Running title: Intolerance of uncertainty and instructed threat of shock

Intolerance of uncertainty is associated with heightened responding in the prefrontal cortex during instructed threat of shock

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Abstract

Heightened responding to uncertain threat is associated with anxiety disorder pathology. Here, we sought to determine if individual differences in self-reported intolerance of uncertainty (IU) underlie differential recruitment of neural circuitry during instructed threat of shock (*n* = 42). During the task, cues signalled uncertain threat of shock (50%) or certain safety from shock. Ratings, skin conductance and functional magnetic resonance imaging was acquired. Overall, participants displayed greater amygdala activation to uncertain threat vs. safe cues, in the absence of an effect of IU. However, we found that high was associated with greater activity in the medial prefrontal cortex and dorsomedial rostral prefrontal cortex to uncertain threat vs safe cues. These findings suggest that, during instructed threat of shock, IU is specifically related, over trait anxiety, to activation in prefrontal cortical regions. Taken together, these findings highlight the potential of self-reported IU in identifying mechanisms that may be related to conscious threat appraisal and anxiety disorder pathology.

Keywords: Instructed threat of shock, Intolerance of Uncertainty, Medial prefrontal cortex, Rostral dorsomedial prefrontal cortex, fMRI

1.1 Introduction

In everyday life, we often experience uncertainty, and will typically try to minimise or resolve it, in order to reduce anxiety and stress (Grupe & Nitschke, 2013; Morriss, Gell, & van Reekum, 2018; Peters, McEwen, & Friston, 2017). Individuals who score high in self-reported intolerance of uncertainty (IU) tend to find uncertainty particularly aversive (Carleton, 2016a, 2016b; Dugas, Buhr, & Ladouceur, 2004; Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994). High levels of IU are observed across many mental health disorders with an anxiety component such as anxiety, depression and obsessive compulsive disorder (Gentes & Ruscio, 2011; Mahoney & McEvoy, 2012). On this basis, there has been a surge in IU-related research in the field of anxiety over the last decade.

Despite progress in understanding the aetiology of IU, there still remain gaps in the literature as to how IU modulates neural circuitry associated with the processing of uncertain threat (Tanovic, Gee, & Joormann, 2018). Only a few studies to date have examined how IU is correlated with neural circuitry during the anticipation of uncertain threat (Morriss, Christakou, & Van Reekum, 2015; Schienle, Köchel, Ebner, Reishofer, & Schäfer, 2010; Simmons, Matthews, Paulus, & Stein, 2008; Somerville et al., 2013). In tasks where the goal of the participant is to tolerate 'known' uncertain threat, individuals high in IU, relative to low IU, have been shown to exhibit heightened amygdala and insula activity to cues signalling unpredictable aversive pictures (Schienle et al., 2010; Shankman et al., 2014), and exaggerated amygdala activity to aversive pictures following unpredictable countdowns (Somerville et al., 2013). Furthermore, in tasks where the contingencies change from threat to safe, individuals high in IU, relative to low in IU display greater amygdala

and medial prefrontal cortex activity to cues previously associated with threat (Morriss et al., 2015). Whilst previous work has provided a starting point for understanding how IU modulates neural circuitry to uncertain threat, further research is needed to assess the robustness and generalisability of IU-related effects. For example, previous studies have conflated different types of uncertainty (i.e. occurrence (if), temporal (when), content (what)). Given the important role of uncertainty in anxiety (Carleton, 2016a, 2016b; Grupe & Nitschke, 2013), it will be important to parse out how IU is related to neural circuitry under different types of uncertain threat (Morriss, 2019). Elucidating how IU is related to the processing of uncertain threat will provide crucial information for advancing our conceptual understanding of IU and its relevance to psychopathology (Shihata, McEvoy, Mullan, & Carleton, 2016).

To assess the relationship between self-reported IU and anticipatory responding during uncertainty of threat occurrence (i.e. if a threat is likely to occur or not), we measured event-related functional magnetic resonance imaging (fMRI), skin conductance response (SCR) and ratings while participants performed an instructed threat of shock task. To induce a sense of uncertain threat, a cue signalled whether a mild electric shock to the finger would occur (50% of the time) (i.e. participants were told that they would sometimes receive a shock at the end of the cued trial). Trials were 9 seconds in length (1 second cue, 8 second anticipatory period), to allow us to examine phasic and sustained threat/safety related activity.

