a wider range of chronic pain populations to determine the generalizability of our findings. This future research could be facilitated by the task validated here. Furthermore, a longer-term objective could be to use such a tool to assess stress management in patients suffering from chronic pain, allowing to offer resilience-promoting interventions for those in need [74].

4.3 Limitations

The SBST was created with the Swiss social benefits system in mind, where medical experts are very frequently involved in deciding on the attribution of financial support. Connections between the simulated and real experiences will be described in further work. Nevertheless, the task could be easily adapted to match other countries' social or insurance systems, given the universal economic concerns and needs for medical and social recognition as well as for financial support amongst individuals struggling with disability due to chronic pain [75].

This study was not pre-registered. As the SBST is a novel paradigm with no prior published data, the study was exploratory by design, seeking to establish feasibility and initial validity. Additionally, the study was initiated in 2021, before pre-registration became routine practice for observational studies under the Swiss Human Research Ordinance (HRO).

The study included only women, based on the heavily skewed hEDS/HSD demographics [37]. Menstrual cycle phase, menopause status, and oral contraceptive use are known modulators of HPA-axis and autonomic reactivity [76] but were not systematically assessed. Although all sessions were conducted at fixed times of day in the afternoon, which may mitigate cycle-related variability [77,78], we cannot fully rule out hormonal influences on cortisol and α-amylase responses. Future studies should record these variables to allow for more precise control of potential hormonal confounds. It is of interest that in a prior stress induction tasks, women displayed a greater increase in subjective distress compared to men, but a lower increase in cortisol [79]. Moreover, the pain experience is more frequently disbelieved in women than in men [32]. Further work is needed to validate the SBST in men and examine potential sex-related difference in stress responses.

Pain ratings were higher after the SBST compared to arrival. However, the task design doesn't allow to disentangle between an increase of pain due to stress, vs the immobilization and prolonged sitting. This would require a control task with similar patients seated without stress induction.

Measurements of α-amylase and cortisol may be accompanied by procedural limitations [80]: for example low blood glucose levels and smoking are associated with blunted cortisol responses and lower α-amylase activity [81]. We limited the effects of these factors by asking patients to have an early lunch (before noon) since the study started at 2pm, and not to drink anything other than water, nor smoke before the start of the experiment.

Since the experiment took place in the early afternoon, the very low cortisol levels and the diurnal decrease made the interpretation of the raw data difficult. A measure of the individual natural variations in diurnal cortisol and α-amylase, collected on another day (e.g. the day before the task) could be another option for the correction. This is to be considered for future studies.

Conclusions

The present study developed the SBST, a new social stress task, and validated it in a chronic widespread pain population of women with hypermobility conditions. This lays the groundwork for future in depth investigations in chronic pain populations into stress responses, and in parallel, stress management and resilience. The SBST could also serve to test therapeutic tools targeting a potential abnormal stress response. Finally, this test could be used to quantify the stress involved in medical expertise processes and attract attention towards this still neglected issue.

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References:

[1] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123:e273–83. https://doi.org/10.1016/j.bja.2019.03.023.

[2] Toye F, Seers K, Allcock N, et al. A synthesis of qualitative research exploring the barriers to staying in work with chronic musculoskeletal pain. Disability and Rehabilitation 2016;38:566–72. https://doi.org/10.3109/09638288.2015.1049377.

[3] Nicola M, Correia H, Ditchburn G, et al. Invalidation of chronic pain: a thematic analysis of pain narratives. Disability and Rehabilitation 2021;43:861–9. https://doi.org/10.1080/09638288.2019.1636888.

[4] Zajacova A, Grol-Prokopczyk H, Zimmer Z. Sociology of Chronic Pain. J Health Soc Behav 2021;62:302–17. https://doi.org/10.1177/00221465211025962.

[5] Chiron A, Fernandez A, Delli Noci C, et al. Douleur chronique primaire : le manque de reconnaissance d'un handicap invisible. Rev Med Suisse 2024;879:1190–3.

[6] Vachon-Presseau E, Roy M, Martel M-O, et al. The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans. Brain 2013;136:815–27. https://doi.org/10.1093/brain/aws371.

[7] Woda A, Picard P, Dutheil F. Dysfunctional stress responses in chronic pain. Psychoneuroendocrinology 2016;71:127–35. https://doi.org/10.1016/j.psyneuen.2016.05.017.

[8] Everly, GS, Lating JM. A Clinical Guide to the Treatment of the Human Stress Response. New York, NY: Springer New York; 2019. https://doi.org/10.1007/978-1-4939-9098-6.

[9] Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 2016;338:114–29. https://doi.org/10.1016/j.neuroscience.2016.06.006.

[10] Coppens E, Kempke S, Van Wambeke P, et al. Cortisol and Subjective Stress Responses to Acute Psychosocial Stress in Fibromyalgia Patients and Control Participants. Psychosomatic Medicine 2018;80:317. https://doi.org/10.1097/PSY.0000000000000551.

[11] Matías Pompa B, López López A, Alonso Fernández M, et al. Stress-Recovery State in Fibromyalgia Patients and Healthy People. Relationship with the Cardiovascular Response to Stress in Laboratory Conditions. International Journal of Environmental Research and Public Health 2020;17:3138. https://doi.org/10.3390/ijerph17093138.

[12] López-López A, Matías-Pompa B, Fernández-Carnero J, et al. Blunted Pain Modulation Response to Induced Stress in Women with Fibromyalgia with and without Posttraumatic Stress Disorder Comorbidity: New Evidence of Hypo-Reactivity to Stress in Fibromyalgia? Behavioral Medicine 2021;47:311–23. https://doi.org/10.1080/08964289.2020.1758611.

[13] Nilsen KB, Westgaard RH, Stovner LJ, et al. Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography. Eur J Pain 2006;10:615–27. https://doi.org/10.1016/j.ejpain.2005.10.001.

[14] Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017;175:8–26. https://doi.org/10.1002/ajmg.c.31552.

