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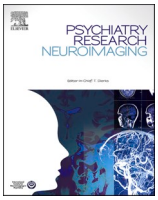

The generalization of behavioral control over physical threats to social stressors in humans: A pilot fMRI study

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ABSTRACT

Behavioral control, the ability to manage one's exposure to a given stressor, influences the impacts of both the present and future stressors. Behavioral control over a stressor may decrease stress caused by the stressor, and promote resilience towards future stressors. A lack of behavioral control may exacerbate the stress response and lead to learned helplessness, a generalized view that one cannot control other, unrelated stressors in their environment. The ventromedial prefrontal cortex (vmPFC) may detect the presence of behavioral control over a stressor and communicate this to subcortical regions involved in stress responses, such as the nucleus accumbens (NAc). Building on previous research in animals and humans, we piloted a paradigm to investigate how behavioral control over a physical threat (electric shocks), generalized to responses for a subsequent social stressor (anticipation of public speaking). Our manipulation of behavioral control effected perceived control between groups, increased stress across but not between groups, and no effects generalized to the subsequent social stressor in behavioral, physiological, or neural responses. We discuss refinements to the paradigm to strengthen the manipulation, the potential impacts of statistical power on the present results, and metrics to measure the generalization of behavioral control in addition to vmPFC-subcortical connectivity.

1. Introduction

Exposure to stressors typically yields adverse consequences in human and animal models; however, these consequences can be modulated by how one experiences and responds to the stressor (Maier and Watkins, 2010). Experiencing behavioral control, the ability to alter the frequency or duration of one's exposure to a stressor may dampen adverse reactions and foster resilience when facing future stressors (Crane and Searle, 2016; Southwick and Charney, 2012). On the other hand, experiencing a lack of behavioral control over a stressor may lead to learned helplessness (Seligman and Maier, 1967), the belief that future stressors are similarly out of one's control. While resilience can help protect against psychopathology arising from exposure to stressors, learned helplessness may be an underlying cause of depression and other psychiatric conditions. Learned resilience or helplessness from one type of stressor, such as a physical threat, may generalize to how other kinds of stressors, such as social or emotional threats, are experienced (Amat et al., 2010; Christianson et al., 2009; Maier, 2015).

Much research on the behavioral and neural effects of stressor controllability has been conducted in animals. Rats first exposed to escapable tail shocks will typically learn the necessary behavior to avoid this stressor, and the behavior will persist even when shocks become inescapable (Amat et al., 2005, 2006). If inescapable shocks are encountered first, the opposite response occurs, and animals will not attempt to avoid later, escapable tail shocks (Overmier, 1968; Overmier and Seligman, 1967). These divergent responses, predicted by the initial controllability of a physical stressor, also generalize to later social stressors (Amat et al., 2010; Baratta et al., 2009; Christianson et al., 2009). Functional connectivity between the ventromedial prefrontal cortex (vmPFC) and dorsal raphe nucleus (DRN) may underlie these

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behavioral responses at the neural level. The vmPFC plays a key role in detecting behavioral control over stressors (Maier and Watkins, 2010). During exposure to controllable stressors, the vmPFC inhibits activity in the DRN via glutamatergic projections, reducing innervation from the DRN to areas engaged during stress responses such as the nucleus accumbens (NAc), periaqueductal gray (PAG), and amygdala. Inhibition of the DRN and its subsequent projections is believed to blunt the negative impact of stressors on the animal. If an uncontrollable stressor is encountered first, the DRN's communication with stress response areas is not inhibited by the vmPFC, and sensitization may occur so that during later exposures to controllable stressors, the DRN remains active, and animals do not learn to escape the stressor.

Efforts to translate these findings in humans have followed the progression of work in animals. Although direct comparisons between human and animal models have been stymied by methodological (e.g., difficulty in accurately measuring activity in deep brain structures) and ethical constraints, results on the effect of stressor controllability and vmPFC activity appear to be consistent. Behavioral studies have found that uncontrollable stressors induce greater anticipatory stress and subsequent negative affect relative to controllable stressors (Gatchel et al., 1975; Miller, 1979; Miller and Seligman, 1975; Thompson, 1981). Recently, Meine et al. (2020), found that participants exposed to an inescapable physical threat experienced increased exhaustion and helplessness relative to an escapable physical threat, and that the inescapable physical threat condition had less efficient escape behavior on a subsequent grid-navigation task (Meine et al., 2021). Imaging studies have found similar results, documenting increased vmPFC-amygdala connectivity when snake-phobic individuals could control their exposure to videos of snakes (Kerr et al., 2012), along with increased vmPFC-amygdala and vmPFC—NAc connectivity during exposure to controllable thermal pain (Salomons et al., 2015). Recently, using a stressor controllability manipulation similar to the manipulations used in various animal models, researchers also detected increased vmPFC activity during exposure to a controllable physical threat (Meine et al., 2021). In this study, participants performed a matching task to end their exposure to controllable threats.

The present pilot study builds upon the existing animal and human literature, using a translationally valid stressor controllability task to manipulate behavioral control over a physical threat. Extending a previous feasibility study (Cremers et al., 2021), we investigated how behavioral control over a physical threat (electric shocks), affected stress, reaction times, and brain activity during a signal detection task based on the monetary incentive delay task, known to elicit NAc activation (Knutson et al., 2000). We then examined how the effects of this behavioral control manipulation generalized to a subsequent social stressor, a social evaluative threat (SET) task. This work builds on Meine et al. (2021) by seeking to both induce learned helplessness with physical stressors and measure its generalization to social stressors. It extends Cremers et al. (2021) with a larger participant sample and implementing the learned helplessness manipulation during MRI. The present study therefore contributes to research on the neuroscience of stress by demonstrating the methods to investigate both the manipulation of behavioral control over stressors, and the generalization of this intervention to future stressors during functional MRI. We hypothesized that a lack of behavioral control during the signal detection task would lead to increased stress, slower reaction times, and decreased activity in the NAc during the task. The effects of a lack of behavioral control over the physical threat were hypothesized to generalize to the SET task, in the form of increased stress, heart rate (HR), changes in heart rate variability (HRV), and decreased vmPFC processing efficiency measured with network analysis (Rubinov and Sporns, 2010).

2. Method

2.1. Ethics

The study was approved by the University of Amsterdam Psychology Research Ethics Committee, and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to their participation. Data and code used for analyses can be found at https://osf.io/ndu7s/ (data) and https://github.com/henkcremers (code).

2.2. Design

To test the effect of threat controllability on stress and vmPFC processing efficiency, a two-group design was used. Participants experienced either a controllable (CT) or uncontrollable (UT) physical threat delay (PTD) task, followed by a social evaluative threat (SET) task. Self-reported stress and vmPFC processing efficiency were measured during the SET task and compared between groups. The design of this experiment is closely based on a previous study conducted by Cremers et al. (2021), in which only the SET task was performed inside the scanner. We build on Cremers et al. (2021) with a larger participant sample and conducting the PTD task during MRI to study the differences in neural activity for controllable and uncontrollable stressor exposure. We also employ novel analyses of reaction time data during the PTD task, heart rate variability during the SET task, and testing of different vmPFC parcellation schemes for network analysis of data from the SET task to more accurately model responses to controllable and uncontrollable stressors.

