Perceived control as a resilience factor: Influences on neural, physiological and affective stress responses and mental health

Running title: Perceived control and multidomain stress responses

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Abstract

Perceived control is a key mechanism implicated in stress resilience. A tendency to perceive control over stressors may protect individuals against negative outcomes across various situations by increasing active coping and preventing exacerbated stress reactions. Assuming that individual differences in perceived control during an uncontrollable stress task may represent an underlying resilience factor, we investigated associations of perceived control with neural, endocrine, and affective responses to a different, psychosocial stressor, and with overall mental health. 116 male participants aged 18-30 completed a psychosocial stress task, and we assessed stress responses via functional magnetic resonance imaging, cortisol levels, and affective state questionnaires. General mental health was assessed via self-report. Perceived control was measured during a second, uncontrollable stress task and growth mixture modeling revealed a high- and a low-control class. Comparison of these classes showed that the high-control class experienced less helplessness during the uncontrollability task and demonstrated more flexible responses to psychosocial stress as reflected in cortisol secretion and activation of the bilateral posterior insula. Further, the high-control class reported fewer psychosomatic symptoms and a less external locus of control. These findings suggest that perceived control acts as a resilience factor, influencing stress processing across multiple domains. The study highlights the potential for perceived control to be harnessed in resilience-building interventions and underscores the need for further experimental and longitudinal research to confirm its role in modulating stress responses.

INTRODUCTION

Stress-related mental impairments are a significant public health issue, yet many people do not develop psychopathology after traumatic events but rather show resilience[1]. Unraveling the mechanisms that drive such resilience could help to prevent stress-related disorders. Perceived control is a mechanism that has been implicated in building resilience by several psychological theories. The transactional stress model and the component process model of emotion suggest that appraisals of control in aversive or threatening situations lead to reduced negative affective reactions[2,3]. These reactions are linked to stress-related disorders according to the PASTOR model of resilience[4]. This model posits that non-negative appraisals, including high controllability, lead to stress resilience by reducing negative stress reactions. Evidence shows that perceived control over negative life events correlates with better mental health outcomes, including reduced depression and increased well-being[5,6]. Furthermore, higher subjective control predicted increased longevity in a longitudinal study[7]. These beneficial effects might be mediated by a control-dependent reduction of stress-reactions, and a better understanding of the physical, neural and psychological pathways mediating the protective effect of control could help to harness its potential as a resilience mechanism.

Rodent studies indicate that on a neural level, the protective effect of control over stressors is mediated by the ventromedial prefrontal cortex (vmPFC) that down-regulates stress-related brain regions in the presence of control (for review, see Maier & Seligman[8]). Human neuroimaging studies as well show increased vmPFC activity and decreased activation in stress-related brain areas when stressors are controllable. For instance, higher BOLD responses in the vmPFC and lower responses in the insula were observed when participants controlled mild electric shocks and white noise[9]. Similarly, controllable videos with phobic content elicited more vmPFC activation and less in the amygdala than uncontrollable videos[10].

Perceived control over nociceptive stimuli reduced activation in pain-related areas such as the anterior cingulate cortex, the insula, and the somatosensory cortex[11]. In sum, human and rodent studies alike indicate that the vmPFC mediates the protective effect of control by inhibiting stress-related regions.

However, rodent studies suggest that control has not only immediate effects on stress processing but also strengthens the connection of the vmPFC with stress-related areas, leading to an immunization effect where even uncontrollable stressors no longer hyperactivate the stress system. In fact, animals immunized by repeated experiences of control neurally respond to uncontrollable stressors like to controllable ones[12], indicating that they *perceive* uncontrollable situations as controllable. Comparing neural stress responses between individuals perceiving high versus low control could thus shed light on the neural mechanisms underlying stress immunization.

Findings on such trans-situational effects of stressor controllability in humans are mixed. In line with the notion that perceived control may represent stress immunization, internal locus of control (LoC) – the generalized belief that outcomes are controlled by onself[13] – is cross-culturally associated with better mental health[14]. One behavioral study observed increased escape efficiency in a task following controllable aversive stimuli, indicating as well that transfer effects of control exist in humans[15]. A neuroimaging study tested the influence of instrumental control over physical stimuli on the processing of social stress but found only marginal differences in vmPFC connectivity[16]. Another study found that objective control over electric shocks did not affect later working memory performance[17], but subjective ratings of control did, and also predicted neural processing in prefrontal regions and the left insula. Hence, there is some evidence that perceived control may generalize and affect multilevel reactions to other stressors, but little is known about the exact underlying processes.

This study aimed to relate perceived control in an uncontrollable stress task as a proxy for stress immunization to multilevel stress responses in another stress task. We intended to build on previous results where we employed a stressor manipulation task with a triadic design and identified latent classes of participants differing in perceived controllability[18]. Here, a sample of healthy participants completed an uncontrollable version of this task ("uncontrollability task") and latent classes of perceived control were similarly derived. Before the uncontrollability task, participants also completed mental health questionnaires and performed a psychosocial stress task while we measured their brain activity with functional magnetic resonance imaging (fMRI), acquired saliva cortisol, and assessed affective stress reactions via self-report. We chose to conduct the uncontrollability task after the psychosocial stress task, to preclude that the uncontrollability task directly influenced the processing of the psychosocial stressor as this has been described in rodent experiments[19]. Rather than investigating direct transfer effects of control, we assumed that the perceived control classes reflect a general tendency to perceive more or less control that constitutes a putative resilience factor. Hence, we hypothesize that in addition to showing reduced stress reactions to the task itself, the class that perceived more control would also show a decreased stress response on multiple response levels to a different stress-eliciting task as well as better mental health.

METHODS AND MATERIALS

Participants and Procedure

We recruited 120 male participants aged 18-40 via flyers, university postings, and the local residency registration office. Exclusion criteria included psychiatric or neurological diagnoses, MRI contraindications, beta blocker or psychiatric medication intake, BMI > 27, and advanced studies in psychology or medical fields. Four participants were excluded from data analysis due to premature MRI termination (1), missing data (1) or dropout (2), resulting in a final sample of $N = 116$.

Participants attended three test appointments within ten days, with the first two reported on here. The first appointment included an MRI measurement with the psychosocial stress task (ScanSTRESS-C[20]) and simultaneous saliva cortisol, electrocardiogram, and skin conductance measurements. The latter two are not within the scope of this article, just as further MRI measurements. To control for elevated morning cortisol levels and diurnal variations, MRI sessions started between 11 and 11:30 am. Prior to the ScanSTRESS-C, participants completed a urine drug screen (SureStep™, Diagnostik Nord GmbH, Schwerin, Germany) and underwent a 45 min cool down phase during which they completed trait questionnaires and remained seated to avoid orthostatic effects on cortisol secretion[21]. On the second testing day, participants underwent an uncontrollable stress task, adapted from Meine et al.[15], during which perceived control was assessed at five timepoints. See Figure 1a for an overview of the procedure.

Participants received a complete study description, gave written informed consent, and were monetarily compensated. A cover story minimized bias by suggesting the study purpose was to measure brain activity during high cognitive performance. Participants were debriefed after the completion of the last test appointment. The study adhered to the declaration of Helsinki and was approved by the local ethical committee of Rhineland-Palatinate (ethics proposal 2018-13270).

Psychosocial stress task: ScanSTRESS-C

During the first appointment's scanning session, participants completed the ScanSTRESS-C[20], an adapted version of the ScanSTRESS task[22]. The paradigm consisted of 6 blocks without stress (noStress) serving as baseline, followed by six stress condition blocks. In the noStress condition, participants solved mental rotation and mathematical subtraction tasks with automated performance feedback. During the stress condition, participants faced the same tasks under time constraints and

while receiving social evaluative feedback via an online webcam broadcasting a live jury of so-called experts rating their performance through visual feedback. Response time windows were adapted to each participant's task performance. After three blocks of stress, the scanner was paused and participants received verbal feedback from the jury via the intercom, telling them to improve their performance, increasing psychosocial stress in the stress condition (see Figure 1b and Sandner et al.[20] for details). The task ran on Presentation® software version 20.1 (Neurobehavioral Systems, Inc., Berkeley, CA, USA; www.neurobs.com). Participants underwent a short training of the task using simpler task examples without psychosocial stress on a laptop outside the scanner to ensure instruction comprehension.