[15] Fernandez A, Aubry-Rozier B, Vautey M, et al. Small fiber neuropathy in hypermobile Ehlers Danlos syndrome/hypermobility spectrum disorder. Journal of Internal Medicine 2022;292:957–60. https://doi.org/10.1111/joim.13539.

[16] Bulbena A, Baeza-Velasco C, Bulbena-Cabré A, et al. Psychiatric and psychological aspects in the Ehlers–Danlos syndromes. American Journal of Medical Genetics Part C: Seminars in Medical Genetics 2017;175:237–45. https://doi.org/10.1002/ajmg.c.31544.

[17] Bogni M, Bassotti A, Leocata G, et al. [Workers with Ehlers-Danlos syndrome: indications for health surveillance and suitable job assignment]. Med Lav 2015;106:23–35.

[18] Hannibal KE, Bishop MD. Chronic Stress, Cortisol Dysfunction, and Pain: A Psychoneuroendocrine Rationale for Stress Management in Pain Rehabilitation. Phys Ther 2014;94:1816–25. https://doi.org/10.2522/ptj.20130597.

[19] Fries E, Hesse J, Hellhammer J, et al. A new view on hypocortisolism. Psychoneuroendocrinology 2005;30:1010–6. https://doi.org/10.1016/j.psyneuen.2005.04.006.

[20] Roma M, Marden CL, De Wandele I, et al. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Autonomic Neuroscience 2018;215:89–96. https://doi.org/10.1016/j.autneu.2018.02.006.

[21] Mathias CJ, Owens A, Iodice V, et al. Dysautonomia in the Ehlers–Danlos syndromes and hypermobility spectrum disorders—With a focus on the postural tachycardia syndrome. American Journal of Medical Genetics Part C: Seminars in Medical Genet Ics 2021;187:510–9. https://doi.org/10.1002/ajmg.c.31951.

[22] Hakim A, O'Callaghan C, De Wandele I, et al. Cardiovascular autonomic dysfunction in Ehlers-Danlos syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet 2017;175:168–74. https://doi.org/10.1002/ajmg.c.31543.

[23] Gazit Y, Nahir AM, Grahame R, et al. Dysautonomia in the joint hypermobility syndrome. The American Journal of Medicine 2003;115:33–40. https://doi.org/10.1016/S0002-9343(03)00235-3.

[24] Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 2012;87:1214–25. https://doi.org/10.1016/j.mayocp.2012.08.013.

[25] Kirschbaum C, Pirke K-M, Hellhammer DH. The 'Trier Social Stress Test' – A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. Neuropsychobiology 1993;28:76–81. https://doi.org/10.1159/000119004.

[26] Johnson MM, Deardorff J, Parra K, et al. A Modified Trier Social Stress Test for Vulnerable Mexican American Adolescents. JoVE (Journal of Visualized Experiments) 2017:e55393. https://doi.org/10.3791/55393.
[27] Sandoz V, Stuijfzand S, Lacroix A, et al. The Lausanne Infant Crying Stress Paradigm: Validation of an Early Postpartum Stress Paradigm with Women at Low vs. High Risk of Childbirth-Related Posttraumatic Stress Disorder. Journal of Personalized Medicine 2021;11:472. https://doi.org/10.3390/jpm11060472.
[28] Wu J, Sun X, Wang L, et al. Error consciousness predicts physiological response to an acute psychosocial stressor in men. Psychoneuroendocrinology 2017;83:84–90. https://doi.org/10.1016/j.psyneuen.2017.05.029.
[29] Yim IS, Quas JA, Rush EB, et al. Experimental manipulation of the Trier Social Stress Test-Modified (TSST-M) to vary arousal across development. Psychoneuroendocrinology 2015;57:61–71. https://doi.org/10.1016/j.psyneuen.2015.03.021.
[30] Broeder C, de Nooij L, van den Eijnden MJM, et al. Laboratory stress research in psychiatric and neurological populations: toward a consensus guideline. Psychoneuroendocrinology 2025;182:107641. https://doi.org/10.1016/j.psyneuen.2025.107641.
[31] Castori M, Camerota F, Celletti C, et al. Ehlers–Danlos syndrome hypermobility type and the excess of affected females: Possible mechanisms and perspectives. American Journal of Medical Genetics Part A 2010;152A:2406–8. https://doi.org/10.1002/ajmg.a.33585.
[32] Chen EH, Shofer FS, Dean AJ, et al. Gender Disparity in Analgesic Treatment of Emergency Department Patients with Acute Abdominal Pain. Academic Emergency Medicine 2008;15:414–8. https://doi.org/10.1111/j.1553-2712.2008.00100.x.
[33] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap 1994;23:129–38.
[34] Poundja J, Fikretoglu D, Guay S, et al. Validation of the French version of the brief pain inventory in Canadian veterans suffering from traumatic stress. J Pain Symptom Manage 2007;33:720–6. https://doi.org/10.1016/j.jpainsymman.2006.09.031.
[35] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health and Social Behavior 1983;24:385–96. https://doi.org/10.2307/2136404.
[36] Lesage F-X, Berjot S, Deschamps F. Psychometric properties of the French versions of the Perceived Stress Scale. Int J Occup Med Environ Health 2012;25:178–84. https://doi.org/10.2478/S13382-012-0024-8.
[37] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment 1995;7:524–32. https://doi.org/10.1037/1040-3590.7.4.524.
[38] French DJ, Noël M, Vigneau F, et al. L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle «Pain Catastrophizing Scale». [PCS-CF: A French-language, French-Canadian adaptation of the Pain Catastrophizing Scale.]. Canadian Journal of Behavioural Science / Revue Canadienne Des Sciences Du Comportement 2005;37:181–92. https://doi.org/10.1037/h0087255.
[39] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 1983;67:361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.
[40] Razavi Darius, Delvaux N, Farvacques C, et al. Validation de la version française du HADS dans une population de patients cancéreux hospitalisés. [Validation of the French version of the Hospital Anxiety and Depression Scale (HADS) in a population of hospitalized cancer patients.]. Revue de Psychologie Appliquée 1989;39:295–307.
[41] Makowski D, Pham T, Lau ZJ, et al. NeuroKit2: A Python toolbox for neurophysiological signal processing. Behav Res 2021;53:1689–96. https://doi.org/10.3758/s13428-020-01516-y.
[42] Boucsein W. Electrodermal Activity. Springer Science & Business Media; 2012.
[43] Quigley KS, Gianaros PJ, Norman GJ, et al. Publication guidelines for human heart rate and heart rate variability studies in psychophysiology—Part 1: Physiological underpinnings and foundations of measurement. Psychophysiology 2024;61:e14604. https://doi.org/10.1111/psyp.14604.

