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# The development of an fMRI protocol to investigate vmPFC network functioning underlying the generalization of behavioral control

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ABSTRACT

Experiencing behavioral control over stress can have long-lasting and generalizing effects. Animal research has shown that vmPFC-subcortical interactions are critical for behavioral control; however, research in humans is sparse. Therefore a paradigm was developed in which participants ($n$ = 18) were first assigned to a controllable or uncontrollable version of a signal detection task associated with mild shocks. Subsequently, subjects underwent an fMRI task on the anticipation of speaking in public while measuring self-reported stress, heart rate, and vmPFC network topology. The signal detection task results revealed faster responses to potential shock trials and a trend difference between the controllable and uncontrollable group. The speech anticipation procedure did not show significant between-group differences on self-reported stress or heart rate. fMRI results indicated higher vmPFC efficiency in the controllable threat group at baseline and recovery but similar to the uncontrollable group during speech anticipation. The current report establishes the feasibility of the protocol. However, to evaluate the generalization effect of controllability on the behavioral, physiological, and neural levels further, adequately-powered follow-up research is needed.

## 1. Introduction

Behavioral control is the ability to alter the onset, termination, duration, intensity, or pattern of a stressor (Maier and Watkins, 2010). The type of exposure broadly divides the effect of behavioral control. Traditionally the focus has been on *learned helplessness*, the failure to escape uncontrollable aversive events (Seligman and Maier, 1967), which has been related to psychiatric disorders such as depression (Seligman and Maier, 1967). Conversely, learning that an outcome of a stressor is dependent on one's behavior (Huys and Dayan, 2009; Maier and Seligman, 2016) can overcome passivity. This process is referred to as *"learned mastery"* and is an integral part of *resilience* for protecting against developing psychopathology (Maier and Watkins, 2010). The experience of behavioral control can have long-lasting, and importantly, generalizing effects: behavioral control over *physical* threat affects subsequent stress responses to *social* threat (Amat et al., 2010; Maier and Watkins, 2010).

Animal research on the neural mechanism of behavioral control typically involves comparing a group exposed to inescapable, to a group exposed to escapable tail shocks. In addition, these groups are often also compared to a control group without experiencing any shocks. A series of experiments have provided a detailed view of the neural mechanisms underlying behavioral control: the ventromedial Prefontal Cortex (vmPFC) displays a modulatory role on Dorsal Raphe Nucleus (DRN) based serotonin secretion (Maier and Seligman, 2016; Maier and Watkins, 2010). For example, blocking vmPFC-DRN connections blocks the beneficial effect of escapable shocks, but activation of the vmPFC-DRN pathways leads to "control like" behavior even when experiencing inescapable shocks (Maier and Seligman, 2016). Thus, the vmPFC plays a crucial role in detecting and processing behavioral control and orchestrates responses in subcortical areas (Maier and Watkins, 2010).

While the role of the vmPFC in emotion regulation, such as fear conditioning, has been well established in human research (Buhle et al., 2014; Diekhof et al., 2011; Hartley and Phelps, 2009), research on controllability and vmPFC functioning in humans is sparse. Brain imaging studies on the controllability of pain have shown a role for the lateral prefrontal cortex (Salomons et al., 2007; Wiech et al., 2006). A study that manipulated the controllability of the presentation of pictures of snakes found increased vmPFC activation and increased vmPCF-amygdala connectivity during controllable picture presentation (Kerr et al., 2012). Another study showed that predictability interacted with controllability on vmPFC activity (Wood et al., 2015), highlighting the complexities of the effect of control over stress (see Abramson et al., 1978; Averill, 1973; Thompson, 1981 for a discussion). The human

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brain imaging work thus broadly shows overlap with animal research. However, the role of the vmPFC in behavioral-control generalization needs to be further established in an experimental paradigm that closely mirrors the classic animal studies. It is also essential to advance our understanding of the complexities of behavioral control by studying the vmPFC in terms of its connectivity and communication patterns with the rest of the brain, with a focus on large-scale network functioning (Bassett and Bullmore, 2009; Bassett and Sporns, 2017; Fornito et al., 2015; Pessoa, 2014).