Affective reactions to the ScanSTRESS-C were measured using the German Multidimensional Mood Questionnaire[23] (MDBF) at four time points during the first testing day. This 24-item questionnaire assesses good/bad mood, alertness/tiredness, and calmness/restlessness. Subscale scores were computed according to the manual.

Saliva cortisol

Nine saliva samples were collected throughout the MRI session by passive drooling into Salivettes® (Sarstedt AG, Nümbrecht, Germany). The first (-25 min relative to stressor onset) and last (+73 min) sample were taken outside of the scanner. The other seven samples were taken at roughly -6, +6, +17, +22, +30, +39, and +56 min relative to stressor onset. The Salivette was placed into the participant's mouth by the experimenter and rested under the tongue for two minutes. All collected saliva samples were frozen and stored at -20 °C and sent in one batch on dry ice for analyses to the Institute of Biopsychology, Technical University Dresden, Germany. After thawing, samples were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence immunoassays with high sensitivity

(Tecan-IBL International, Hamburg, Germany). The intra- and interassay coefficients of variance were below 9%.

fMRI acquisition and analysis

Images were acquired on a 3T Siemens Trio (Siemens, Erlangen, Germany) using a 32-channel head-coil. Functional T2*-weighted images were obtained with a multiband echo planar imaging sequence with an acceleration factor of 4, 60 slices per run, and the following parameters: TR = 1000ms, TE = 29ms, flip angle = 56°, voxel size = 2.5mm isotropic, FOV = 220mm. Slices were measured in interleaved order. In addition, T1-weighted MPRAGE images were acquired (TR = 1900ms, TE = 2.52ms, flip angle = 9°, voxel size 1mm isotropic, FOV = 250mm). The task consisted of three runs, i.e., a condition without stress (noStress) serving as baseline and two stress runs, which were separated by oral instructions to improve performance. Data were preprocessed and statistically analyzed using SPM 12 (Wellcome Center for Human Neuroimaging, London, UK) running on Matlab 2017b (The Mathworks Inc., Natick, Massachusetts, USA). Fourteen participants were excluded due to head movement (>2.5mm, n=8) and incomplete data (n=6), resulting in a final MRI sample of N = 102. To account for scanner equilibrium effects, the first four images of each run were discarded. Images were reoriented to the SPM T1-template. Movement artifacts were corrected by spatially realigning the functional images to the first image using a six-parameter rigid body transformation. Realigned images were then co-registered to the participant's individual structural image in native space. Estimated parameters from forward deformations resulting from segmentation of participant's structural image, were used to normalize images into the Montreal Neurological Institute (MNI) standard space. During normalization, images were resampled to 2mm isotropic and finally smoothed using a Gaussian kernel of 8mm full width at half maximum.

First-level analyses used a general linear model with noStress and stress regressors, modelling the onsets of the respective blocks with a fixed duration of 40s and 20s pause in-between blocks, plus six motion regressors. Main contrasts were stress > no-stress and no-stress > stress.

Uncontrollability task

At the second study appointment, participants completed a task adapted from Meine et al.[15]. It included stressful stimulation with white noise bursts via headphones (Sennheiser HD 380 Pro, Sennheiser, Wedemark, Germany) at 85dB and aversive electric shocks administered through a wasp electrode attached to the back of the left hand and produced by a Digitimer DS7A current stimulator (Digitimer Ltd, Welwyn Garden City, UK). Electric shock intensity was calibrated for each participant individually to be unpleasant, yet not painful. The perceptual threshold was determined, and shock intensity increased in steps of 0.5 mA, until a rating of *unpleasant* to *very unpleasant* was reached, corresponding to 4-5 on a scale from 1 (*barely noticeable*) to 10 (*extremely painful*).

The task included 45 trials, each starting with a fixation cross, followed after 1 s by stressful stimulation in the form of concurrent double shocks 20ms apart, every 1.5s +/-0.25s and white noise bursts divided by short breaks of 50-200ms. After a variable time interval (see below), a green triangle, a square or a circle was presented on screen. Participants were told that each shape was assigned to one of three designated arrow keys (up, left, or right) and they would be able to stop the aversive stimulation by figuring out the shape-key assignment and pressing the correct key fast enough. In reality, the total duration of stimulation in each trial was predetermined: Each participant completed the same randomized sequence of preset trial durations ranging from 7.13 to 11.38s (M=9.12, SD=1.16). The shape was presented at a random time point uniformly distributed between 4.75 to 0.75s before the end of the

trial. Consequently, the trial sometimes ended shortly after the shape was presented, which could give participants the impression that they terminated the stressor by their key press, while in other trials, the aversive stimulation continued. Each trial was followed by an intertrial interval (ITI) of 3s +/-0.25s.

Unpleasantness, perceived helplessness, and control were rated after every ninth trial on a 7-point Likert scale from *not at all* to *very much*. State anxiety, depression, and negative affect were assessed before and after the task using the German versions of the state-trait-anxiety-depression inventory - state (STADI-S[24]), and positive negative affect schedule (PANAS[25]). We obtained sum scores as described in the test manuals and computed difference scores by subtracting pre from post scores.

Self-report measures

Mental health over the last couple of weeks was measured with the General Health Questionnaire German Version (GHQ-28[26,27]), assessing somatic symptoms, anxiety, social dysfunction, and depression. Higher scores indicate worse mental health. Participants also completed the German versions of the IE-4, a short instrument assessing internal and external locus of control[28] and the General Self-Efficacy Scale (GSE[29]).

Statistical analyses

Analyses of the behavioral and endocrine data were performed in R version 4.3.3[30] running in RStudio[31]. Data and analysis code are available at https://osf.io/g6au5/. Due to data protection reasons, the neuroimaging data is only available upon reasonable request from the corresponding author.

Analysis of perceived control: Growth mixture modeling

To investigate individual differences in subjective control, growth mixture models (GMMs) were estimated based on the trajectories of perceived control during the uncontrollability task. One to six class models with random intercepts and slopes were fitted using the package lcmm[32] and resulting models were compared based on the Bayesian Information Criterion (BIC), entropy and theoretical plausibility. Lower BIC and entropy closer to 1 indicate better model fit and discriminant power of the model and entropy greater than .7 is acceptable[33]. Classes smaller than 10% of the sample were deemed too small to allow for robust interpretation of the results. Derived class membership was then used as a grouping variable to identify differences in endocrine and neural stress responses to the ScanSTRESS-C task, in affective responses to the uncontrollability task, and in mental health. As generalized control beliefs like LoC may be related to the perceived control classes, we additionally examined class-differences in LoC and correlations of LoC with all stress outcomes.

Analysis of self-report measures:

As manipulation checks we assessed the changes in self-reported affect induced by the two tasks in the full sample. For the ScanSTRESS-C, we computed one-way rmANOVAs for good mood, alertness and calmness with the within-subject factor time (4 levels). Greenhouse-Geisser correction was applied if the assumption of sphericity was violated. Post-hoc tests comparing the measurements 2 and 3 before and after the ScanSTRESS-C were computed using the emmeans package[34] and corrected with the Tukey method. For the uncontrollability task, we conducted three paired *t*-tests between pre and post measures of the STADI-S subscales depression and anxiety and the PANAS.

To investigate the effect of perceived control on multilevel stress reactions, we compared the GMM classes in self-report measures of affect and mental health. To that aim, we conducted a MANOVA with the factor class and eight dependent

variables: Helplessness, change in state depression, state anxiety and negative affect over the course of the uncontrollability task, and the four subscales of the GHQ-28 (somatic, depression, anxiety, and social dysfunction). Because the assumption of covariance homogeneity was violated, the rank-based Wilk's lambda was chosen as test statistic[35]. The MANOVA was followed up with Welch-tests, *p*-values were Holm-corrected for multiple comparisons.