[44] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology 1988;54:1063–70. https://doi.org/10.1037/0022-3514.54.6.1063.
[45] Dickerson SS, Kemeny ME. Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. Psychological Bulletin 2004;130:355–91. https://doi.org/10.1037/0033-2909.130.3.355.
[46] Sandoz V, Stuijfzand S, Lacroix A, et al. The Lausanne Infant Crying Stress Paradigm: Validation of an Early Pos tpartum Stress Paradigm with Women at Low vs. High Risk of Childbirth- Related Posttraumatic Stress Disorder. Journal of Personalized Medicine 2021;11:472. https://doi.org/10.3390/jpm11060472.
[47] Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull 2004;130:355–91. https://doi.org/10.1037/0033-2909.130.3.355.
[48] Bakdash JZ, Marusich LR. Repeated Measures Correlation. Frontiers in Psychology 2017;8.
[49] Gaudreau P, Sanchez X, Blondin J-P. Positive and Negative Affective States in a Performance-Related Setting: Testing the Factorial Structure of the PANAS Across Two Samples of French-Canadian Participants. European Journal of Psychological Assessment 2006;22:240–9. https://doi.org/10.1027/1015-5759.22.4.240.
[50] Miller R, Plessow F. Transformation techniques for cross-sectional and longitudinal endocrine data: Application to salivary cortisol concentrations. Psychoneuroendocrinology 2013;38:941–6. https://doi.org/10.1016/j.psyneuen.2012.09.013.
[51] Lopez-Duran NL, Mayer SE, Abelson JL. Modeling neuroendocrine stress reactivity in salivary cortisol: adjusting for peak latency variability. Stress 2014;17:285–95. https://doi.org/10.3109/10253890.2014.915517.
[52] Miller R, Plessow F, Kirschbaum C, et al. Classification Criteria for Distinguishing Cortisol Responders From Nonresponders to Psychosocial Stress: Evaluation of Salivary Cortisol Pulse Detection in Panel Designs. Biopsychosocial Science and Medicine 2013;75:832. https://doi.org/10.1097/PSY.0000000000000002.
[53] Tegegne BS, Man T, van Roon AM, et al. Reference values of heart rate variability from 10-second resting electrocardiograms: the Lifelines Cohort Study. Eur J Prev Cardiol 2020;27:2191–4. https://doi.org/10.1177/2047487319872567.
[54] De Wandele I, Rombaut L, Leybaert L, et al. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers–Danlos syndrome. Seminars in Arthritis and Rheumatism 2014;44:93–100. https://doi.org/10.1016/j.semarthrit.2013.12.006.
[55] Braithwaite JJ, Watson DG, Jones R, et al. A guide for analysing electrodermal activity (EDA) & skin conductance responses (SCRs) for psychological experiments. Psychophysiology 2013;49:1017–34.
[56] Man ISC, Shao R, Hou WK, et al. Multi-systemic evaluation of biological and emotional responses to the Trier Social Stress Test: A meta-analysis and systematic review. Frontiers in Neuroendocrinology 2023;68:101050. https://doi.org/10.1016/j.yfrne.2022.101050.
[57] Crettaz B, Marziniak M, Willeke P, et al. Stress-induced allodynia--evidence of increased pain sensitivity in healthy humans and patients with chronic pain after experimentally induced psychosocial stress. PLoS One 2013;8:e69460. https://doi.org/10.1371/journal.pone.0069460.
[58] Zetterman T, Markkula R, Miettinen T, et al. Heart rate variability responses to cognitive stress in fibromyalgia are characterised by inadequate autonomous system stress responses: a clinical trial. Sci Rep 2023;13:700. https://doi.org/10.1038/s41598-023-27581-9.
[59] Thieme K, Rose U, Pinkpank T, et al. Psychophysiological responses in patients with fibromyalgia syndrome. Journal of Psychosomatic Research 2006;61:671–9. https://doi.org/10.1016/j.jpsychores.2006.07.004.
[60] Ashtiani A, Shaygannejad V, Ghobadi F, et al. Acute Response of Stress System in Multiple Sclerosis. Archives of Neuroscience 2021;8. https://doi.org/10.5812/ans.115781.
[61] de Brouwer SJM, van Middendorp H, Stormink C, et al. The psychophysiological stress response in psoriasis and rheumatoid arthritis. British Journal of Dermatology 2014;170:824–31. https://doi.org/10.1111/bjd.12697.