The current study's primary goal is to develop and test the feasibility of a brain imaging procedure that investigates behavioral control and physical-to-social threat generalization. The experiment consists of a signal detection task, where performance feedback is paired with either controllable or uncontrollable shocks. An fMRI social evaluative threat protocol then follows this task (anticipating speaking in public; Cremers et al., 2015; Wager et al., 2009b). We utilize a graph theoretical approach (Bullmore and Sporns, 2009) to explore vmPFC network topology during social threat and test the effect of prior exposure to controllable and uncontrollable physical threat. We hypothesize that this prior exposure to controllable physical threat would be associated with markers of greater vmPFC interconnectivity during the subsequent social threat.

## 2. Method

### 2.1. Participants

18 participants (10 male / 8 Female; mean age = 38.5, SD = 11.34) were recruited through the local participants database of the CNPRU lab. Exclusion criteria for the participants were current diagnosis of DSM-IV psychiatric disorder as established with the Structured Clinical Interview for DSM Diagnoses (SCID-IV; (First et al., 1997) for syndromal disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; (Pfohl et al., 1997) and general MRI contraindications. All subjects gave written informed consent. The study was approved by the institutional review board of the University of Chicago.

A pseudorandom list with the order of the controllable threat (CT) and uncontrollable treat (UT)[1] Group conditions was generated (starting with two controllable conditions, a maximum of 3 subsequent conditions of the same kind, and having more controllable than uncontrollable conditions until the final condition was reached). Each incoming participant was assigned to the next available condition. Participants assigned to the uncontrollable condition were yoked to the task of a previous participant in the controllable condition, matched for gender, and approximately matched for age.

### 2.2. Procedure, materials, and tasks

Before the experiment, participants completed a series of online questionnaires through Survey Monkey (www.surveymonkey.com), including locus of control (Rotter, 1966), The brief COPE (Carver, 1997), perceived stress scale (Cohen et al., 1983), NEO-FFI personality questionnaire (Costa and McCrea, 1992) and general self-efficacy (Chen et al., 2001), and Liebowitz Social Anxiety Scale (Fresco et al., 2001) see Table 1. Participants were told that they would perform the Physical Threat Delay task (PTD, see Fig. 1 and description below) outside the scanner, and then complete a series of scans (SET procedure, see Fig. 1 and description below) followed by a final task outside the scanner. Additionally, subjects were told that during the scanning procedure, they would receive additional instructions on the final tasks outside the scanner, but no details were revealed. During scanning, subjects received an instruction that they were to perform a public speaking task, and a few minutes later, they were told they are "not selected" for that task after all. After completing the scanning procedure, subjects were debriefed on the study, and the rationale for the deception was explained.

#### 2.2.1. Physical threat delay (PTD) task

Participants performed a simple signal detection task (the Physical Threat Delay task, derived from the monetary incentive delay task; (Knutson et al., 2000), in which they had to press a button when a briefly presented target (200–500 ms) appeared on a screen. Feedback followed (1000 ms) in the form of a green square for a hit (response is within the presentation time of the target) or a red square after a miss. Before each target appearance, a cue (1000 ms) indicated whether the current trial is either a potential shock feedback trial (triangle) or safe (circle), each of which occurred 30 times. The safe and shock trials were presented in a pseudorandom order, allowing a maximum of two trials of the same type in a row.

In the CT version of the PTD task, participants only received a shock for a miss, but not for a hit trial. In the UT version, the administration of a shock in the shock trials occurred at the same time as the participant in the CT version to witch the UT participant was yoked. The shock occurred on the same trials as the CT participant, but the shock was thus independent of the reaction time. An adaptive algorithm was employed to ensure an approximate 66 percent hit rate per condition: the target's presentation time was increased 20 ms after a miss and reduced 10 ms after a miss. Participants rated their current stress level on a scale from 1 (no stress) to 9 (extremely stressed) before and after the PTD task.

The electric shocks were administered with a PsychLabs SHK 1 pain stimulator (Psychlab, Cambridge, MA, USA). Electrodes were attached with surgical tape to the index finger of the left hand. Before the start of the PTD task (see below), a shock work-up procedure was followed. The shock intensity started from 0 mA and was increased with steps of 0.02 mA until subjects indicated that the shock became painful. The last level before that was then used throughout the experiment.