2.3. Participants

A sample of 39 healthy participants (M_{age} = 21.08 years, SD = 2.34 years, 30 female) took part in the study in 2017. This was a pilot study, and the sample size was the largest that available funding permitted. The first two participants were excluded from analyses as the paradigm was not yet finalized, and one participant was excluded due to imaging data artifacts, leaving 17 participants in the CT group (M_{age} = 21.05, SD = 2.29, 13 female) and 19 in the UT group (M_{age} = 21.11, SD = 2.47, 14 female). Group allocation was pseudorandomized such that the first two (pilot) participants were assigned to the CT group and there were always more CT participants than UT participants until the final participant was tested. This allowed participants in the UT group to be yoked to participants in the CT group. All participants had a good understanding of English, and none were colorblind. Exclusion criteria included taking psychopharmaceutic medication, colorblindness, and contraindications for MRI.

2.4. Procedure

2.4.1. Pre-experiment

Participants were recruited through the University of Amsterdam subject pool (Sona Systems, Tallin, Estonia). Eligibility was screened via an online survey (Qualtrics, Provo, USA), containing items to check for age, colorblindness, medication use, English competency, and MRI contraindications. Participants were scheduled to take part in the main experiment at the Spinoza Center for Neuroimaging, University of Amsterdam.

2.4.2. Experiment

On the day of the experiment, participants received an overview of the procedures, practiced the physical threat delay task outside the scanner, and underwent a calibration procedure to determine the intensity of electrical shocks for the physical threat. Scanning began with a T1-weighted structural scan of the participant's brain. Participants then completed the PTD task, containing the behavioral control

manipulation, followed by the SET task (Wager et al., 2009a, described below. After the SET task, participants were removed from the scanner and debriefed (see Fig. 1 for an outline of the procedure).

2.4.2.1. PTD task. Before scanning, the electrical shock intensity was calibrated for each participant to be unpleasant but not painful. Shock intensity began at 0.01 mA and was increased in steps of 0.5 mA until participants reported feeling pain. The shock intensity just prior to the pain threshold was used for the task. Participants were then placed in the scanner and Kendall H135TSG MR compatible electrodes (Cardinal Health, Dublin, Ireland) were attached to the left ankle to deliver the shocks. Controllable and uncontrollable threat was induced with an adaptation of Knutson's monetary incentive delay task (Fig. 1a) (Knutson et al., 2000). Participants were instructed to respond with a button press as soon as they saw a target appear on screen to avoid a potential electric shock. Before each target appeared, a cue (circle or triangle) was displayed for 500 ms, followed by a fixation cross displayed for 1000–2000 ms. Circle cues indicated a visual feedback only (safe) trial, while triangles indicated a potential physical feedback (shock) trial. Responses made within the correct response window (hit) were indicated with a green square, and responses outside the correct response window (miss) were indicated with a red square. During potential shock trials, missed trials had a 33% chance of resulting in an electrical shock to the participant's ankle, concurrent with the visual feedback. Participants first practiced the task outside the scanner, without receiving shocks, and did not proceed until achieving a 66% hit rate. The task consisted of 60 trials, during which the task adjusted to participants' performance, adding 20 ms to the response window following missed trials, and subtracting 10 ms from the response window following hit trials, so that all participants performed at roughly a 66% hit rate.

Participants were pseudo-randomly assigned to either the controllable threat or uncontrollable threat condition. In the CT condition, participants were informed that the circle and triangle cues determined whether the trial employed visual or physical feedback on their performance. Participants in the UT condition received the same instructions, but were yoked to participants in the CT condition so that they received the same number of shocks at the same time intervals, which appeared to occur at random. The manipulation gave participants in the CT condition behavioral control over the shocks based on their task performance (a controllable physical threat), while participants in the UT condition experienced an uncontrollable threat. Participants rated their stress on a 1–9 scale before and after the PTD task, with a score of 1 indicating "no stress" and 9 indicating "extremely stressed".

2.4.2.2. SET task. After completing the PTD task, participants underwent an anticipatory version of the Trier Social Stress Test (Fig. 1b; (Kirschbaum et al., 1993), the SET task (Cremers et al., 2015; Wager et al., 2009). The task consisted of three phases: baseline, anticipatory stress, and recovery. Participants viewed a fixation cross for five minutes during the baseline phase. Anticipatory stress was induced when participants were given instructions that they may be selected to deliver a five-minute speech to a group of researchers after exiting the scanner. They were informed that the topic of their speech will be selected for them, and the speech will be recorded. After five minutes, the recovery phase began when participants were informed that they were not selected to give a speech, and that the scanning would continue for five additional minutes. During the task, participants rated their stress on the 1–9 scale once a minute, five times per SET phase.

2.4.3. Post-experiment

Following the SET task, participants were removed from the scanner and debriefed. Participants rated on a 1–9 scale whether they believed

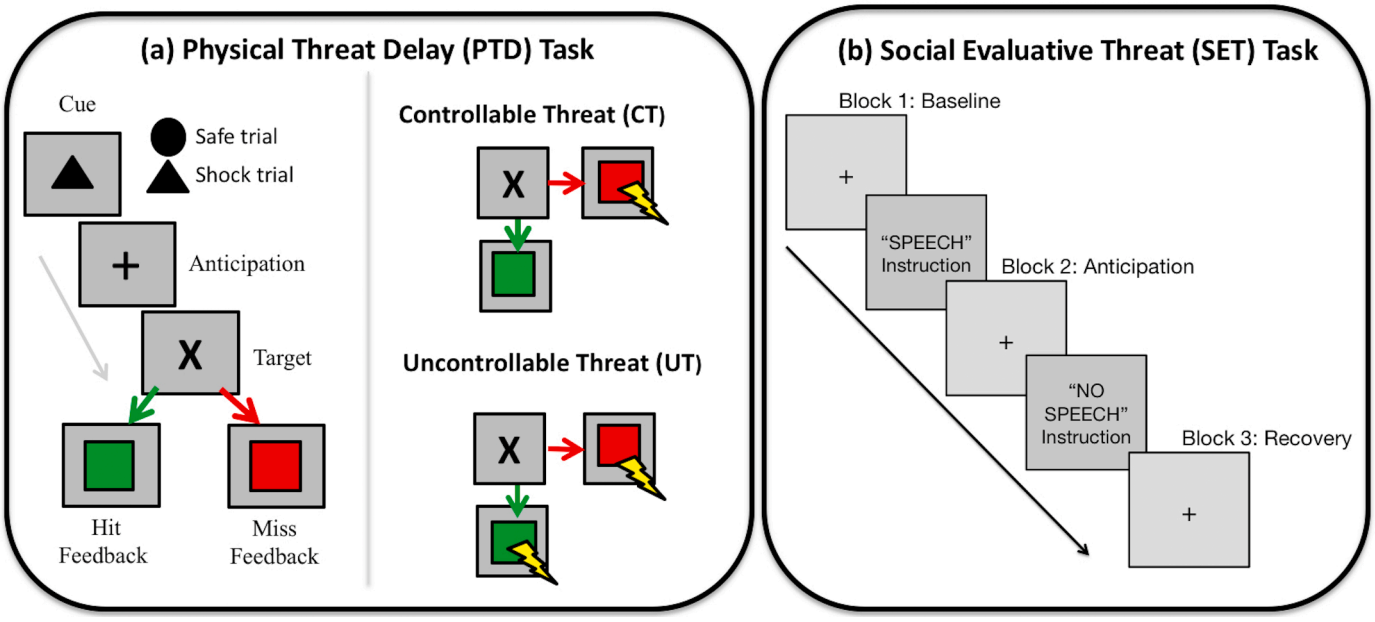

Fig. 1. PTD and SET procedures.