[62] Coppens E, Kempke S, Van Wambeke P, et al. Cortisol and Subjective Stress Responses to Acute Psychosocial Stress in Fibromyalgia Patients and Control Participants. Psychosomatic Medicine 2018;80:317. https://doi.org/10.1097/PSY.0000000000000551.
[63] Mohsenipour SM, Nasiri A, Pirzad-Jahromi G, et al. A reduced response to acute psychosocial stress in the chronic musculoskeletal pain patients. Journal of Bodywork and Movement Therapies 2025;45:393–9. https://doi.org/10.1016/j.jbmt.2025.09.011.
[64] Estrella E, Frazier PA. Healthcare experiences among adults with hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder in the United States. Disability and Rehabilitation 2024;46:731–40. https://doi.org/10.1080/09638288.2023.2176554.
[65] Nirjhar EH, Arthur W, Chaspari T. Perception of Stress: A Comparative Multimodal Analysis of Time-Continuous Stress Ratings from Self and Observers. Proceedings of the 26th International Conference on Multimodal Interaction, New York, NY, USA: Association for Computing Machinery; 2024, p. 397–406. https://doi.org/10.1145/3678957.3685746.
[66] Manetti L, Rossi G, Grasso L, et al. Usefulness of salivary cortisol in the diagnosis of hypercortisolism: comparison with serum and urinary cortisol. European Journal of Endocrinology 2013;168:315–21. https://doi.org/10.1530/EJE-12-0685.
[67] Jantaratnotai N, Rungnapapaisarn K, Ratanachamnong P, et al. Comparison of salivary cortisol, amylase, and chromogranin A diurnal profiles in healthy volunteers. Archives of Oral Biology 2022;142:105516. https://doi.org/10.1016/j.archoralbio.2022.105516.
[68] Southard V. What are The Best Outcome Measures for Persons with Hypermobile Ehlers-Danlos Syndrome and HSD: A Pilot Study? 2022.
[69] Rampazo ÉP, Rehder-Santos P, Catai AM, et al. Heart rate variability in adults with chronic musculoskeletal pain: A systematic review. Pain Practice 2024;24:211–30. https://doi.org/10.1111/papr.13294.
[70] Mathias CJ, Owens A, Iodice V, et al. Dysautonomia in the Ehlers–Danlos syndromes and hypermobility spectrum disorders—With a focus on the postural tachycardia syndrome. American Journal of Medical Genetics Part C: Seminars in Medical Genetics 2021;187:510–9. https://doi.org/10.1002/ajmg.c.31951.
[71] Riva R, Mork PJ, Westgaard RH, et al. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology 2012;37:299–306. https://doi.org/10.1016/j.psyneuen.2011.06.014.
[72] Costa AR, Freire A, Parraca JA, et al. Heart Rate Variability and Salivary Biomarkers Differences between Fibromyalgia and Healthy Participants after an Exercise Fatigue Protocol: An Experimental Study. Diagnostics 2022;12:2220. https://doi.org/10.3390/diagnostics12092220.
[73] Paso GAR del, Coba P de la. Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: An electrodermal study. PLOS ONE 2020;15:e0241154. https://doi.org/10.1371/journal.pone.0241154.
[74] Martin-Soelch C, Schnyder U. Editorial: Resilience and Vulnerability Factors in Response to Stress. Front Psychiatry 2019;10:732. https://doi.org/10.3389/fpsyt.2019.00732.
[75] Macchia L, Oswald AJ. Physical pain, gender, and the state of the economy in 146 nations. Social Science & Medicine 2021;287:114332. https://doi.org/10.1016/j.socscimed.2021.114332.
[76] Kirschbaum C, Kudielka BM, Gaab J, et al. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med 1999;61:154–62. https://doi.org/10.1097/00006842-199903000-00006.
[77] Wilson MC, Lorenz TK, Heiman JR. Salivary Afternoon Cortisol and Relationship Status in Healthy Women with Regular Menstrual Cycles. Womens Reprod Health (Phila) 2018;5:170–82. https://doi.org/10.1080/23293691.2018.1490079.
[78] Hamidovic A, Karapetyan K, Serdarevic F, et al. Higher Circulating Cortisol in the Follicular vs. Luteal Phase of the Menstrual Cycle: A Meta-Analysis. Front Endocrinol 2020;11. https://doi.org/10.3389/fendo.2020.00311.
[79] Geva N, Golan S, Pinchas L, et al. Sex effects in the interaction of acute stress and pain perception. Pain 2022. https://doi.org/10.1097/j.pain.0000000000002743.

[80] Rohleder N, Nater UM. Determinants of salivary α-amylase in humans and methodological considerations. Psychoneuroendocrinology 2009;34:469–85. https://doi.org/10.1016/j.psyneuen.2008.12.004.

[81] Strahler J, Skoluda N, Kappert MB, et al. Simultaneous measurement of salivary cortisol and alpha-amylase: Application and recommendations. Neuroscience & Biobehavioral Reviews 2017;83:657–77. https://doi.org/10.1016/j.neubiorev.2017.08.015.

Figure 1: Design of the Social Benefits Stress Test (SBST). Participants underwent baseline, anticipation, stress, and recovery phases followed by a debriefing. Salivary samples (S1-S7) and stress and pain Visual Analog Scales (VAS1-VAS9) were collected at several timepoints. Positive Affects and Negative Affects (PANAS) questionnaires were filled before and after the stress phase. Physiological parameters were recorded continuously throughout the task (dotted line) and analyzed for EDA and HRV over specific 5-min windows (blue brackets).

Figure 2: **Subjective measures during the SBST**. a) Self-reported subjective stress (green, Visual Analog Scale –VAS) and b) Self-reported subjective pain (orange, Visual Analog Scale –VAS). As pre-determined, the presented statistics are the baseline vs stress-task and end-of-stress-task vs recovery post-hoc tests, the other statistics can be found in supplementary. The orange frames show the timeframe where the task occurred, asterisks indicate significant reported post-hoc between successive SBST phases: **** for $p < 0.0001$, *** for $p < 0.001$, ** for $p < 0.01$ and * for $p < 0.05$. Boxplots show the median and interquartile range (IQR; whiskers extend to 1.5 × IQR). Dots represent individual participant values. Diamonds indicate group mean ± standard error of the mean (SEM). Dashed vertical lines denote phase boundaries.

Figure 3: Autonomic nervous system responses across the stress task. a) Heart rate (bpm), b) low-frequency power (LF), c) high-frequency power (HF), d) LF/HF ratio, e) root mean square of successive differences (RMSSD; ms), and f) electrodermal activity skin conductance responses (EDA SCR; number of peaks). Boxplots show the median and interquartile range (IQR; whiskers extend to 1.5 × IQR). Dots represent individual participant values. Diamonds indicate group mean ± standard error of the mean (SEM). Dashed vertical lines denote phase boundaries.