#### 2.2.2. Social evaluative threat (SET) procedure

An adapted SET procedure (Cremers et al., 2015; Wager et al., 2009b) immediately follows the PTD task, which is essentially an anticipation version of the Trier social stress task (Kirschbaum et al., 1993). Right before entering the MRI scanner for the SET task, participants were reminded that another task would have to be performed after the scanning protocol, and further instruction on the following task would be presented on screen in the scanner. In the scanner, participants rated their stress level on a scale from 1 (no stress) to 9 (extremely stressed) by selecting (with a button box) the number on the screen (this screen was presented for 6 s). This was followed by a screen displaying a fixation cross for 54 s. This sequence was repeated 5 times and resulted in a 5-minute *baseline phase* (Fig 1b, block 1). Next, a 36 second series of instructions appeared informing participants their post-scan task is to perform a speech in front of the researchers, that the speech will be recorded for further investigation, and that the speech topic will be provided later. The 5-minute stress rating/fixation sequence was then repeated (*speech anticipation phase*; Fig. 1b, block 2). Next, participants saw on the screen that they are selected *not* to perform the public speech in the second series of instructions (30 s total). A third 5-minute stress-rating/fixation sequence was run (*recovery phase*; Fig 1b, block 3). The total duration of the SET task was thus approximately 16 min. During scanning, heart rate (Peripheral Pulse Unit; PPU) and respiration were recorded.

[1] Note that this terminology differs from the Escapable /Inescapable Shock used in animal paradigms (Maier and Watkins, 2010), but refers to a mostly similar experimental manipulation.

**Table 1**
Basic demographics and questionnaire results.

| | Control (*N* = 9) | No Control (*N* = 9) | Overall (*n* = 18) | Difference |
|---|---|---|---|---|
| Age | 38.6 (13.6) | 38.5 (9.02) | 38.5 (11.3) | t(15) = 0.01 *p* = 0.992 |
| Gender (F/M) | 4/5 | 4/5 | 8/10 | |
| PSS | 33.4 (13.2) | 37.8 (5.68) | 35.5 (10.3) | t(15) = −0.85 *p* = 0.407 |
| NGSE | 33.1 (2.85) | 34.6 (4.53) | 33.9 (3.74) | t(14) = −0.79 *p* = 0.441 |
| LOC | 19.8 (2.60) | 18.9 (2.95) | 19.3 (2.73) | *t*(14) = 0.63 *p* = 0.539 |
| LSAS avoidance | 14.5 (11.3) | 13.6 (12.5) | 14.1 (11.5) | t(14) = 0.15 *p* = 0.886 |
| LSAS fear | 11.9 (7.66) | 17.9 (9.78) | 14.9 (9.03) | t(14)) = −1.37 *p* = 0.193 |
| Neuroticism | 29.6 (6.63) | 27.9 (8.51) | 28.8 (7.43) | t(14) = 0.46 *p* = 0.653 |
| Extraversion | 40.4 (4.24) | 42.0 (2.73) | 41.2 (3.54) | t(14) = −0.91 *p* = 0.377 |

PSS; Perceived Stress Scale, NGSE, General Self-Efficacy, LOC; Locus of Control. LSAS; Liebowitz Social Anxiety Scale, fear, and avoidance subscale.