Note. A: Physical threat delay task. Participants were shown a screen containing either a circle or a triangle for 500 ms, with circles indicating safe trials and triangles indicating potential shock trials. Only the performance of participants in the CT condition determined the timing of their shocks, while participants in the UT condition were yoked to receive the same sequence of shocks as one of the CT participants. Participants then viewed a fixation cross for 1000–2000 ms, followed by the target screen, containing a square in the center of the screen. Participants were instructed to respond by pressing a button once the target appeared. The response window was determined by a learning algorithm which ensured that approximately 66% of responses are successful by adding and subtracting 10 ms to the response window based on whether or not the previous response was successful. A successful response was indicated by the target square turning green, and unsuccessful responses were indicated by the square turning red, and the chance of an electric pulse in the potential shock trials. B: Social evaluative threat task. Participants viewed a fixation cross and rated their stress level on a 1–9 scale once every minute for 15 min. After five minutes, the baseline phase, participants received on screen instructions that they may be selected to give a five minute speech on a predetermined topic for an audience, which would be recorded. After another five minutes, the anticipation phase, the participant was informed that they were not selected to give a speech. The last five minutes of the SET was a recovery phase.

the circle and triangle cues accurately predicted that they were in a safe trial during the PTD task, and the extent to which the visual feedback following a trial corresponded with whether they received a shock. They also rated whether they believed that they would have to give a speech following the SET task.

2.5. Analyses

2.5.1. Behavioral and physiological data

2.5.1.1. PTD. To check the effect of the behavioral control manipulation, self-reported stress levels during the PTD task were analyzed with a robust 2 × 2 mixed model ANOVA treating stress scores pre and post task as a within subjects, repeated measures factor, and condition (CT, UT) as a between subjects factor. Reaction time data was analyzed in a linear mixed-effect model using the nlme package in R (https://cran.r-project.org/web/packages/nlme/index.html) with subjects and trial type (safe, potential shock) as random intercept and slope, and group as a fixed effect.

2.5.1.2. SET. Self-reported stress levels during the SET task were analyzed with a robust 3 × 2 mixed model ANOVA, treating SET scores across the three task phases (baseline, anticipation, recovery) as a within subjects, repeated measures factor, and condition (CT, UT) as the between-subjects factor. Stress scores should be higher during the stress phase of the task, relative to baseline and recovery phases, indicating the SET task is producing a stress response.

Photoplethysmographic units (PPU) were measured through a fingertip heart rate monitor at a 500 Hz sampling rate (Jeyhani et al., 2015; Shaffer and Ginsberg, 2017). PPU signal was analyzed with the PhysIO toolbox (http://www.translationalneuromodeling.org/tnucheckphysretroicor-toolbox/). PPU peak detection was further visually inspected and corrected using custom code in MATLAB. Peak-to-peak intervals time-series were derived and outliers were replaced with spline interpolation. The percentage of outliers for each subject was less than 10%. The root-mean-square of differences (RMSSD) between subsequent peak-to-peak intervals, a measure of HRV (Rajendra Acharya et al., 2006) and HR were calculated separately for each SET task phase.

2.5.1.3. Debriefing. To assess group differences in response to the debriefing questions concerning participant's awareness of behavioral control over the physical threat, two sample *t* tests were used. To assess group differences in belief of the social stressor manipulation, Pearson's chi squared test was used.

2.5.2. Imaging data

2.5.2.1. Acquisition. Data were collected using a Phillips Achieva 3 Tesla scanner with a maximum gradient strength of 40 mT/m, bore diameter of 60 cm, field-of-view of 45 cm (head-feet direction), and a 32 channel head coil. A structural MRI was taken with a T1 weighted gradient echo sequence. Functional scans were taken during the PTD and SET tasks, utilizing T2* weighted gradient echo planar images (TR = 2000 ms, voxel size = 3 × 3 × 3 mm, echo time = 27.63 ms, flip angle = 76.1°, matrix = 80 × 80, field of view = 240 × 240, slice thickness = 3 mm, slice gap = 0.3 mm, 38 slices per volume, sensitivity encoding factor = 2) with a 32-channel SENSE head coil.

2.5.2.2. Preprocessing. Anatomical images were skull stripped with the Brain Extraction Toolbox (BET; Smith, 2002). Subsequent preprocessing was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm). Functional scans were realigned to correct for motion artifacts, low frequency drift, temporal autocorrelation, and spatial abnormalities. Structural scans were co-registered to the mean EPI space, and data was normalized and registered to MNI space. A Gaussian spatial smoothing kernel of 6 mm FWHM was applied to the functional images.

Data from the SET task were processed further to correct for additional confounders. The following nuisance variables were regressed from the data: 1. Retrospective image correction (RETROICOR; (Glover et al., 2000); 2. Respiratory volume per time; 3. Heart rate variability (HRV; 1–3 estimated with the PhysIO toolbox); 4. The instruction and rating periods convolved with the hemodynamic response function; 5. First- and second-order polynomials of time; 6. The mean time series of the white matter and cerebrospinal fluid; 7. Six motion regressors for the rigid body transformation; 8. Outlier volumes, detected with the Artifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect/) and dependent on deviations in scan-to-scan difference of the z-normalized BOLD signal or composite motion parameters.

2.5.2.3. PTD. Functional images from the PTD task were modeled on a design matrix with columns containing the three anticipation conditions (shock, no shock, safe), the successful trial outcomes (hit-shock, hit-no shock, and hit-safe), the unsuccessful trial outcomes (miss-shock, miss-no shock and miss-safe) and six motion regressors for rigid-body transformation. First level analyses contrasted the anticipation of potential shock trials to the anticipation of safe trials within-subjects, and second-level analyses compared this contrast across CT and UT groups. A mask of the bilateral NAc created with the Harvard-Oxford Subcortical Structures Atlas (probability threshold: 0.5) was applied to the images for region of interest (ROI) analysis, and the average beta parameter of the entire region was analyzed. Exploratory, whole-brain analyses were also conducted. A significant effect for the NAc ROI analysis was determined as $p < 0.05$, and significant effects for whole-brain analysis were determined as $p_{FWE} < 0.05$.