Analysis of endocrine responses

For the saliva cortisol data, responders were identified as participants with a baseline-to-peak increase of >= 1.5 nmol/l[36]. The success of the ScanSTRESS-C in inducing an endocrine stress response was tested with a mixed ANOVA on the cortisol measurements with the within-subject factor time (9 measurements) and the between-subject factor responder (yes/no) and the interaction. As measures of total cortisol secretion and increase in response to the stressor, we computed the area under the curve with respect to ground (AUC_g) and with respect to increase (AUC_i), respectively[37]. We only included the time points 2-7 (-6min, +39min) for these measures as saliva cortisol typically peaks 20-30 min after onset of psychosocial stress[20,38]. A recovery index was computed as the difference between individual peaks and the last measurement (+73 min). To assess differences in cortisol response to the ScanSTRESS-C between the perceived control classes, we computed a MANOVA with the dependent variables AUC_i, AUC_g, and recovery index and the factor class. Only responders were included in the MANOVA and it was followed up by separate ANOVAs that were Holm-corrected for multiple comparisons.

Analysis of neural data

For the second-level analyses of the neuroimaging data, a one-sample *t*-test was performed to determine the acute stress induction's effect (i.e. stress > noStress, noStress> stress). The significance level was set to p=.05, whole-brain family-wise error (FWE) corrected at voxel level. To assess class-differences in the neural stress response, the contrast images stress>noStress were entered into a two-sample *t*-test comparing the two classes. We used a statistical threshold of p=.05, FWE corrected at the cluster level, with a cluster forming threshold of uncorrected p=.001. Individual parameter estimates for the peak voxels of significant clusters were extracted with a custom Matlab script for the stress and noStress regressors.

RESULTS

Manipulation Checks

Affective stress response

For affective responses to the ScanSTRESS-C, rmANOVAs revealed a significant effect of time on positive mood, $F(2.41,270.36)=91.21$, $p<.001$, $\eta^2g=.21$, alertness $F(1.95,218.03)=33.15$, $p<.001$, $\eta^2g=.08$, and calmness, $F(2.52,282.73)=134.721$, $p<.001$, $\eta^2g=.29$. Post-hoc tests showed a significant decrease from measurement 2 to 3 (pre vs. post stress intervention) in good mood ($p<.001$), alertness ($p=.003$), and calmness ($p<.001$; see Figure S1a-c).

For the affective responses to the uncontrollability task, paired t-tests revealed a significant increase from pre to post for state depression, $t(115)=-8.65$, $p<.001$, for state anxiety, $t(115)=-7.43$, $p<.001$ and for negative affect, $t(115)=-6.30$, $p<.001$ (see Figure S1e-g)

Cortisol response

For the analysis of endocrine responses to the ScanSTRESS-C, 18 participants had to be excluded due to missing cortisol data. Of the remaining 98 participants, 62 (63.3%) were classified as responders. The mixed ANOVA on the cortisol measures showed significant effects for responder, $F(1,83)=25.54$, $p<.001$, $\eta^2g=.13$, time, $F(3.63,301.18)=12.52$, $p<.001$, $\eta^2g=.07$, and the interaction responder*time, $F(3.63,301.18)=18.36$, $p<.001$, $\eta^2g=.10$. Post-hoc tests revealed that, for non-responders, adjacent measurements did not differ significantly. For responders, there was a significant rise in cortisol from measurement 3 to 4 ($p<.001$) and significant decreases from measurements 5 to 6 ($p=.005$), 7 to 8 ($p=.017$) and 8 to 9 ($p=.018$), see Figure S1d. Hence, the ScanSTRESS-C successfully induced activation of the hypothalamic-pituitary-adrenal (HPA) axis in responders.

Neural stress response

The main effect stress>noStress showed activations in regions related to the executive control network, including the middle frontal gyrus, inferior parietal lobule and dorsal precuneus, and of the salience network, most notably the anterior insula. Moreover, the supplemental motor area and widespread parts of the occipital lobe were activated.

The reversed contrast noStress>stress revealed activations in regions of the default mode network, such as the posterior cingulate cortex, and medial frontal cortex, but also sensorimotor cortices, the cerebellum, posterior insula and the striatum. Please refer to Table S1 and Figure S2 in the supplement for details.

Perceived control trajectories: Growth mixture modeling

To identify latent classes representing differing trajectories of perceived control during the uncontrollability task, we fitted GMMs with 1-6 classes on the control rating trajectories. See Table 1 for model comparisons. The 2-class model had the best fit.

Predicted and observed trajectories of perceived control of the two classes can be seen in Figure 2. The bigger class (n=68) had very low perceived control that decreased even more over the course of the uncontrollability task, as indicated by a significant negative slope (b=-0.009, p=.014). The smaller class (n=48) had a higher level of perceived control and a non-significant slope, b=0.005, p=.454. See Table 2 for descriptive statistics of the derived classes. Although perceived control is likely to be related to generalized control beliefs like LoC, the classes differed only marginally in LoC and LoC was not statistically related to any of the outcomes measures (all rs < .30, all ps > .05, see Table S1 for details).

Differences in stress responses between the perceived control classes

Class differences in self-report measures

The rank-based one-way MANOVA on self-report measures showed a significant effect of class, $\chi^2(8)=39.24$, p<.001, Wilk's Λ=0.70. The follow-up Welch-tests revealed that the high-control class reported significantly lower helplessness, $t(88.69)=5.51$, p_{Holm}<.001, d=1.06, and fewer somatic symptoms in the GHQ-28, $F(107.2)=3.09$, p_{Holm}=.018, d=0.58. The effect of class on negative affect did not survive correction for multiple comparisons, $t(113.97)=2.43$, p_{Holm}=.101, d=0.44. There was no effect of class on change in state depression, $t(109.17)=0.38$, p_{Holm}>.999, and anxiety, $t(106.37)=0.57$, p>.999, in response to the uncontrollability task, or the GHQ-28 subscales depression, $t(113.99)=0.68$, p_{Holm}>.999, anxiety, $t(104.38)=0.51$, p_{Holm}>.999, and social dysfunction, $t(100.48)=0.72$, p_{Holm}>.999 (Figure S2).

Class differences in endocrine stress response

The one-way MANOVA on the cortisol measures revealed a significant effect of class, $F(3,53)=3.56$, p=.020, Pillai's trace=0.17. The follow-up ANOVAs demonstrated that the high-control class showed significantly higher cortisol secretion indicated by

AUC_g, $F(1,55)=7.82$, $p_{Holm}=.021$, $\eta^2=.12$; but no difference in cortisol increase (AUC_i), $F(1,55)=2.07$, $p_{Holm}=.291$, or cortisol recovery, $F(1,55)=2.18$, $p_{Holm}=.291$ (Figure 3).

Class differences in neural stress response

The 2-sample t-test for the contrast stress>noStress revealed three clusters that differed significantly between classes in the bilateral posterior insula (PI), R: peak at 40 -20 16, $T=4.44$, $p_{FWE}=.011$, 409 voxels; L: peak at -36 -20 16, $T=4.27$, $p_{FWE}=.007$, 455 voxels, and the postcentral gyrus, peak at 40 -20 62, $T=4.28$, $p_{FWE}<.001$, 777 voxels (Table S23). Parameter estimates indicated that for the high-control class, the activation in the PI was reduced under stress, compared to noStress, while no such difference between the conditions was observable in the low-control class (see Figure 4). For the inverse contrast, no activations differed between the classes.

DISCUSSION

The goal of the present study was to identify the influence of perceived control over an uncontrollable aversive event on responses to an independent psychosocial stressor as well as general mental health. To this end, we identified latent classes of individuals based on their control rating during an uncontrollable stress task and compared the obtained classes with respect to multilevel stress responses and mental health. Our results indicate that participants who perceive more control in the uncontrollability task report reduced helplessness during the task, but also show a differential neural and endocrine response to a psychosocial stress task and report better mental health.