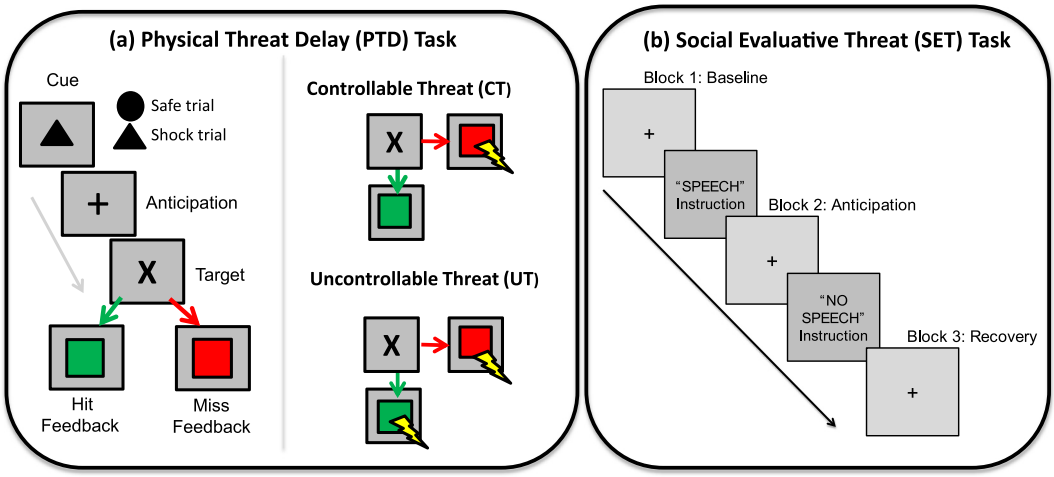


**Fig. 1. Outline of the Physical-to-Social Threat Experiment.** (a) **Physical Threat Delay (PTD)** task: Participants press a button when a target appears, followed by feedback, possibly coupled with a shock. Participants were assigned to either the *Controllable Threat* (CT; shocks only follow after a miss) or *Uncontrollable Threat* (UT; shock trials are yoked to a participant in the CT condition, and can follow either a hit or a miss) version of the PTD task. (b) **Social Evaluative Threat (SET)** task: In the MRI scan, after a 5-minute baseline measurement (baseline phase), participants are informed about a post-scan task which involves giving a short speech, followed by a 5-minute scan (speech anticipation phase), an instruction on the screen indicating they are selected not to perform the public speech and a final 5-minute scan (recovery phase).

### *2.3. Analysis*

#### *2.3.1. fMRI and physiology*

*2.3.1.1. fMRI: data acquisition and preprocessing.* MRI data were acquired using a Philips Achieva Quasar 3T MRI scanner at the Brain Research Imaging Center at The University of Chicago and an 8 channel head coil. A structural MRI was obtained after the functional scans with a T1-weighted gradient-echo sequence (484 sagittal slices, repetition time/TR = 7.1 ms, echo time/TE = 3.4 ms; flip angle/FA = 8°, field of view/FOV = 250 × 250 mm, slice thickness = 0.6 mm). fMRI images were obtained with high-field functional MRI utilizing T2*-weighted gradient-echo planar imaging (EPI) sensitive to the BOLD (blood oxygenation level dependent) signal (TE = 25 ms, TR = 2000 ms, FA = 70°, FOV = 240 × 240 mm; voxel size = 3.75 × 3.75 × 4 mm, 35 axial slices approximately parallel to the AC-PC line, 484 vol).

Structural images were skull-stripped using BET (Smith, 2002) and subsequent preprocessing was carried out in SPM12 (Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to correct for head motion and slice-time corrected; each subject's structural image was co-registered to the mean functional image and segmented and normalized to MNI space. Then functional images were normalized to the MNI space, and a Gaussian spatial smoothing kernel of 6 mm FWHM was applied.

*2.3.1.2. fMRI: statistics.* After preprocessing, the fMRI data were subjected to linear regression analysis, with a model including (a) First and second-order polynomial of time (b) The rating and instruction phases convolved with the hemodynamic response function (HRF), (c) the average time-series of the white matter and CSF (d) 6 motion regressors, (e) indicator regressors for outlier volumes (based on deviation in the scan-to-scan difference of z-normalized BOLD signal or composite motion (displacement) parameters) as identified with the Artifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect/) (f) physiological "noise" regressors: RETRICOR (Glover et al., 2000), heart rate convolved with the cardiac response function (Chang et al., 2009) and the respiration convolved with the respiratory response function (Birn et al., 2008). These physiological modeling regressors were estimated using the PhysIO toolbox (http://www.translationalneuromodeling.org/tnu-checkphysretroicor-toolbox/), and PPU signal peak detection was visually inspected and adjusted using custom Matlab code. Two subjects with a mean displacement (Van Dijk et al., 2012) of >0.1 mm were excluded from further analyses.

Subsequent analyses were performed on the residual data resulting from this regression analysis to generate connectivity measurements for between-group analysis. The brain parcellation described in Craddock et al., 2012 was used, resulting in 219 cortical and subcortical brain regions (see Fig. 3). For each region, the grey-matter density-weighted average time series across voxels was obtained (Varoquaux and Craddock, 2013). Subsequently, a sparse connectivity matrix was estimated per task phase (baseline, speech anticipation, and recovery) by applying the graphical LASSO (Friedman et al., 2008)

algorithm with a regularization parameter of *lambda* = 0.01. The connectivity matrices were subjected to network analyses using the brain connectivity toolbox (Rubinov and Sporns, 2010), estimating the global efficiency and local vmPFC efficiency, vmPFC participation coefficient, and vmPFC betweenness centrality (Rubinov and Sporns, 2010).