2.5.2.4. SET. A parcellation scheme including 489 ROIs based on different cortical and subcortical atlases was used to define brain regions for network analysis, see https://github.com/canlab/Neuroimaging_Pattern_Masks/tree/master/Atlases_and_parcellations/2018_Wager_combined_atlas for details (Glasser et al., 2016). By region, the residual MR signal was weighted with the gray matter density and averaged across voxels. Sparse connectivity matrices based on partial correlations were obtained for each participant, in each SET phase (baseline, speech anticipation, recovery), using the graphical LASSO (Friedman et al., 2008) with lambda set at 0.01 (Foygel and Drton, 2010). The connectivity matrices (weighted and absolute values) were used to calculate global efficiency (capacity for information transfer and integrated processing across the entire brain; (Bullmore and Sporns, 2012), local vmPFC efficiency (the efficiency of communication between first neighbors of the vmPFC when the vmPFC is taken out; (Latora and Marchiori, 2001), vmPFC participation coefficient (the distribution of edges connected to the vmPFC; (Joyce et al., 2010), vmPFC betweenness centrality (what extent the vmPFC connects other areas of the brain with each other; (Rubinov and Sporns, 2010), vmPFC strength (the sum of the weights of the edges connected to vmPFC; (Rubinov and Sporns, 2010), and vmPFC eigenvector centrality (to what extent it is connected to other well-connected areas; (Bonacich, 2007).

The vmPFC was defined as the nodes of the parcellation scheme (nodes number 329 and 330, Fig. 2a) that completely overlapped with a vmPFC map created with Neurosynth (https://neurosynth.org), using the keyword "ventromedial prefrontal cortex". Exploratory analyses were carried out in the same way on nodes that only partially overlapped with vmPFC. These were defined as vmPFCextended-1 (nodes 127 and 128, Fig. 2b), vmPFC-extended-2 (nodes 129 and 130, Fig. 2c), and vmPFC-extended-3 (nodes 175 and 176, Fig. 2d). The centrality measures for these nodes were averaged to obtain the final indices used for analysis, as they represent the same area left and right (for details on the nodes, see Table 1). All nodes of interest were part of the parcellation of the human cerebral cortex proposed by Glasser et al. (2016).

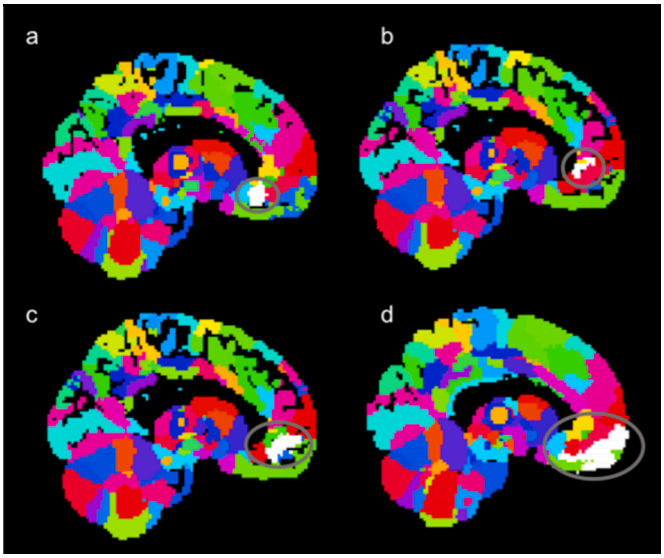

Fig. 2. Network analysis parcellation scheme.
Note. Parcellation scheme. White areas represent the regions of interest that centrality measures were calculated for. A: vmPFC, (b) vmPFC-extended-1, (c) vmPFC-extended-2, (d) vmPFC-extended-3.

Table 1
vmPFC nodes for network analyses.

Name	Node in parcellation	Name in Glasser et al., 2016	MNI coordinates x	y	z
vmPFC	329	s32 left	−8	34	−14
	330	s32 right	4	33	−12
vmPFC-extended-1	127	p32 left	−11	47	−1
	128	p32 right	10	46	−1
vmPFC-extended-2	129	10r left	−8	49	−8
	130	10r right	4	48	−7
vmPFC-extended-3	175	10v left	−5	52	−18
	176	10v right	2	51	−15

Note. This table details the four vmPFC nodes used in the network analyses of SET task data. MNI: Montreal Neurological Institute. vmPFC: ventromedial prefrontal cortex.

3. Results

3.1. Normality check

The distributions for the SET stress ratings, manipulation check responses, RMSSD, global efficiency, vmPFC local efficiency, vmPFC participation coefficient, and vmPFC betweenness showed deviations from a normal distribution, determined with Shapiro-Wilk tests (all $p < 0.05$). Therefore, bootstrapped ANOVAs ($n_{boot} = 2000$), robust to violations of normality, and modified one-step estimators were performed (Mair et al., 2017) using the sppba, sppbb, and sppbi functions from the WRS2 R package (https://cran.rproject.org/web/packages/WRS2/WRS2.pdf). Post-hoc comparisons and differences between means were tested with robust *t*-tests based on trimmed means using the yuenbt and yuend functions from the WRS2 R package (Field and Wilcox, 2017). A trimming level of 0.2 was applied. Robust effect sizes were calculated with the explanatory measure of effect size (Mair and Wilcox, 2020). Effects of $\xi < 0.15$ were considered small, 0.15 – 0.35 small to medium, 0.35 – 0.5 medium to large, and >0.5 large.

3.2. PTD

3.2.1. Physical stressor

The median number of shocks participants received was 10 (SD = 1.17, range = 7–12). The mean shock intensity was 4.61 mA (*SD* = 0.93). Changes in stress level were not correlated with the number of shocks received ($r = 0.011$, $p = 0.821$) or participants' individual shock intensity ($r = 0.016$, $p = 0.655$).

3.2.2. Self-reported stress

Self-reported stress ratings across groups were significantly larger after ($M = 3.95$) than before ($M = 3.28$) the PTD task, $\Psi = 0.76$, $p = 0.0065$, $\xi = 0.22$ (Fig. 3). The time by group interaction showed a non-significant trend, $\Psi = -0.69$, $p = 0.094$, $\xi = 0.15$, $M_{CT\ post\text{-}PTD} = 3.48$, $M_{UT\ post\text{-}PTD} = 4.50$, with UT participants trending towards higher stress ratings post-task than CT participants, in line with the hypothesized increase in stress for participants without behavioral control, though nonsignificant. The main effect of group was also not significant ($p = 0.51$).

3.2.3. Reaction times

Reaction times showed a significant effect of trial type (safe, shock); $\chi^2(5) = 11.37$, $p = 0.007$, indicating that the reaction times were faster in the potential shock compared to the safe trials. There was no significant effect of group $\chi^2(6) = 3.24$, $p = 0.072$ or interaction between trial type and group $\chi^2(7) = 2.70$, $p = 0.1$, which did not support our hypothesis of slower RTs in the UT group.