Figure 4: **Salivary biomarkers evolution during the stress task**. a) Salivary α-amylase concentrations (U/mL) across experimental timepoints b) Salivary cortisol raw data concentrations (nmol/L, log scale) across experimental timepoints. Red dots represent responders to the SBST with at least a 15.5% baseline to peak salivary cortisol increase. Grey dots represent non-responders. c) Peak-aligned salivary cortisol evolution, baseline-adjusted and Box-Cox transformed (t = 0, red dashed line). The yellow area (on the left) represents the activation phase (rising cortisol) and the green area (on the right) the recovery phase (declining cortisol). Boxplots show the median and interquartile range (IQR; whiskers extend to 1.5 × IQR). Dots represent individual participant values. Diamonds indicate group mean ± standard error of the mean (SEM). Dashed vertical lines denote phase boundaries.

Baseline
30 min

Anticipation
10 min

10 min
Interview (5 min) **Arithmetic task** (5 min)
Ehlers-Danlos, pain, fatigue, disability...
2033 - 13 = 2020
2020 - 13 = 2007
2007 - 13 = 1994...

Recovery
30 min

Debriefing
We believe you! +++

t = 0 min

Time

VAS1 0 — 10 → **S1** → **VAS2** 0 — 10 → **PANAS1**

+30 min → **S2** → **VAS3** 0 — 10

+40 min

VAS4 0 — 10

+50 min → **S3** → **VAS5** 0 — 10 → **PANAS2**

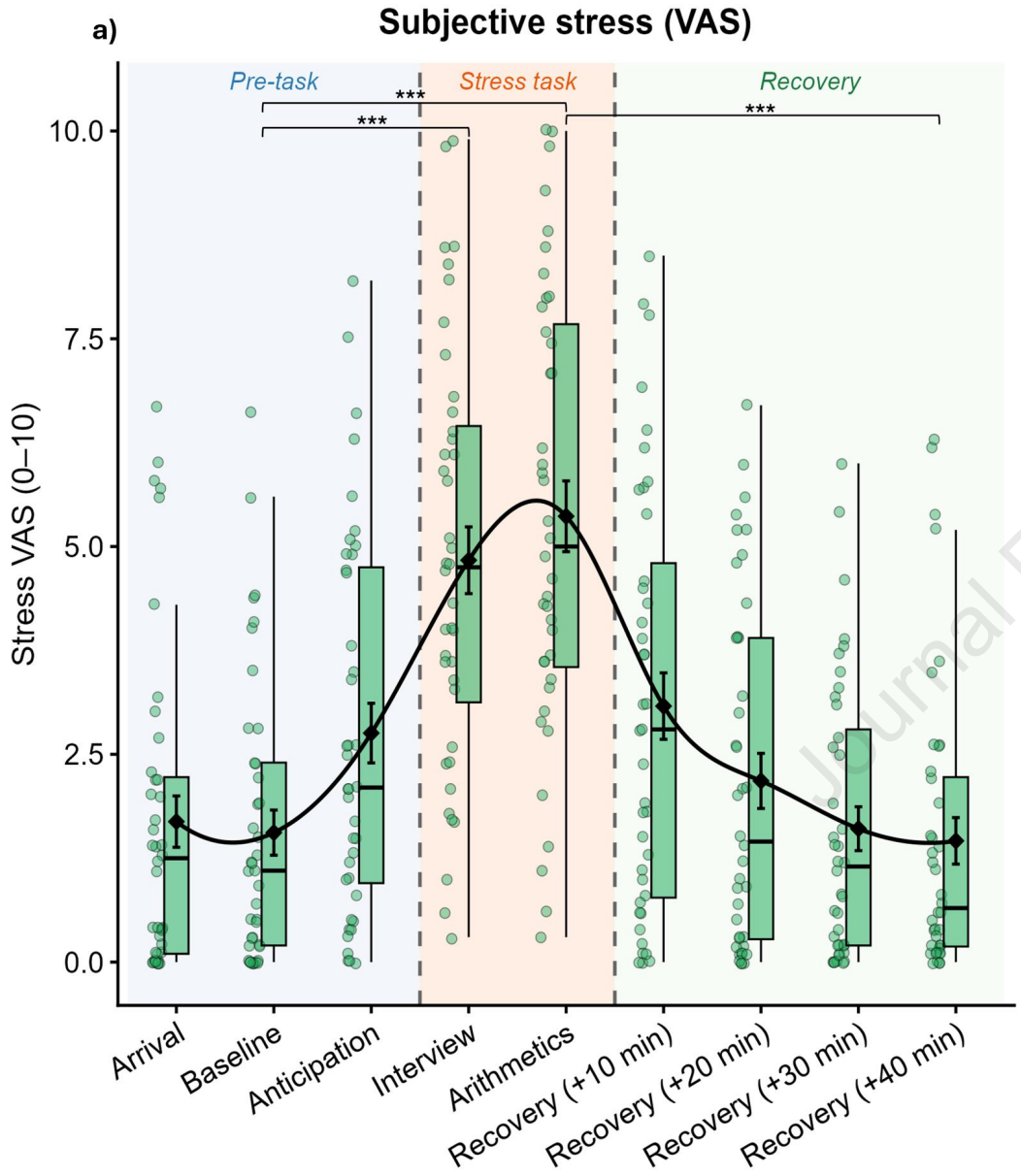
+60 min → **S4** → **VAS6** 0 — 10

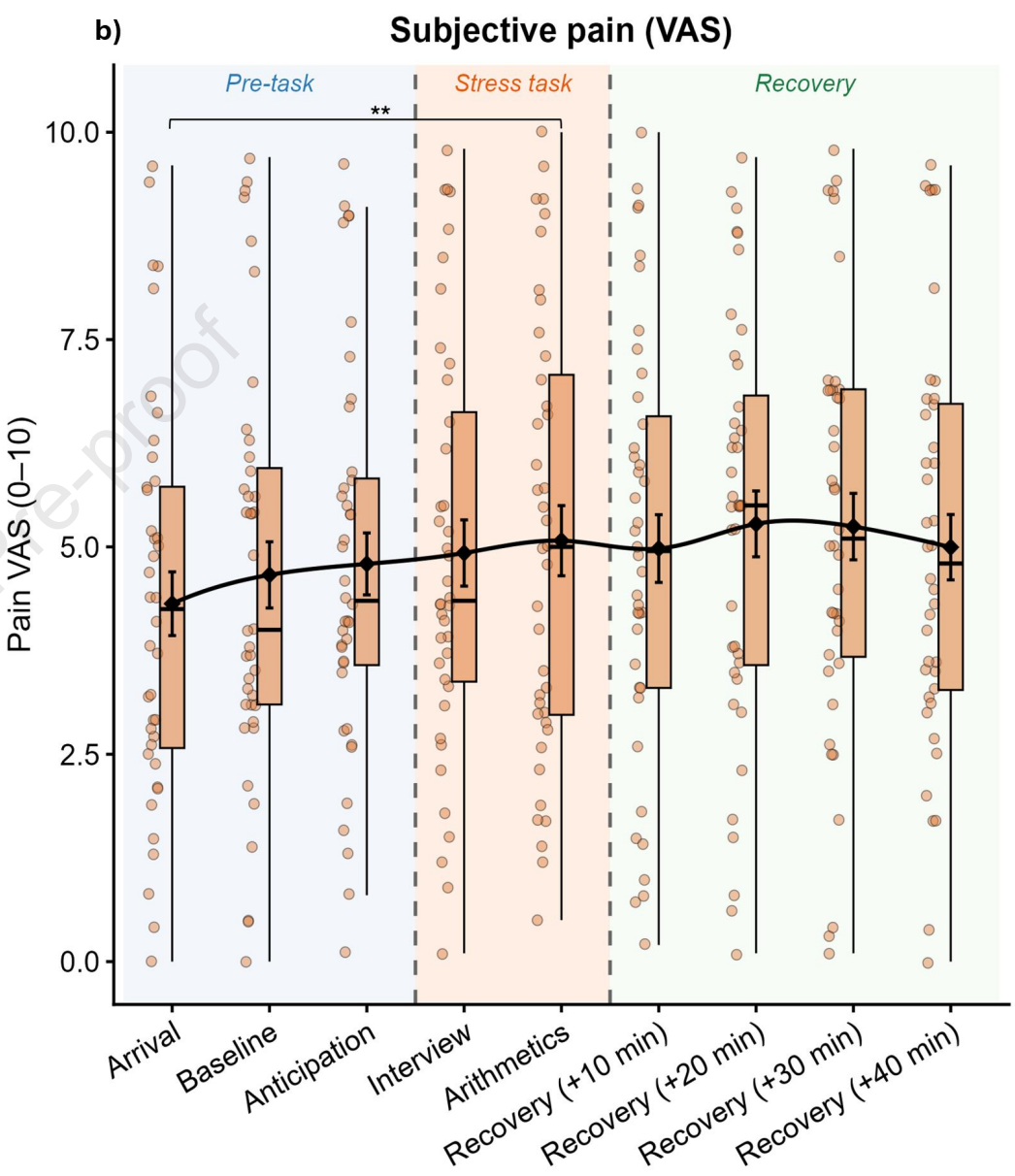
+70 min → **S5** → **VAS7** 0 — 10

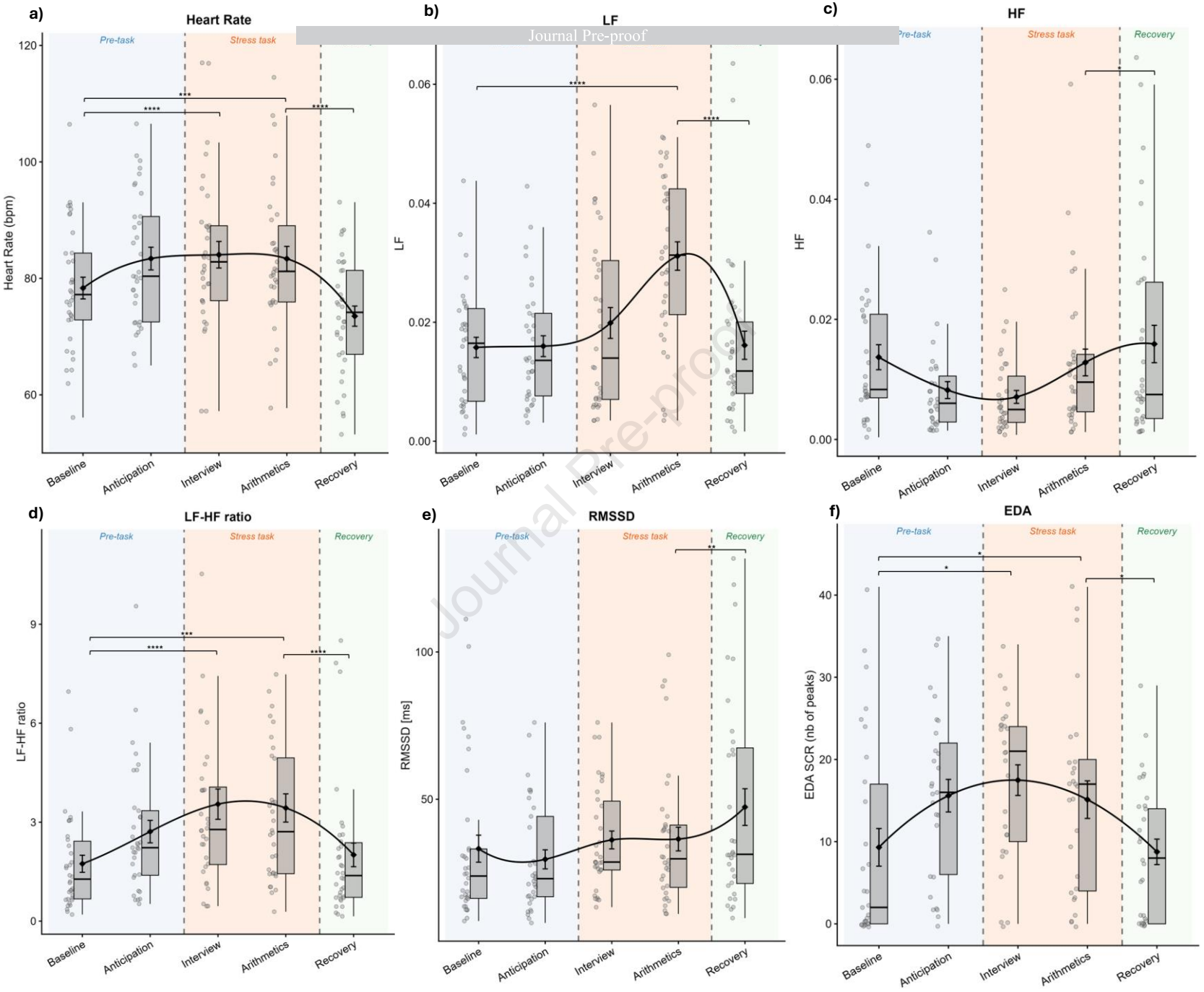
+80 min → **S6** → **VAS8** 0 — 10

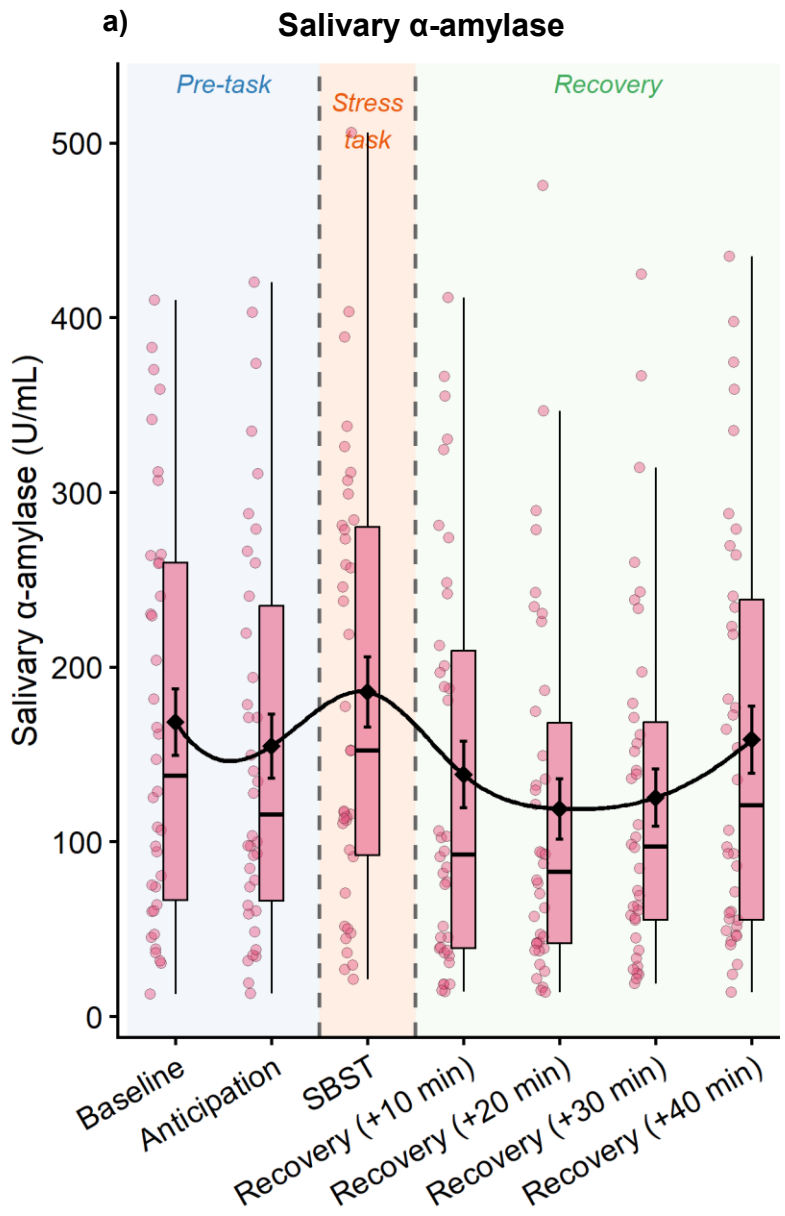
+90 min → **S7** → **VAS9** 0 — 10 → **Questionnaires**