#### 2.3.2. Statistical analyses

Data were analyzed in a linear mixed-effect model framework using the nlme package in R (https://cran.r-project.org/web/packages/nlme/index.html). For the PTD task, one model assessed *stress ratings* as a dependent variable, with *Time* (pre-post task) as random and *Group* (CT, UT) as a fixed effect. A second model assessed median *reaction time*, with *Condition* (safe/potential shock) as random and *Group* as a fixed effect. For the SET procedure, the mean subjective stress ratings, heart rate, and network metrics (Global efficiency, vmPFC efficiency, centrality and participation coefficient) per task phase (baseline, anticipation, and recovery) were each modeled separately as a random effect (factor *Time*, testing linear and quadratic contrast) and *Group* as a fixed effect. A p-value of $< 0.05$ was considered as statistically significant and a p-value of $< 0.1$ considered as a trend.

Lastly, Spearman's rank-order correlations were calculated between all key outcome measures of the experimental procedure (reaction time, self-reported stress, heart rate, and vmPFC network measures), and the questionnaire data as an exploratory analysis. A false discovery correction of $q < 0.05$ was applied to correct for multiple comparisons.

## 3. Results

### 3.1. PTD

**Reaction time** showed a significant effect of Condition (Safe/Shock); ($\chi^2(5) = 9.52$, $p = 0.002$), and a trend interaction between condition and group ($\chi^2(7) = 3.23$, $p = 0.072$). The results indicated that the reaction times were faster in the Potential shock compared to the safe condition (see Fig. 2).

**The self-reported stress** showed a significant effect of time ($\chi^2(5) = 10$, $p = 0.0016$), but no other significant group x condition or group x time interaction effects (all $p > 0.4$).

### 3.2. SET

**Self reported stress** showed a significant main effect of time, ($\chi^2(6) = 7.91$, $p = 0.019$); the quadratic contrast, comparing the anticipation phase with the baseline and recovery phase, showed a significant effect ($t(32) = 2.55$, $p = 0.016$, $b = 0.24$, 95% CI95 = 0.07–0.42). This effect indicates that subjects rated their stress levels higher while anticipating giving a public speech compared to baseline or during recovery. No other main or interaction effects were detected (all $p > 0.2$). The **heart rate** data showed a trend effect of time ($\chi^2(6) = 5.82$, $p = 0.054$) but no other main or interaction effects. With respect to the brain network data, **vmPFC efficiency** showed a significant Group x Time (quadratic contrast) interaction effect ($t(28) = 2.1$ $p = 0.046$, $b = 0.009$, CI95 = 0.0008–0.019). The other network measures (global efficiency, vmPFC betweenness centrality, and participation coefficient) did not show significant main or interaction effects.

### 3.3. Correlational analysis

The correlational analyses did not show an FDR corrected ($q < 0.05$) correlation between any of the experimental measures or with the questionnaire data (the correlation between the two LSAS scales wat the only FDR corrected effect). However, it may be of note that the reaction time effect of the PTD (shock-safe) and vmPFC efficiency effect (quadratic), showed an uncorrected positive correlation ($\rho = 0.71$ $p = 0.003$, CI95 = 0.29–0.88) and so did both measures with the LSAS fear and avoidance scales (see Fig. 4).

## 4. Discussion

The goal of the current study was to develop and test the feasibility of a brain imaging paradigm investigating the generalization of physical-to-social threat controllability. Subjects were assigned to either a controllable or uncontrollable physical threat paradigm, which involved the occasional administration of shocks. Subsequently, participants entered the MRI scanner and underwent a social evaluative threat protocol. Overall this entire protocol was relatively short, with approximately 25 min of pure scanning time, allowing for the potential efficient use of available scanning time (e.g., three subjects in two hours). The behavioral results showed that subjects were indeed faster on trials when they expected a potential shock compared to the trials without shocks. In addition, a trend interaction between the group condition (controllable/uncontrollable) and median RT trial differences (Shock – Safe) was observed in the expected direction. CT compared to UT participants responded relatively faster on shock trials, perhaps reflective of the higher level of control. Furthermore, the self-reported stress ratings showed an increase due to the PTD task (after-before), but did not show a significant group difference. In sum, the PTD paradigm seems to be a promising approach to manipulate controllability experimentally, but more research is needed to further establish the behavioral effects of the PTD task.

The second part of the protocol aimed to test the generalization effect of physical treat controllability on social stress. Social stress anticipation was measured with a version of the social evaluative threat (SET; (Cremers et al., 2015; Wager et al., 2009b) paradigm. In line with these previous studies (Cremers et al., 2015; Wager et al., 2009b; 2009a), the results showed that subjects rated their stress levels as higher when they were anticipating giving a speech compared to a baseline and recovery phase. The heart rate data showed a similar pattern. Neither SET induced self-reported stress, nor heart rate changes differed between the CT and UT group. Interestingly the investigation of vmPFC brain connectivity showed a significant effect of vmPFC efficiency, but not in the expected direction: subjects in the CT condition showed higher vmPFC efficiency at baseline and recovery but similar vmPFC efficiency to UT during the speech anticipation phase. None of the other brain network metrics (betweenness-centrality, participation coefficient) showed an effect of the controllability manipulation.