3.2.4. Imaging results

To test the hypothesis that NAc activity would decrease during exposure to uncontrollable physical threat, we contrasted anticipation of potential shock trials with safe trials between CT and UT groups, with a mask for bilateral NAc. ROI analysis for bilateral NAc did not detect a significant difference in activation between the CT ($M_{parameter\ estimate} = 0.42$, $SD = 0.55$) and UT ($M_{parameter\ estimate} = 0.2$, $SD = 0.42$, Fig. 4) groups for the shock-anticipation versus safe-anticipation trials contrast $t(34) = 1.36$, $p = 0.18$, which did not support the hypothesized difference between groups. Across groups, NAc activity was significantly greater during potential shock anticipation trials compared to safe trials $t(35) = 3.71$, $p = 0.001$, in line with the expectation that potential shock trials provoke a stronger stress response than safe trials. During exploratory whole-brain analysis, regions that showed increased activation during potential shock anticipation trials relative to safe trials (across groups) included anterior cingulate cortex (Fig. 5a), bilateral insula (Fig. 5b), bilateral superior temporal pole (Fig. 5c), and cerebellar lobules of Vermis IV, V (all $Z > 6$, $p_{FWE} < 0.001$ Table 2).

3.2.5. Debriefing

Responding to the question, "When you saw the triangle cue at the beginning of a trial, how strongly did you feel you could control the delivery of a shock?" participants in the CT group gave higher scores ($M = 5.33$) compared to the UT group ($M = 2.28$), trimmed $M_{diff} = 4.19$, $Yt = 7.48$, $p < 0.001$, $\xi = 0.78$, indicating a greater sense of control in the CT group. The same pattern was observed in response to the question, "When you saw the feedback (green or red square), how certain were you that you would or would not receive a shock?" with participants in the CT group ($M = 8.19$) more confident than the UT group ($M = 1.78$), trimmed $M_{diff} = 7.12$, $Yt = 17.73$, $p < 0.001$, $\xi = 0.93$, that the feedback accurately predicted whether or not a shock would occur.

3.3. SET

3.3.1. Self-reported stress

The main effect of SET phase on self-reported stress was significant ($\Psi_{anticipation\text{-}baseline} = 0.76$, $\Psi_{baseline\text{-}recovery} = 0.52$, $\Psi_{anticipation\text{-}recovery} = 0.95$, $p < .0001$, Fig. 6). The main effect of group and the interaction

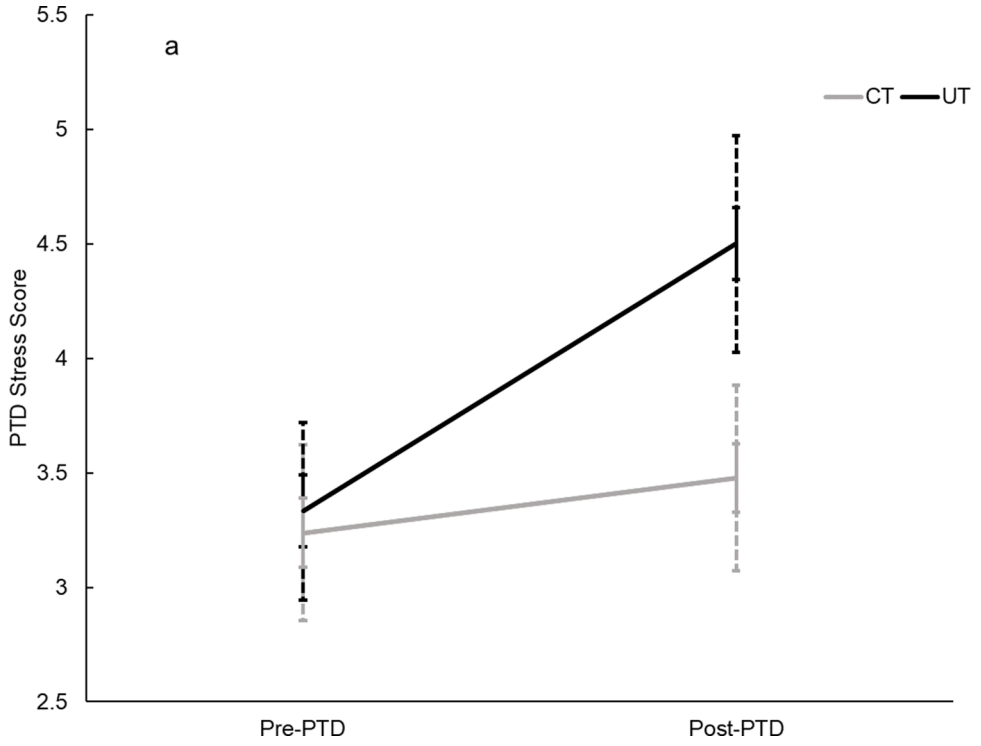

Fig. 3. Self-reported stress before and after PTD task.
Note. Self-reported stress ratings pre to post PTD task, between groups. Dashed error bars represent between-subjects standard errors, and solid lines represent within-subjects standard errors.

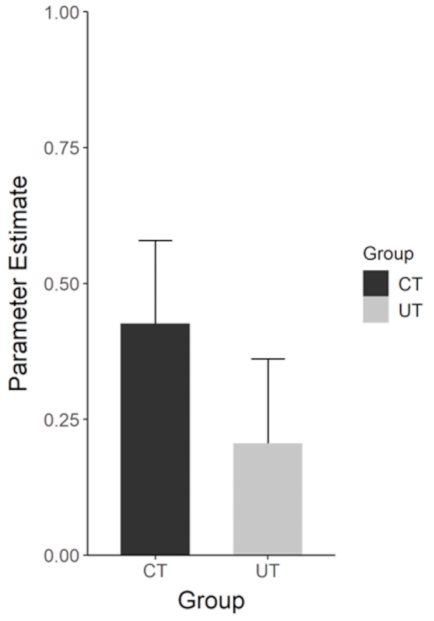

Fig. 4. Parameter estimates for NAc activity during PTD task.
Note. Parameter estimates for the "shock anticipation" over "safe anticipation" trials contrast between the controllable- ($n = 19$) and uncontrollable threat ($n = 16$) groups. Error bars indicate SEM.

effect were not significant (all $p > 0.43$), which did not support the hypothesized higher stress ratings during the anticipation phase for participants in the UT group. A quadratic contrast indicated that stress ratings were significantly larger during anticipation ($M_{anticipation} = 3.59$) compared to baseline and recovery ($M_{baseline+recovery} = 2.53$, trimmed $M_{diff} = 0.97$, $Yt(24) = 4.08$, $p = 0.0004$, $\xi = 0.48$).

3.3.2. HR and HRV

For RMSSD, the main effect of group, the main effect of blocks and their interaction were not significant (all $p > 0.33$, Fig. 7a). For HR, the main effect of the SET blocks was significant ($\Psi_{anticipation\text{-}baseline} = 1.23$, $\Psi_{baseline\text{-}recovery} = -1.20$, $\Psi_{anticipation\text{-}recovery} = 0.47$, $p = 0.0095$), while the main effect of group and the interaction effect were not significant (all $p > 0.35$, Fig. 7b), which did not support the hypothesized differences between CT and UT groups for RMSSD and HR. A quadratic contrast indicated that HR was significantly larger during anticipation ($M_{anticipation} = 70.84$) compared to baseline and recovery ($M_{baseline+recovery} = 69.11$), trimmed $M_{diff} = 1.39$, $Yt(22) = 2.90$, $p = 0.0083$, $\xi = 0.11$ (small effect size), in line with the expectation that the anticipation phase would provoke a stronger physiological response than the baseline and recovery phases. The quadratic contrast did not differ between groups ($p = 0.17$).