In line with previous results from our group[18], there was substantial heterogeneity in perceived control in the uncontrollability task and participants could be classified by

GMM as belonging to one of two classes, a high- and a low-control class. The high-control class reported lower helplessness in response to the uncontrollability task, mirroring earlier results[18]. Helplessness induced by uncontrollable stress has been indicated as an etiological factor in clinical depression[39]. That a substantial proportion of participants was protected from feeling helpless despite an objectively uncontrollable stressor underlines the relevance of subjective - even illusory - control for resilience. Perceived control may constitute a malleable target for cognitive interventions and prevent stress-related impairments.

Targeting perceived control with adequate interventions is only valuable, however, if the tendency to perceive control over stressors is relatively stable and influences stress responses across different situations. Hence, the main goal of the present study was to show that higher perceived control over a stressor contributes to more adaptative stress responses in an unrelated task. Indeed, we found that the classes identified by their trajectory of perceived control in the uncontrollability task also varied in their reactions during a psychosocial stress task. More precisely, the high-control class showed increased cortisol secretion and reduced neural activation in the PI in response to psychosocial stress. Moreover, the high-control class reported fewer psychosomatic symptoms in the preceding weeks. Remarkably, locus of control, which is thought to reflect generalized expectancies regarding control, was only marginally more external in the low-control class and – in contrast to class membership – was not statistically related to stress outcomes or mental health. This indicates that the control rating in the uncontrollability task may be better than self-reported locus of control represents an underlying latent variable or resilience factor that seems to be related to stress processing across different situations and domains, aspects of mental health and personality.

To shed more light on this underlying factor, we examined these differences in detail. The higher total cortisol secretion as indicated by the AUC_g in the high-control compared to the low-control class contradicts previous findings where perceived

control and a more internal locus of control were related to attenuated cortisol reactions[40,41]. Yet, another study, in line with ours, found higher perceived control to be associated with higher cortisol increase in response to cognitively demanding tasks[42], indicating a complex association of cortisol, perceived control, and stress. In fact, cortisol modulates stress responses intricately: Basal cortisol levels permit other fast-acting stress hormones like catecholamines to unfold their effect when a stressor occurs, while a stress-induced increase of cortisol prevents overshooting stress reactions and prepares the organism for future stressors[43]. This means that cortisol likely mobilizes resources for active coping but also downregulates the stress response once it is no longer necessary. Dampened HPA axis activity in individuals who perceive little control over stress may impair flexible initiation and termination of coping responses when confronted with stressors.

We observed a similar lack of flexible responding in neural responses to the ScanSTRESS-C: While the high-control class showed deactivation of the PI under stress, compared to the noStress condition, no such stress-related adaptation of PI activation was found in the low-control class. This challenges findings of either no controllability-dependent modulation of PI activation[9,16], or even increased activation of the PI in response to controllable stress[44]. However, these studies compared controllable to uncontrollable stress, whereas we compared individuals with differing perceived control in an uncontrollable situation. Higher activation of the PI under controllable stress[44] may indicate that the controllable condition was less stressful and thus elicited reduced stress-related deactivation of the PI. This is in line with our observation that, across classes, the PI was generally less activated under stress, mirroring findings of Sandner et al.[20] who found a similar cluster to ours (labelled as Rolandic operculum) to be deactivated under stress. The posterior part of the insula has mostly been linked to pain processing[45,46] which may seem surprising as the ScanSTRESS-C involves no physical stressor or pain. Yet, down-regulation of a pain-related area under acute stress may be adaptive as lowered pain-sensitivity may allow

an individual to escape from a harmful situation despite an injury. Interestingly, a decreased cortisol reaction to social stress, as found in our low-control class, has been longitudinally linked to increased pain sensitivity and musculoskeletal pain[47]. Moreover, attenuated morning cortisol has been found in patients with persistent pain who also reported stronger depressed mood and dysfunctional coping strategies[48]. This is in line with our finding that the low-control class not only showed reduced cortisol secretion but also failed to down-regulate a pain-processing region and reported more psychosomatic symptoms. Hence, individuals who perceive little control over stressors may fail to flexibly respond to stress on endocrine and neural levels and this may manifest over time in psychosomatic distress.

While our study provides important evidence that perceived control is related to differential stress processing on multiple response levels, it has some important limitations. First, we cannot make claims about the causal direction of the observed effects, as we did not run a longitudinal design and because our classes were derived empirically, not experimentally. Yet, as researchers using experimental manipulations have struggled to find trans-situational effects of stressor controllability[16,17], the present study helps to fill a research gap. The classes identified by the uncontrollability task may provide important insights on the systems that are related to perceived control and inform future experimental studies on the outcomes in which controllability-dependent effects can be expected. Second, future studies should include more and faster-acting stress markers such as, for instance, salivary alpha-amylase[49] to provide valuable information on the interplay of different stress-hormones in relation to perceived control. Finally, our sample consisted only of rather educated, healthy young males, which limits the generalizability of our findings and necessitates replication in more heterogeneous samples. Moreover, it could be of interest to investigate if classes with differential perceived control also exist in clinical populations with varying psychopathological symptoms.

In the present study we highlighted the association of subjectively perceived control over an uncontrollable physical stressor with stress responses to a different, i.e. psychosocial stress task as well as mental health. From the two classes identified by GMM, the one perceiving low control reported increased helplessness in response to the uncontrollable task, but also reduced cortisol secretion and less flexible responding in the insula during the psychosocial stress task as well as increased somatic symptoms of mental distress. On a cautious note, we assume that these effects are related to an underlying tendency to perceive less control over important negative aspects of life and associated maladaptive changes in stress-processing that may also be related to impaired mental health. The association between perceived control and endocrine as well as neural stress responses might also indicate different therapeutic interventions: Cognitive-behavioral measures could support individuals in identifying ways of controlling negative aspects of their lives, possibly supported by neurofeedback. Pharmaceuticals or neurostimulation could increase systemic cortisol levels and activation of the insula and in turn influence perceived control from a physical level. However, as our results are purely correlational, experimental and longitudinal studies are needed to confirm perceived control as a resilience factor modulating multilevel stress responses.

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Conflict of Interest

The authors declare no conflict of interest.