The exploratory correlational analysis did not reveal any FDR corrected effects, but the relationship between vmPFC local efficiency, PTD reaction time differences, and social anxiety ratings could be considered promising. Social anxiety was related to less differentiation of shock and safe trials . In addition, social anxiety is related to a larger SET induced vmPFC local efficiency increase. It is imperative to underscore these observations' exploratory character and highlight that these results did not survive multiple comparisons correction. Yet it may hint at the clinical utility of this protocol to investigate brain connectivity patterns, for instance, in social anxiety disorder.

Overall the developed paradigm thus is a *feasible* approach with the potential to uncover the generalization effect of threat controllability. It is a well-known fact that the results from underpowered (small sample) studies produce unreliable results (e.g. Button et al., 2013a; 2013b; Cremers et al., 2017; Yarkoni, 2009). With respect to fMRI data, the network measures approach (using high-level network measures) does not suffer from the same need for stringent multiple comparison corrections as mass-univariate approaches. Nevertheless, with the current sample size, even with a conventional $\alpha = 0.05$ (and this can be considered liberal, since no further multiple comparison correction was applied to the primary analyses), only strong effects (Cohen's $d = 1.2$) for the between-group comparisons can be detected with 80% statistical power. Therefore, it is unclear whether the vmPFC network efficiency effects would replicate and whether the effects would be in a similar direction. As mentioned, the current study's primary goal was to develop the paradigm, establish the feasibility, and outline several key outcome measures. It is evident that adequately powered follow-up