3.3.3. Imaging results

The Group x SET Blocks interaction, the main effect of group and the main effect of blocks were not significant for vmPFC efficiency, participation coefficient, and betweenness (all $p > 0.26$). A non-significant trend for the main effect of SET blocks was detected for vmPFC strength ($\Psi_{anticipation\text{-}baseline} = 0.083$, $\Psi_{baseline\text{-}recovery} = -0.12$, $\Psi_{anticipation\text{-}recovery} = 0.017$, $p = 0.021$) and eigenvector centrality ($\Psi_{anticipation\text{-}baseline} = 0.0021$, $\Psi_{baseline\text{-}recovery} = -0.0021$, $\Psi_{anticipation\text{-}recovery} = -0.0001$, $p = 0.015$), while the interaction effect and the main effect of group were not significant (all $p > 0.40$), which did not support our hypothesis of decreased vmPFC efficiency in the UT group. Post-hoc tests for the main effect of SET blocks on strength and eigenvector centrality were not significant (all $p > 0.13$). The line chart for vmPFC strength is shown in Fig. 8a. For global efficiency, the main effect of SET blocks was significant ($\Psi_{anticipation\text{-}baseline} = 0.00014$, $\Psi_{baseline\text{-}recovery} = -0.00026$, $\Psi_{anticipation\text{-}recovery} = -0.00029$, $p = 0.007$), while the interaction effect and the main effect of group were not significant (all $p > 0.38$, Fig. 8b), which again did not support the hypothesized decrease in vmPFC efficiency in the UT group. Post-hoc tests for the main effect of

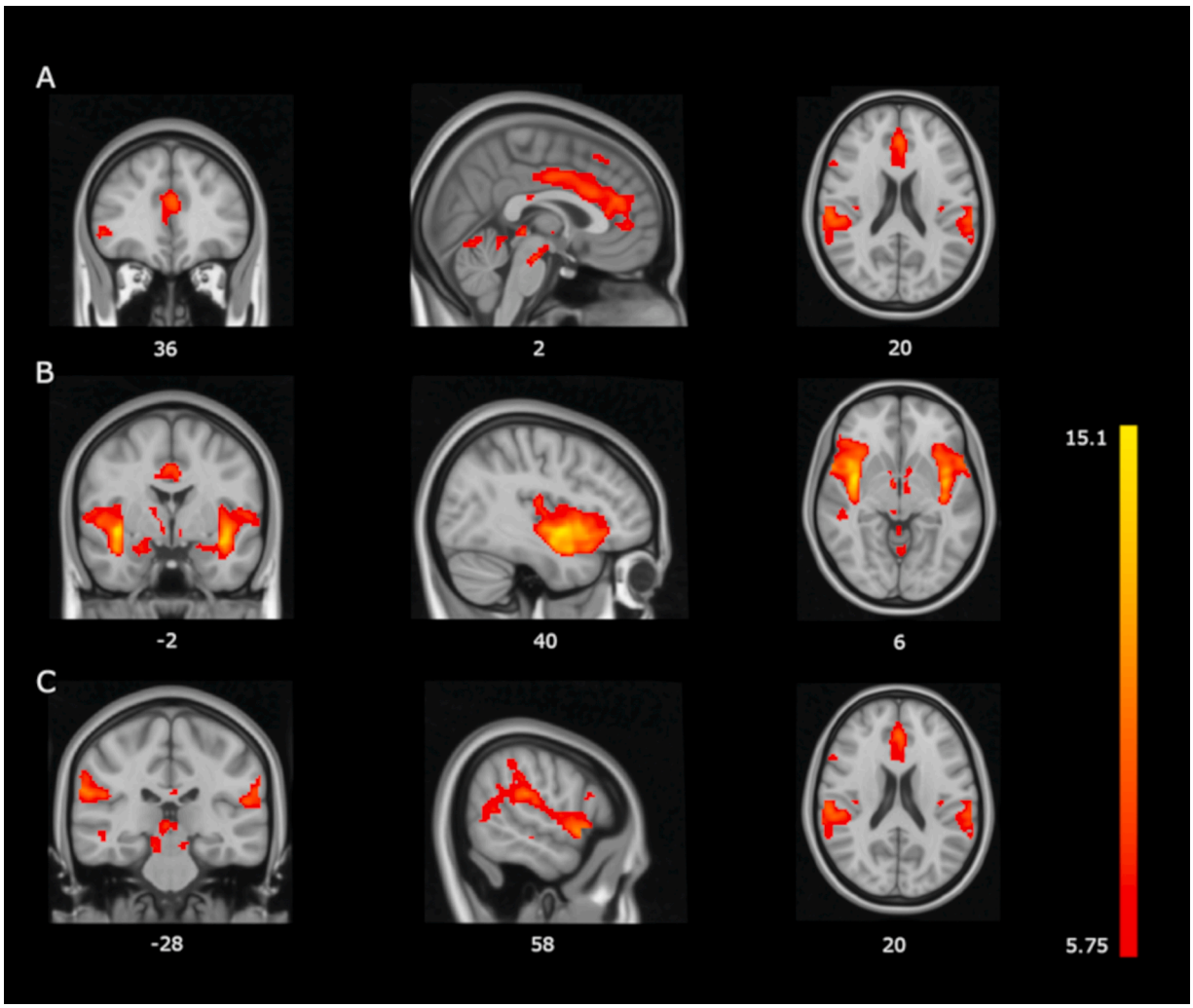

Fig. 5. Whole brain analysis of PTD task.
Note. Clusters of significant activation in the shock anticipation > no shock contrast. A: Anterior cingulate cortex. B: Bilateral insula. C: Bilateral superior temporal gyrus. Scale indicates *Z* scores. All clusters significant at *p*FWE < 0.001.

Table 2
Shock anticipation > No shock contrast clusters of activation.

Region		MNI coordinates			*Z*	P_{FWE}	Voxels
		X	Y	Z			
insula	L	−36	0	14	>6	<0.001	1637
	R	40	−4	8	>6	<0.001	2233
superior temporal gyrus	L	−64	−32	28	>6	<0.001	167
	R	60	−26	22	>6	<0.001	291
anterior cingulate cortex		0	38	20	>6	<0.001	532
lobule IV, V of Vermis		4	−30	2	>6	<0.001	13

Note. Table reports significant clusters of activation from whole brain analysis in the Shock > No Shock anticipation contrast. MNI: Montreal Neurological Institute. FWE: Familywise Error. L: Left. R: Right.