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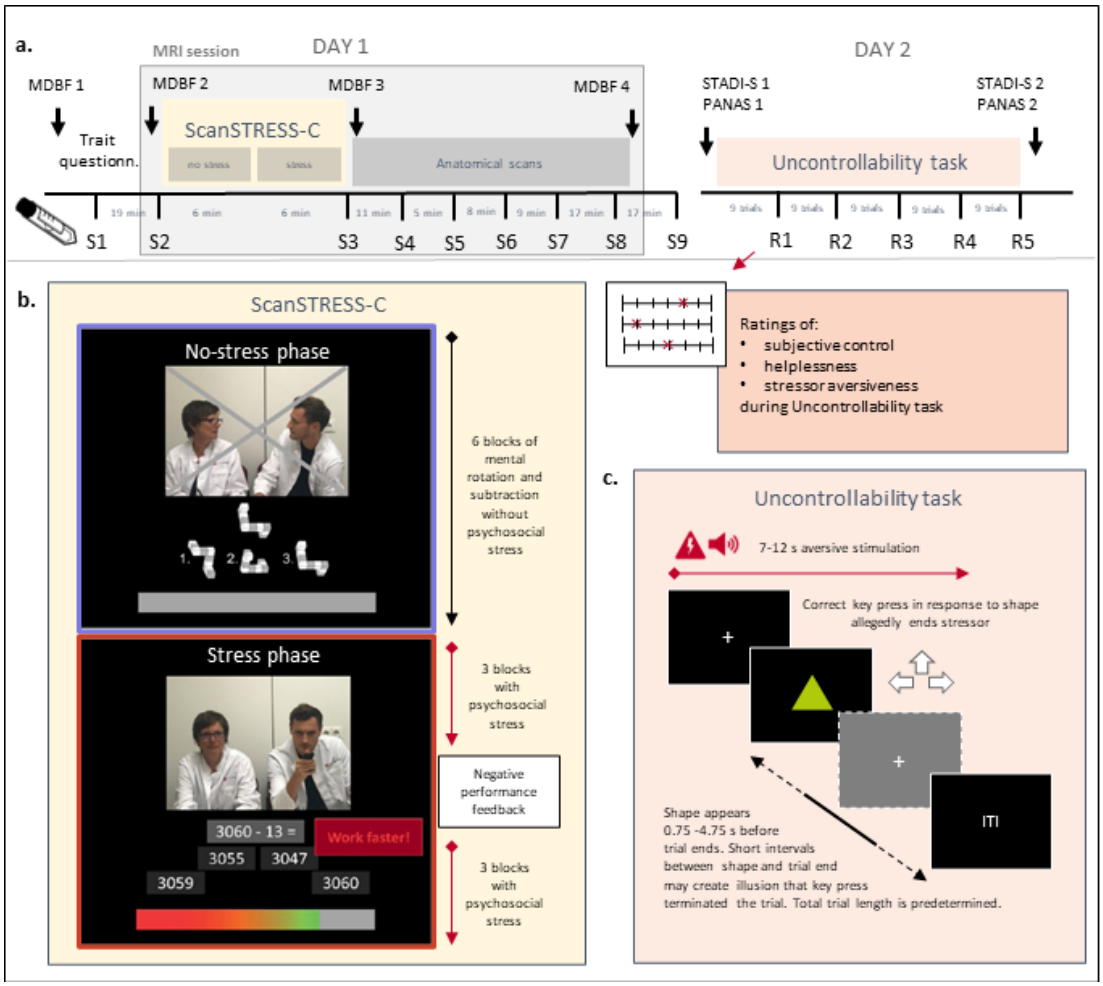
FIGURES

Figure 1

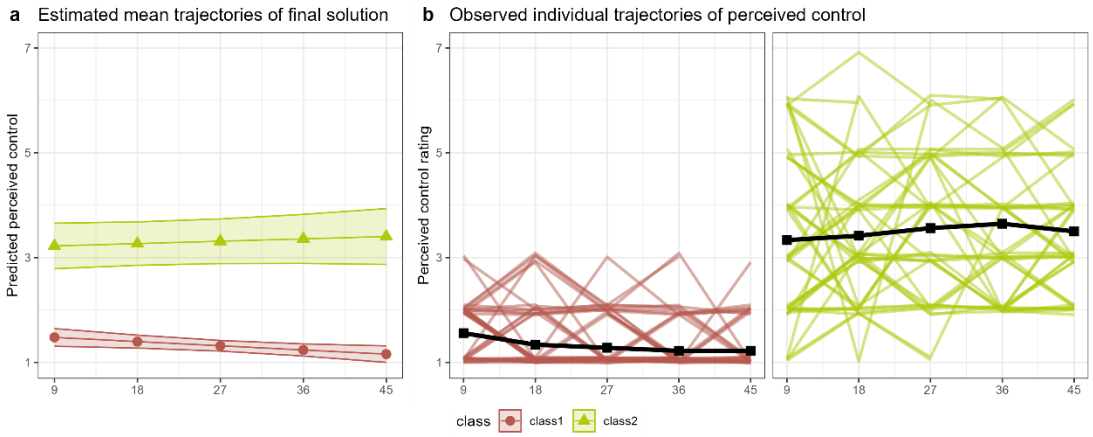
Experimental procedure



Note. (a) Overview of the experimental procedure with MRI session including the psychosocial stress task ScanSTRESS-C on day 1 and the uncontrollability task on day 2. (b) ScanSTRESS-C with demonstration of the two cognitive tasks that had to be solved (mental rotation and subtraction) in noStress and stress blocks. Jury not watching in the noStress phase but watching and criticizing slow and inaccurate performance in stress blocks, additional time limit indicated by the colored bar. (c) Uncontrollability task with aversive stimulation that is supposedly terminated by correct arrow key presses in response to a geometric shape. Trial termination is unrelated to key presses, but variable trial lengths can create the illusion of control over stimulation. S1-S9: Saliva samples; R1-R5: Ratings of subjective experience; MDBF: multidimensional mood questionnaire; STADI-S: State-trait anxiety and depression inventory state version; PANAS: positive and negative affect scale, ITI: Inter trial interval. (b) Reprinted and adapted from *Psychoneuroendocrinology*, 118, Sandner, M., Lois, G., Streit, F., Zeier, P., Kirsch, P., Wüst, S., & Wessa, M., Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. 104660, Copyright Elsevier Ltd. (2020), with permission from Elsevier.

Figure 2

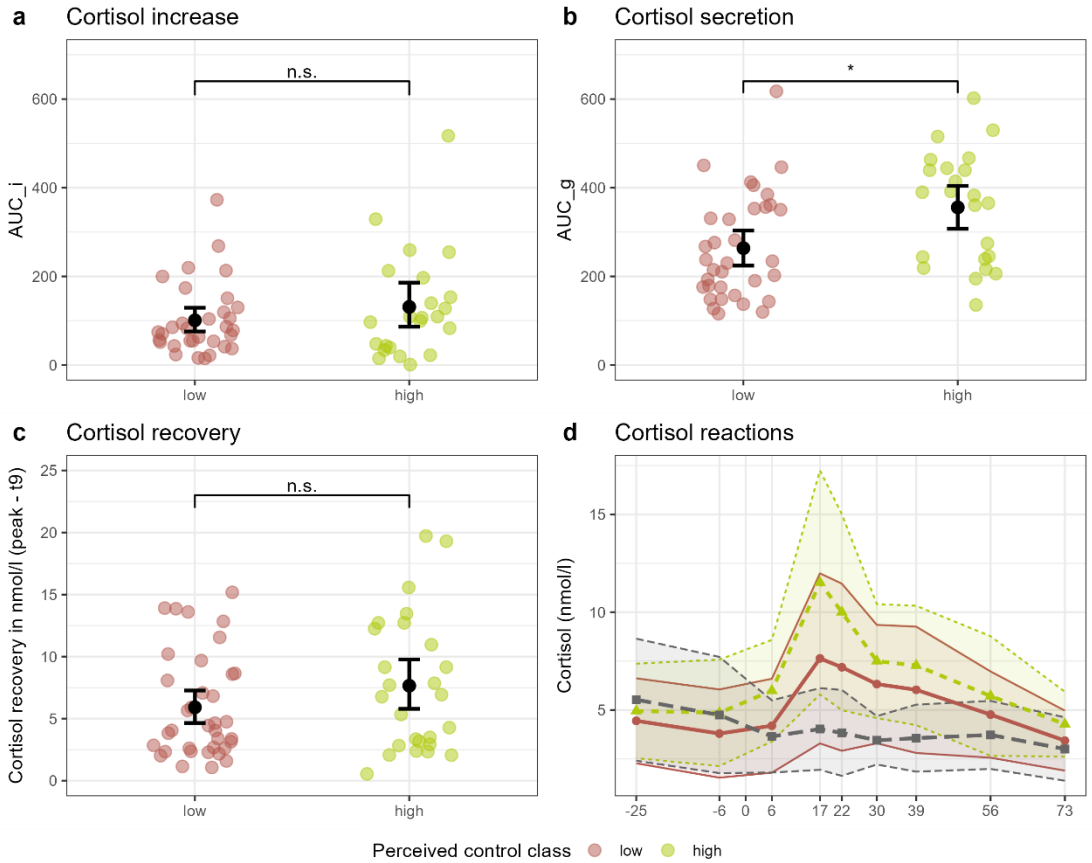
Predicted and observed trajectories of perceived control of the latent classes identified with GMM



Note. The best-fitting growth mixture model was a model with two latent classes. Estimated (a) and observed (b) trajectories of these classes differed in mean level of perceived control, resulting in a low-control and a high-control class. The low-control class had a negative slope, indicating that perceived control decreased even more over time for these participants.