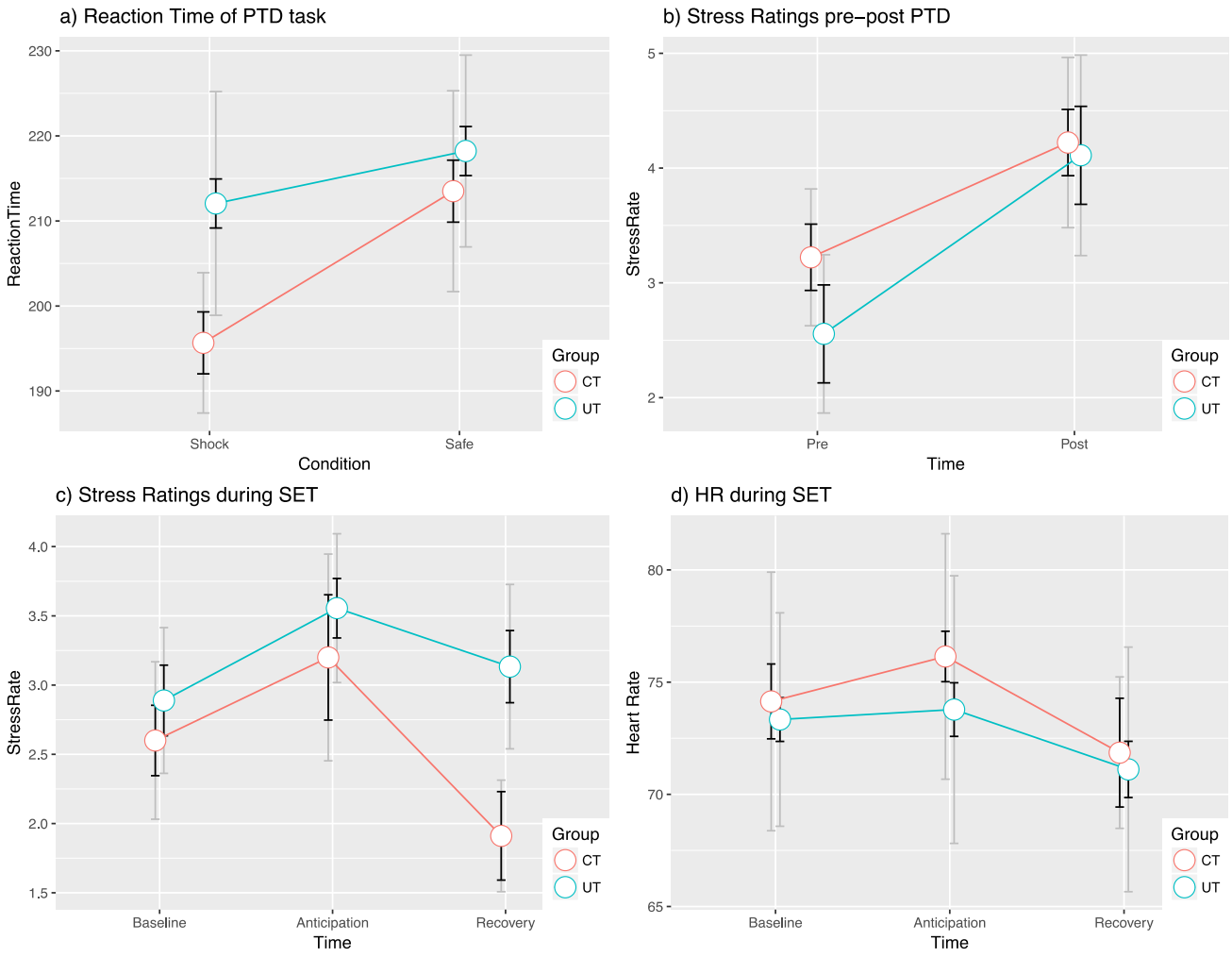


**Fig. 2. Behavioral and Physiological results of the PTD and SET task.** (a) Reaction time on the PTD task, (b) Self-reported stress before and after the PTD task, (c) self-reported stress during SET task (d) Heart rate during the SET task. CT: *Controllable Threat* UT; *Uncontrollable Threat.* Error bars represent the within-subject (Morey, 2008) (black) and between-subject standard error (grey).

studies are needed to establish the effect of the controllability manipulation on the behavioral, physiological, and vmPFC network measures further.

Next to the minimal statistical power, several factors concerning the experimental design should be taken into account. First, the current approach was set up as a between-subject design since the version of the SET procedure (due to the deception that it involves) does not lend itself for repeated measures. Yet the essential advantage of the current paradigm is that it involves a naturalistic threat manipulation and allows investigating naturally evolving changes in brain functioning (Cribben et al., 2012; 2013; Lindquist et al., 2007). A second consideration is to conduct the PTD task during scanning. In the current study, since the focus was on the generalization effect and we aimed to minimize scanning time, we decided to perform the PTD task outside the scanner. However, PTD-related neural processing could be relevant for understanding this paradigm's impact. For instance, we would hypothesize increased ventral striatal activity and connectivity (Knutson et al., 2008) when contrasting the CT and UT group on anticipating potential shock trials. In follow up studies, a fMRI–adapted version of the PTD will hence be relevant to reconsider. A third critical deliberation is the inclusion of a third "control" group that performs the same PTD task but does not receive shocks (comparable to animal research). Such a condition would be necessary to investigate the specificity of any possible results: whether any observed difference between controllable or uncontrollable threat differs from a no-shock control condition. This experimental consideration closely mirrors the debate on whether the lack of control (learned helplessness) or the experience of behavior control (leaned mastery) is the determining factor (Maier and Seligman, 2016).

## 5. Conclusion

In this feasibility and pilot fMRI study, we tested a paradigm and analytic strategy aimed at investigating the generalization of behavioral control. The protocol was feasible, efficient, and, therefore may be a potentially fruitful approach for testing the effect of behavioral control over a physical threat to the subsequent processing of social threat. Adequately powered follow-up research is needed to further test the generalization of behavioral control on the behavioral, physiological, and neural levels.