SET blocks revealed that global efficiency was significantly smaller at baseline (*M* across groups = 0.0370) compared to recovery (*M* across groups = 0.0372), trimmed $M_{diff} = -0.00028$, $Yt(21) = -3.03$, $p = 0.0064$, $\xi = 0.13$. The other post-hoc comparisons were not significant (all $p > 0.15$). We performed exploratory analyses for the extended vmPFC. A non-significant trend was found for the main effect of group on vmPFC-extended-1 eigenvector centrality ($\Psi = 0.0036$, $p = 0.082$, $M_{CT\ across\ SET\ blocks} = 0.032$, $M_{UT\ across\ SET\ blocks} = 0.030$). For the other analyses in the extended vmPFC, no significant effect was found (all $p > 0.12$). When repeating the analyses controlling for mean network strength, no significant effect was found for vmPFC (all $p > 0.16$), vmPFC-extended-2 (all $p > 0.30$) and vmPFC-extended-3 (all $p > 0.20$). Regarding vmPFC-extended-1 eigenvector centrality, the non-significant trend for the main effect of group was maintained ($p = 0.088$). The other effects for vmPFC-extended-1 were not significant (all $p > 0.16$).

3.3.4. *Debriefing*

In response to the question "When you read the instructions on the screen about having to give a public speech, did you think you really had to give the speech?" answer rates did not differ between CT and UT groups ($\chi 2\ (1) = 0.096$, $p = 1$). Eight participants in the CT group, and six participants in the UT group indicated that they did not believe the speech manipulation.

4. Discussion

In the present pilot study, we employed a translational design to investigate how behavioral control over a physical threat affected behavioral, physiological, and neural responses to a later social stressor. We measured self-reported stress before and after the physical threat, the PTD task, and during all three phases of the social stressor, the SET task. Reaction times were also measured during the PTD task, along with HR and HRV during the SET task. fMRI was recorded during both tasks

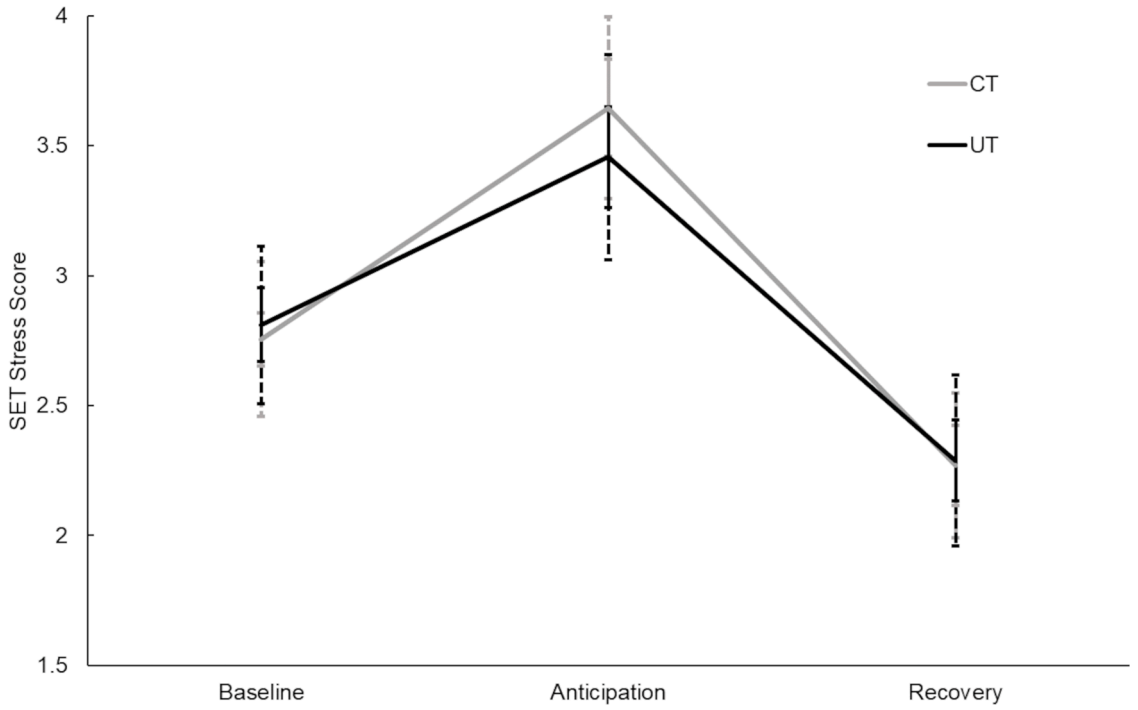

Fig. 6. Self-reported stress during SET task.
Note. Mean self-reported stress score during SET. Dashed error bars represent between-subjects standard errors, and solid lines represent within-subjects standard errors.

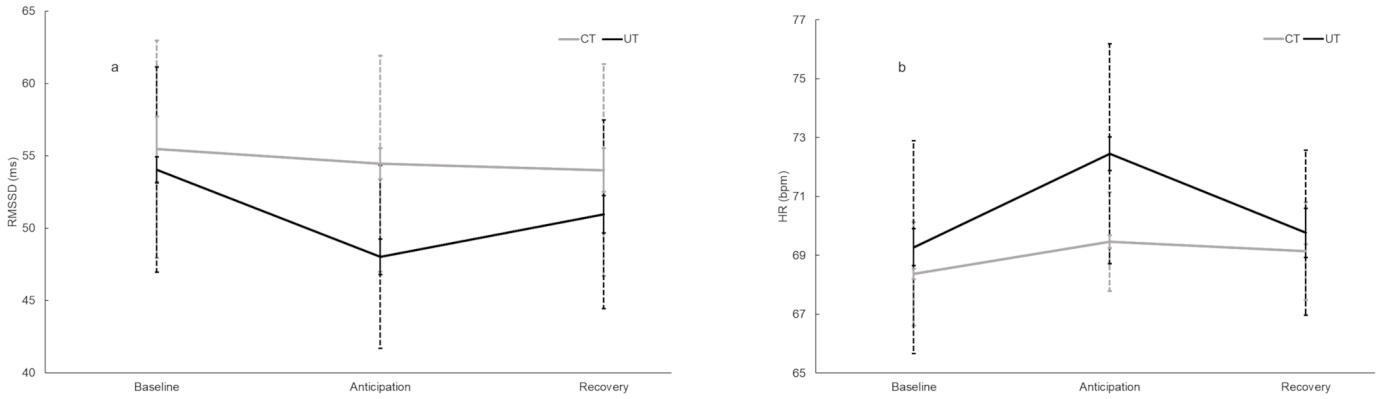

Fig. 7. RMSSD and HR during SET task.
Note. A: RMSSD, a measure of high frequency HRV, during the SET task, B: HR during the SET task. Dashed error bars represent between subjects standard errors, and solid lines represent within-subject standard errors.

for ROI and whole-brain activation analyses on the PTD task and network analysis on the SET task.