Figure 3

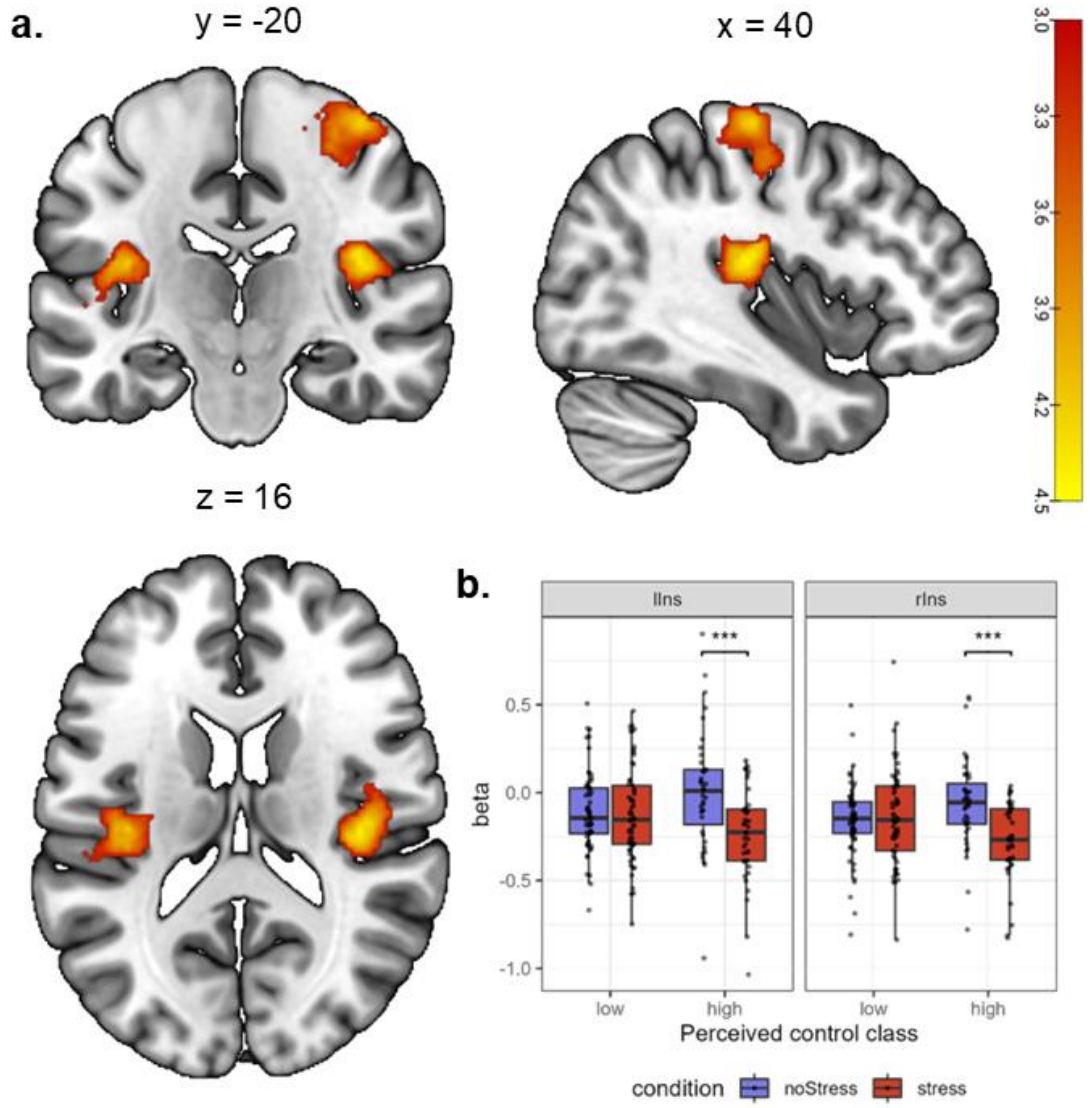
Class differences in cortisol response to psychosocial stress



Note. Cortisol increase (a), total cortisol secretion (b), cortisol recovery (c) and mean cortisol reaction (d) in response to the ScanSTRESS-C task for the two perceived control classes derived from growth mixture modeling. Non-responders not included in plots a-c, errorbars denote bootstrapped 95% confidence intervals. Margins in (d) are standard deviations. AUC_i: Area under the curve with respect to increase, AUC_g: Area under the curve with respect to ground, n.s.: non-significant, * p_{Holm} <.05.

Figure 4

Class difference in neural response to psychosocial stress



Note: Significant clusters (a) and parameter estimates at peak voxels of posterior insula clusters (b) for the comparison of the low and high-class for the contrast stress>noStress. Activation maps are thresholded at p=.05 FWE-corrected on cluster-level and overlayed onto SPM152 template. lIns = left insula, rIns = right insula, *** p < .001.

TABLES

Table 1

Model comparison for growth mixture models

G	Max LL	conv	npm	BIC	Entropy	% participants in classes					
						1	2	3	4	5	6
1	-862.97	1	6	1754.5	1.00	100					
2*	**-814.01**	**1**	**10**	**1675.6**	**0.73**	**58.6**	**41.4**				
3	-807.43	1	14	1681.4	0.79	15.5	57.8	26.7			
4	-806.63	1	18	1698.8	0.77	52.6	15.5	7.8	24.1		
5	-805.95	1	22	1716.5	0.78	7.8	8.6	53.5	25.0	5.2	
6	-800.64	2	16	1724.9	0.84	7.8	5.2	7.8	12.1	51.7	15.5

Note. Model fit for growth mixture models with different numbers of latent classes. The 2-class model had the best fit indicated by the lowest BIC, acceptable entropy and reasonable class sizes.

Model formula: control rating ~ trial, subject = ID, random = ~1 + trial

G = number of classes, Max LL = maximum loglikelihood, conv = converged (1=yes, 2=no), npm = number of parameters, BIC = Bayesian Information Criterion

* chosen model

Table 2

Descriptive statistics for the latent classes

Variable	Low	High	Full sample	*t*/X^2	*p*
N	68 (58.6%)	48 (41.4%)	116		
Age	26.32 (5.37)	26.60 (5.66)	26.44 (5.47)	-0.27	.789
Highest educational degree					
None	-	-	-		
Middle school	2 (2.9%)	1 (2.1%)	3 (2.6%)		
High school	29 (42.6%)	13 (27.1%)	42 (36.2%)		
Apprenticeship	9 (13.2%)	10 (20.8%)	19 (16.4%)		
University degree	27 (39.7%)	24 (50%)	51 (44%)		
Not reported	1 (1.5%)	-	1 (0.9%)		
General self-efficacy	30.91 (3.68)	30.15 (3.56)	30.60 (3.64)	1.11	.271
Locus of control					
internal	4.38 (0.55)	4.36 (0.56)	4.38 (0.56)	0.17	.866
external	1.97 (0.51)	1.77 (0.65)	1.89 (0.58)	1.85	.067
Stressor aversiveness	5.64 (0.99)	5.00 (1.20)	5.38 (1.12)	3.04	.003**
Shock intensity	3.72 (2.48)	4.29 (2.53)	3.96 (2.51)	-1.20	.233
Stimulation duration per trial	9.13 (1.16)	9.13 (1.16)	9.13 (1.16)		
		Cortisol			
N	59 (60.2%)	39 (39.8%)	98		
Cortisol responders	36 (61%)	26 (66.7%)	62 (63.3%)	0.13	.724

Note. Description of the latent classes derived from growth mixture modeling. The classes did not differ in age or general self-efficacy. External locus of control was higher in the low class with a trend towards significance. The low class reported greater subjective stressor aversiveness, but the classes did not differ in objective shock intensity, indicating that this was not caused by differing shock levels. One participant from the low class had to be excluded from the comparison, as due to technical difficulties, his shock intensity had to be set to the maximum of 99.9 mA. For continuous variables: Mean (SD). For categorical variables: Count (Percent). *T,* X^2 and *p* values derived from *t*-tests and X^2-test. ***p*<0.01.