## Funding

This study was internally funded

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later

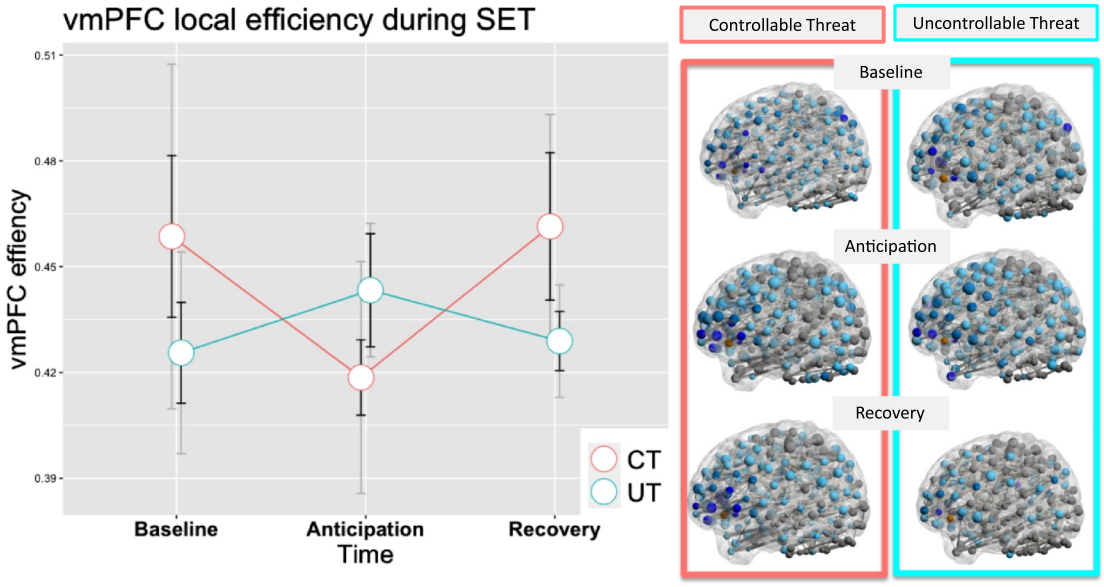


**Fig. 3.** Local efficiency of the vmPFC during social evaluative threat. (left) vmPFC efficiency for different phases of the SET task (right) vmPFC (orange) connectivity patterns; dark blue: direct connections of the vmPFC, light blue: second-order connections. Error bars represent the within-subject (Morey, 2008) (black) and between-subject standard error (grey). The results showed a time x group interaction effect for the quadratic contrast of vmPFC local efficiency. Local efficiency of the vmPFC was similar during the stress anticipation for both groups but higher for the controllable group during baseline and recovery.

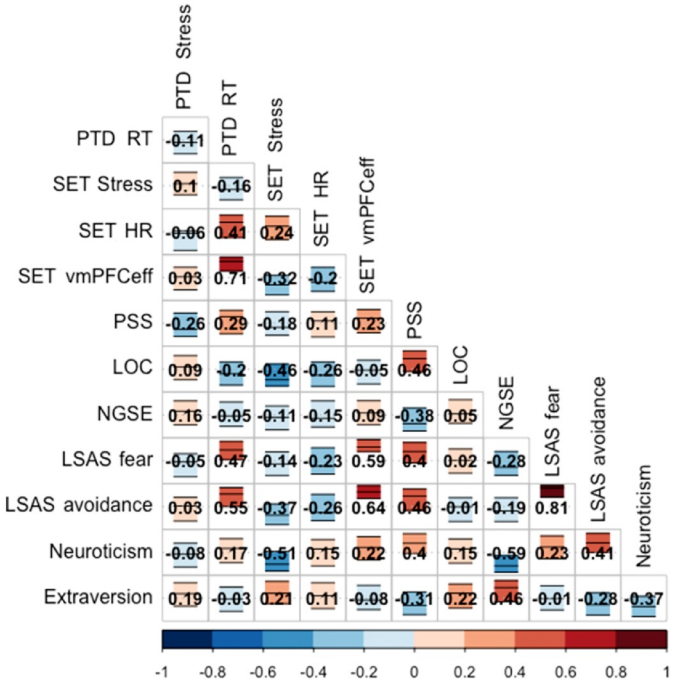


**Fig. 4.** Spearman correlations between all variables. Numbers denote the correlation coefficient, the coloured rectangle denote the 95% confidence interval, and the color indicates the strength of the correlation coefficient. PSS; Perceived Stress Scale, NGSE, (New) General Self-Efficacy, LOC; Locus of Control. LSAS; Liebowitz Social Anxiety Scale fear and avoidance subscale. PTD RT; median Reaction time difference (Shock-Safe) of PTD task. PTD stress; difference in stress ratings (Post-Pre). SET HR, the quadratic effect of the heart rate measurement during the SET procedure, SET stress; is the quadratic effect of self-reported stress ratings during the SET procedure. SET vmPFC eff; quadratic effect of vmPFC local efficiency ratings during the SET procedure.

amendments or comparable ethical standards.

## Declaration of Competing Interest

Authors Keedy and Cremers declare that they have no conflict of interest. Author Coccaro reports that he is on the Scientific Advisory Board of Azevan Pharmaceuticals., Inc. and that he has stock options in Azivan Pharmaceuticals, Inc., through this role

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