The PTD task was found to increase self-reported stress in both the CT and UT groups, with the manipulation of behavioral control over the physical threat yielding a non-significant trend towards a greater self-reported stress increase in the UT group, in line with previous work using this task (Cremers et al., 2021). We observed a trend towards slower reaction times during potential shock trials in the UT group compared to the CT group, similar to previous studies that manipulated control over physical (Kerr et al., 2012) and emotional threats. The UT group participants reported experiencing less control over the physical threat, a finding also documented in related work (Kerr et al., 2012; Meine et al., 2021; Salomons et al., 2015). This suggests that while the task produced differences in experienced behavioral control, the effect on perceived stress was less than expected and may not have induced learned helplessness in the UT group. While behavioral data from the PTD task suggest that the behavioral control manipulation may have had the expected effect on experienced control, the imaging results did not detect hypothesized differences between groups in stress response in the NAc. Across groups, however, the NAc was more active during potential shock trials relative to safe trials. Given that the difference in self-reported stress between the CT and UT groups was relatively small, the sample size was likely too small to detect an equally small effect in neural activation (Cremers et al., 2017) regardless of evidence for this effect in previous animal (Amat et al., 2005, 2006) and human (Kerr et al., 2012) research. When contrasting anticipation for potential shock versus safe trials across groups, we found activation in areas involved in stress processing such as bilateral insula and ACC, a finding that replicates similar work on this topic (Meine et al., 2021). Therefore, the PTD task may be a reliable means of inducing stress related to a physical threat and offers a vehicle for manipulating behavioral control over a physical threat. However, refinements are necessary to increase the

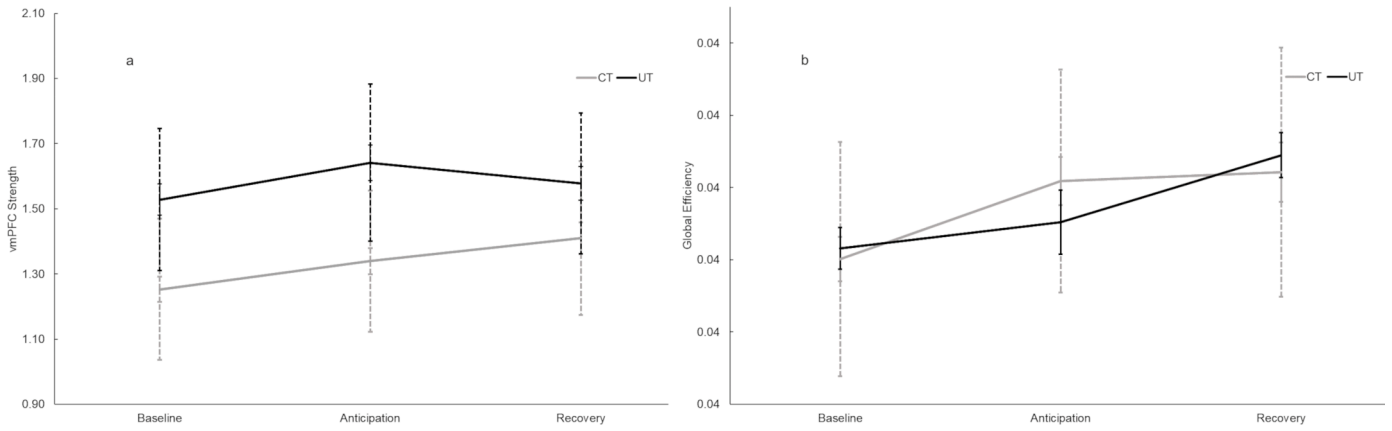

Fig. 8. vmPFC strength and global efficiency during SET task.
Note. A: vmPFC strength during the SET task, B: fMRI global efficiency during the SET task. Dashed error bars represent between-subjects standard errors, and solid lines represent within-subjects standard errors.

strength of the manipulation such that larger differences between groups manifest. This could potentially be accomplished by adjusting task parameters such as difficulty or duration of the task to better reinforce the presence or lack of behavioral control between groups. Additionally, the CT group could receive instructions that they will inevitably receive a number of shocks given that the task's difficulty increases based on their reaction times, thereby inoculating them from stress associated with the physical threat.

The absence of a more robust effect on stress levels and corresponding neuroimaging results may be due to ethical considerations that preclude a more direct translation of animal studies, and methodological differences between other research that has documented stronger effects. Importantly, whereas animal studies typically used more painful aversive stimuli that were not calibrated to individual sensory perception, potentially driving stronger effects of behavioral control, it would not be ethical to replicate these methods with human participants. Although there was no correlation between the number of shocks received or their intensity with perceived stress, the low number and intensity of shocks across all participants likely yielded a weaker stress manipulation relative to studies on animals. Meine et al. (2021), wh0 found a stronger effect on stress following a similar stressor controllability manipulation, used a within-subjects design in which control was exerted over stopping an ongoing aversive stimulus, not preventing it from occurring as was this case in the present experiment. The fact that participants could not prevent the occurrence of aversive stimuli in both conditions and instead controlled their termination, along with the statistical strength of a within-subjects control, may explain the difference between these results and those of the present study. Though not possible to include more participants in the current pilot study, a larger sample size is warranted in future research to provide more reliable estimates of potential effects (Button et al., 2013).

The SET task increased self-reported stress and HR in both groups during the anticipation phase as expected, replicating previous studies using this task (Cremers et al., 2015; Wager et al., 2009). However, we did not observe the hypothesized difference between groups on either of these metrics, nor on measures of HRV or vmPFC connectivity. Regarding HRV, there may have been relatively little cause for variation in heart rate in either group within each five-minute phase of the task, as participants were not frequently switching between high and low states of arousal. Other studies have found differences in vmPFC activation between controllable and uncontrollable threats (Kerr et al., 2012; Meine et al., 2021) but did not detect differences in vmPFC connectivity (Meine et al., 2021). In this case, similar to the PTD results, the lack of difference between groups may be explained by insufficient power, or an insufficient difference in stress levels from the behavioral control manipulation. Additionally, vmPFC processing efficiency may not the best suited metric to measure differences in behavioral control in humans The dorsolateral prefrontal cortex, for one, may also play a role in (resilience to) learned helplessness and warrants further investigation (Taylor et al., 2014).

To conclude, we piloted methods with the PTD and SET tasks to induce stress related to controllable and uncontrollable physical and social stressors. This work adds to previous studies with similar designs (Cremers et al., 2021; Meine et al., 2021) by measuring neural activity during both a manipulation of behavioral control over physical stressors, as well as exposure to a subsequent social stressor. We also iterated on previous analyses of physiological and neural data collected during these tasks (Cremers et al., 2021) to more accurately measure responses to controllable and uncontrollable stressors. As can be seen from the consistently large margins of error in the results, this pilot lacked statistical power. A larger sample size would reduce the uncertainty seen in these results (Button et al., 2013; Cremers et al., 2017). With refinements, the PTD and SET tasks may be effective methods of manipulating behavioral control and studying its generalization across stressors, but studies with more participants and greater statistical power would be needed to corroboroate this approach.

Ethics approval

This study received ethical approval from the University of Amsterdam Psychology Research Ethics Committee.

Availability of data and materials

All data for this study can be found at https://osf.io/ndu7s/

Code availability

MRI analyses were conducted in SPM version 12 running on MATLAB 2020A. Behavioral data was analyzed with SPSS version 22. Custom code for network analysis of MRI data can be found at https://github.com/henkcremers

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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