Supplementary information

Table S1

Correlations of internal and external LoC with stress outcomes and mental health

		Internal LoC		External LoC	
	N	*r*	*p*	*r*	*p*
Helplessness	114	0.13	>.999	0.05	>.999
STADI-S depression	114	0.03	>.999	0.00	>.999
STADI-S anxiety	114	-0.18	>.999	0.19	>.999
PANAS negative	114	0.02	>.999	0.09	>.999
GHQ28 depression	114	-0.23	.225	0.25	.168
GHQ28 anxiety	113	-0.20	.678	0.10	>.999
GHQ28 somatic	113	-0.10	>.999	0.27	.086
GHQ28 social dysfunction	114	-0.04	>.999	0.03	>.999
Cortisol AUC_i	84	0.04	>.999	-0.12	>.999
Cortisol AUC_g	84	-0.07	>.999	-0.10	>.999
Cortisol recovery	93	-0.02	>.999	-0.10	>.999

Note. Associations of internal and external Locus of Control (LoC) with self-report and endocrine stress outcomes and mental health. *p*-values are Holm-corrected. STADI-S: State-trait anxiety and depression inventory – state version. GHQ28: General Health Questionnaire, 28 item version. AUC_i: Area under the curve with respect to increase, AUC_g: Area under the curve with respect to ground.

Table S2

Significant clusters for the stress effect in the ScanSTRESS-C

Region		MNI coordinates			*T*	p^{FWE}	Voxels
		x	y	z			
Stress > NoStress							
Inferior frontal gyrus (pars opercularis)	L	-42	10	28	11.58	<.001	3081
	R	46	14	26	11.07	<.001	6180
Middle occipital gyurs	R	42	-72	26	10.76	<.001	15286
Thalamus	R	6	-26	-6	10.03	<.001	1205
Middle frontal gyrus	L	-22	8	54	7.77	<.001	318
	R	34	56	0	5.19	.001	58
Cerebellum 9	L	-12	-46	-48	7.51	<.001	91
Superior frontal gyrus medial part	R	4	30	48	7.00	<.001	423
orbital part	R	22	50	-12	6.54	<.001	114
Precuneus	R	18	-54	20	6.60	<.001	128
Superior temporal gyrus	R	50	-20	-6	6.42	<.001	145
Supramarginal gyrus	L	-46	-38	32	5.33	.010	14
NoStress > Stress							
Postcentral gyrus	L	-44	-24	62	12.04	<.001	2865
Angular gyrus	L	-52	-64	40	10.50	<.001	552
Putamen	L	-18	6	-6	10.24	<.001	988
	R	16	8	-8	8.47	<.001	294
Cerebellum 8	R	18	-58	-48	7.96	<.001	75
Cerebral crus 1	R	36	-78	-34	7.75	<.001	121
Superior frontal gyrus	L	-14	44	44	7.29	<.001	729
medial part	L	-6	56	4	6.78	<.001	339
Middle temporal gyrus	L	-60	-20	-20	6.51	<.001	160
Posterior cingulate	L	-2	-40	32	6.44	<.001	329
Cerebellum 4 5	R	18	-48	-22	6.07	.002	39
Precentral gyrus	R	36	-14	68	5.56	.007	20
Superior temporal gyrus	R	56	-2	0	5.22	.014	10
	L	-56	-10	6	5.19	.010	15

Note. Significant clusters with ≥ 10 voxels for the 1-sample *t*-tests stress>noStress and noStress>Stress across the whole sample, independent of perceived control class, anatomical labels derived with local maxima labelling using SPM toolbox AAL2, FWE = whole-brain family-wise error corrected on voxel-level

Table S3

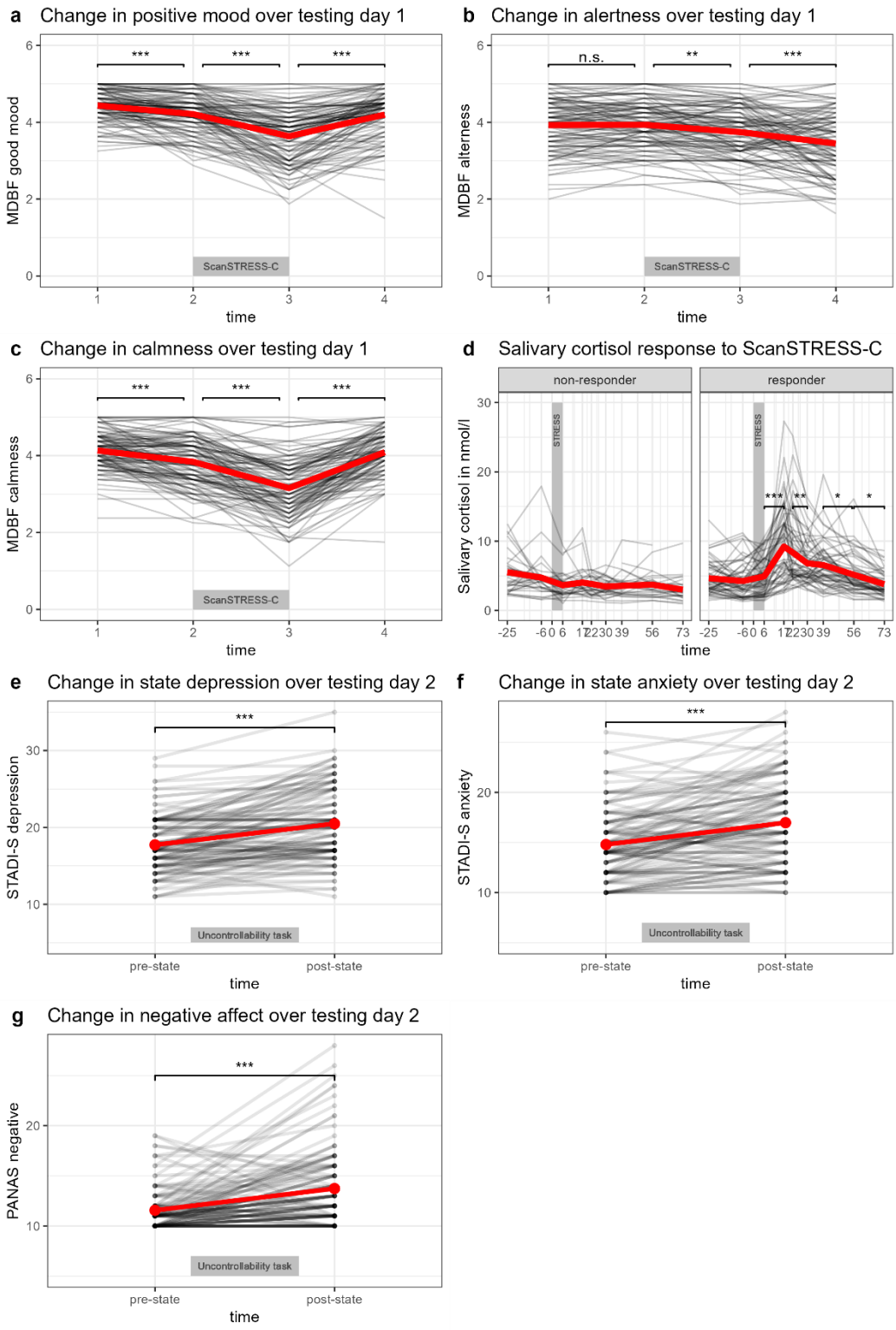
Clusters significantly differing between the classes in the ScanSTRESS-C

Region		MNI coordinates			*T*	p^{FWE}	voxels
		X	Y	Z			
Stress > NoStress							
Insula	R	40	-20	16	4.44	.011	409
Postcentral gyrus	R	40	-20	62	4.28	<.001	777
Insula	L	-36	-20	16	4.27	.007	455
NoStress > Stress							
No suprathreshold clusters							

Note. Clusters of activation significantly differing between the perceived control classes for the contrast stress > baseline. MNI = Montreal Neurological Institute, FWE = whole-brain family-wise error corrected on cluster-level.