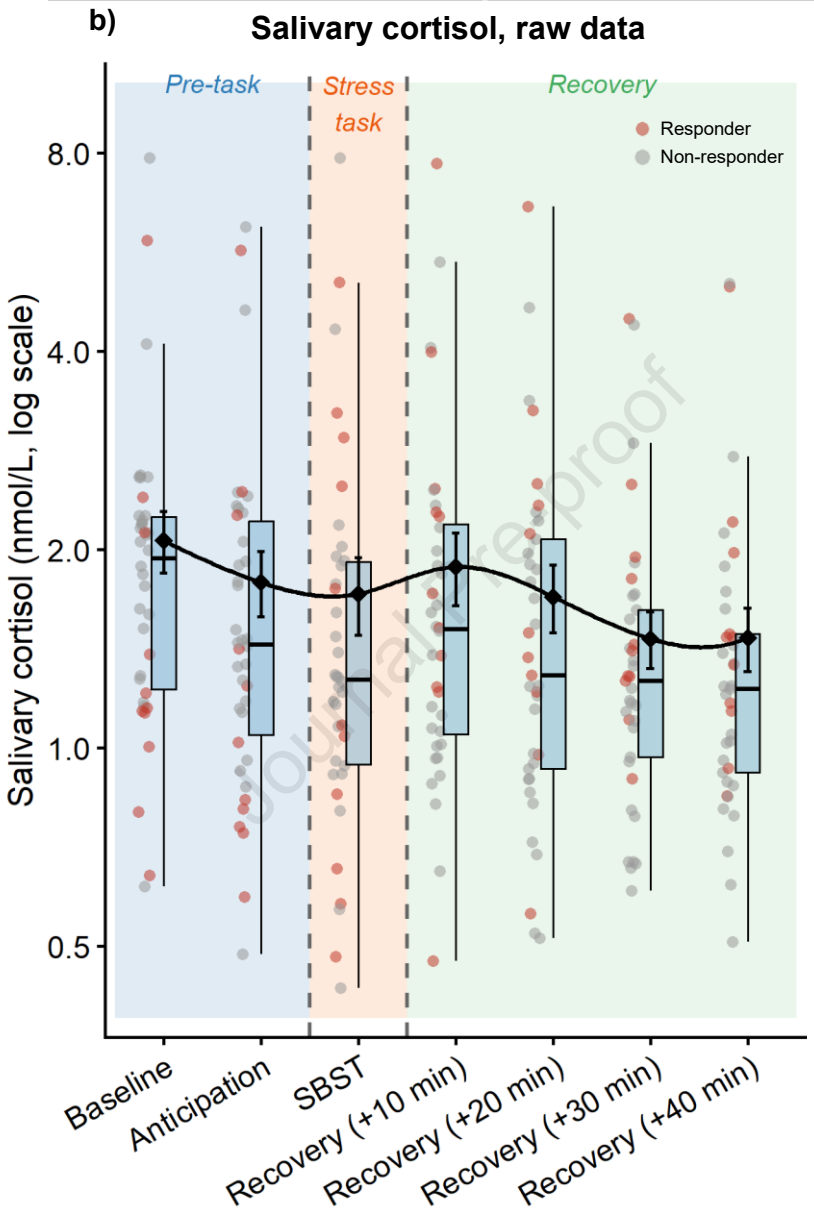
EDA / ECG

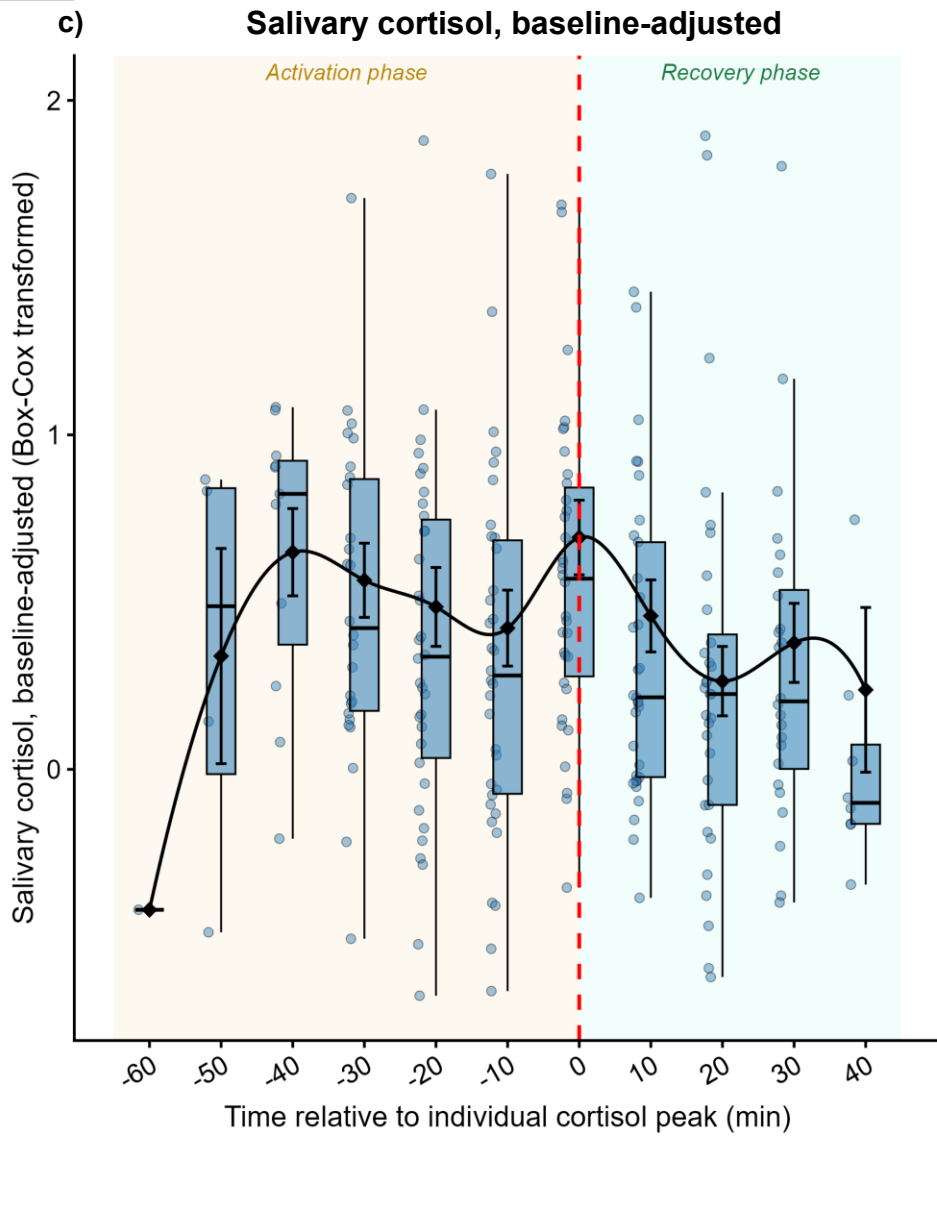












Highlights

- Maladaptive stress responses are involved in chronic pain maintenance and worsening
- Current paradigms like the Trier Social Stress Test are not adapted to chronic pain
- The Social Benefits Stress Test (SBST) could be a relevant task in chronic pain
- The SBST led to subjective and physiological stress responses
- The SBST will allow research on the interactions between chronic stress and pain

Disclosures:

The data that support the findings of this study are openly available in Zenodo at https://zenodo.org/record/12698226, reference number 10.5281/zenodo.12698226.

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