Figure S1

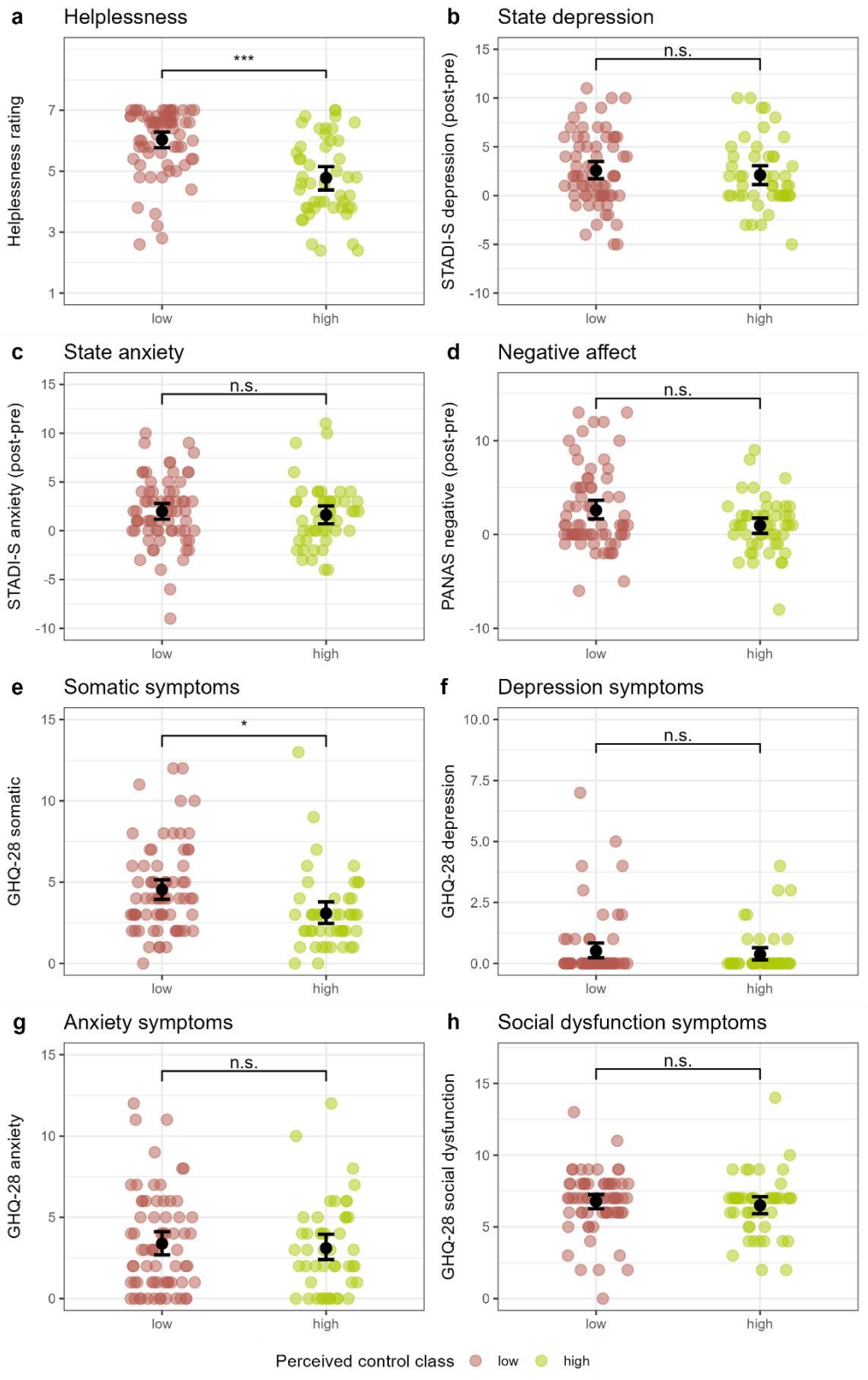
Manipulation checks



Note. Changes in self-reported affect and cortisol over the course of the experimental manipulations on testing days 1+2 for all participants (aggregated across perceived control classes).

Figure S2

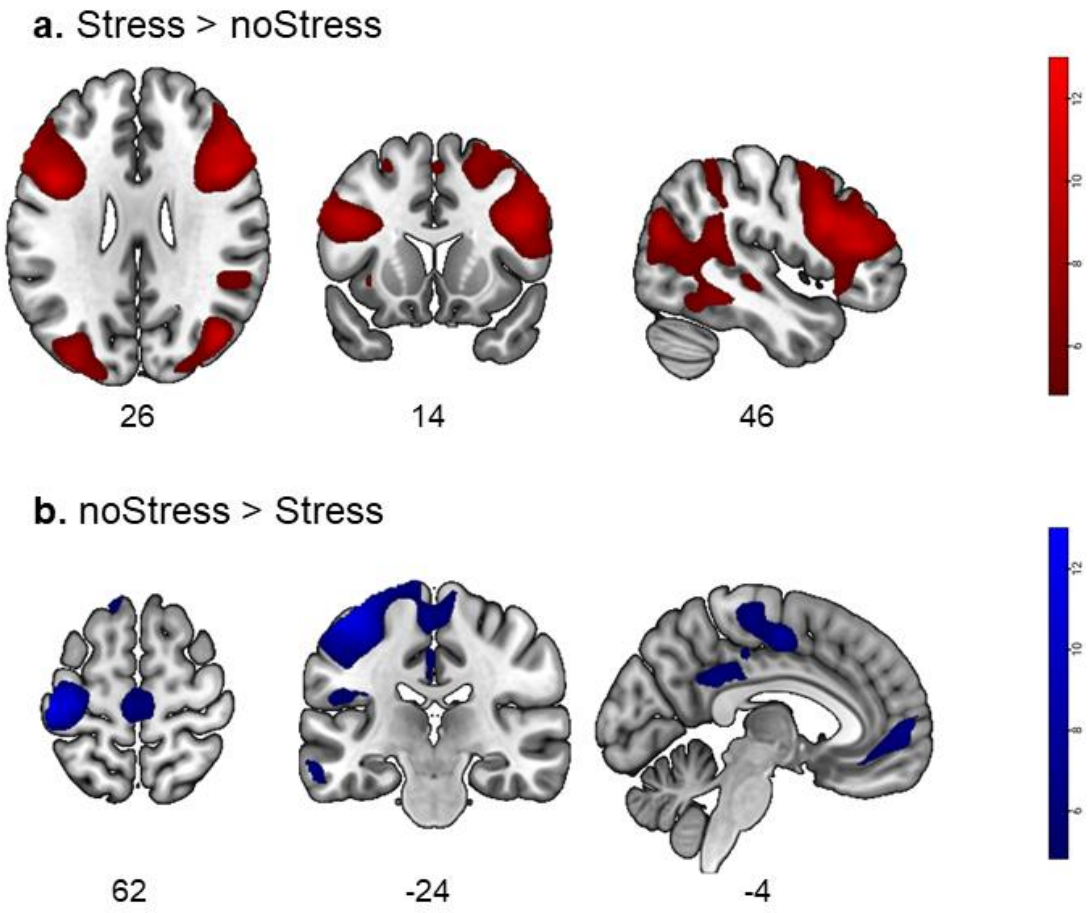
Differences between the perceived control classes in self-report measures



Note. Plots of all outcomes included into the self-report MANOVA by perceived control class. Errorbars denote bootstrapped 95% confidence intervals. n.s.: non-significant, * pHolm < .05, ** pHolm < .01, *** pHolm < .001.

Figure S3

Neural response to ScanSTRESS-C across classes



Note. Significant clusters for the effects of stress (a) and no stress (b) in the ScanSTRESS-C aggreagated across perceived control classes. Activation maps are thresholded at p=.05 FWE-corrected on peak-level and overlayed onto SPM152 template.