We hypothesized that, during the instructed threat of shock task, we would observe typical patterns of phasic and sustained activation in circuitry associated with the processing of threat and safety (Etkin, Egner, & Kalisch, 2011; Mechias,

Etkin, & Kalisch, 2010; Morriss, Gell, et al., 2018), i.e. (1) greater activation in the amygdala, putamen, caudate, insula and rostral prefrontal cortex to threat trials and (2) greater medial prefrontal cortex activity to safe trials. Moreover, we hypothesized that participants would display greater SCR to the threat vs. safe trials, and rate the threat trials as more negative and arousing than the safe trials.

Based on past research (Morriss et al., 2015; Schienle et al., 2010; Shankman et al., 2014; Simmons et al., 2008; Somerville et al., 2013), we hypothesised that higher IU would be associated with: (1) greater phasic and sustained activation in the amygdala and insula during threat, relative to safe trials, and (2) modulation of the medial prefrontal cortex during threat, relative to safe trials. Given the shortage of research on the relationship between IU and activation in the medial prefrontal cortex, we did not hypothesise a particular direction of effect. Lastly, we hypothesised that higher IU would be associated with greater SCR to the threat vs. safe trials, as well as higher ratings of negativity and arousal to the threat vs. safe trials.

We tested the specificity of the involvement of IU by comparing it with broader measures of anxiety (for discussion see Morriss, Christakou, & Van Reekum, 2016), in this case the Spielberger State-Trait Anxiety Inventory, Trait Version (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

2. Methods

2.1 Participants

42 right-handed female volunteers were recruited from the local area through advertisements (*M* age= 33 yrs, *SD* age= 7.33 yrs). All participants had normal or

corrected to normal vision and were medication-free. We selected female participants because the study was part of a larger programme of research examining the role of conspecifics (i.e. romantic partner, friend) in the processing of threat (Morriss, Bell, Johnstone, van Reekum, & Hill, 2018).

Participants provided written informed consent and received a picture of their brain and £15 for their participation. The University of Reading's Research Ethics Committee approved the study protocol.

2.2 Instructed threat of shock task

The possibility of receiving an unpleasant electrical shock to the index and middle finger of the right hand was used to induce threat. Electric shocks were delivered via an ADInstruments ML856 PowerLab 26T Isolated Stimulator using an MLADDF30 stimulating bar electrode with 30 mm spacing of 9 mm contacts. Each participant's stimulation level was set by first exposing them to an electric stimulation of 1 mA (10 pulses at 50 Hz, with a pulse duration of 200 μs) and increasing the current in steps of 0.5 mA, up to a maximum of 10 mA. This continued until a suitable participant-specific threshold was found that was uncomfortable but not painful. This level was then used throughout the threat of shock task for that subject (electric stimulation level: M= 2.21 mA; SD= 1 mA).

Participants were required to passively view cues that represented either threat of shock or safety from shock. Only two cues were presented, a threat cue where there was 50% chance of receiving a shock and a safety cue where there was 0% chance of receiving a shock. At the beginning of the experiment participants were informed that one cue would signal shock some of the time and the other cue

would signal no shock. Each trial consisted of: a white cue (e.g. X, O, D, T) presented on a black background (1 second), a white fixation anticipation cue presented on a black background (8 seconds), a small circle cue signalling the end of the trial (1 second) and a black blank screen (4-6 seconds) (see Figure 1). Participants completed 1 run of 36 trials (18 Threat, 18 Safe). To rule out any cue-specific effects, half the participants received X and O cues, whilst the other half received D and T cues.

2.3 Procedure

Participants arrived at the laboratory and were informed of the experimental procedures. First, participants completed a consent form as an agreement to take part in the study. Second, participants completed questionnaires by pen and paper. Next, participants were taken to the MRI unit and the shock procedure was carried out. We used an instructed threat of shock task in the scanner whilst concurrently recording skin conductance. After scanning, participants rated the threat and safe cues from the instructed threat of shock task.

2.4 Questionnaires

To assess anxious disposition, we used Intolerance of Uncertainty (IU) (Freeston et al., 1994) and the Spielberger State-Trait Anxiety Inventory, Trait Version (STAI) (Spielberger et al., 1983). Similar distributions and internal reliability of scores were found for the anxiety measures, IU (M = 66.07; SD = 17.03; range = 34-102; α = .93) and STAI (M = 40.92; SD = 10.31; range = 25-61; α = .91).

2.5 Ratings

Participants rated the valence and arousal of the threat and safe cues using 9 point Likert scales ranging from 1 (Valence: negative; Arousal: calm) to 9 (Valence: positive; Arousal: excited). 1 participant did not complete the ratings, leaving 41 participants with ratings data.

2.6 Skin conductance acquisition and reduction

Identical to previous work (Morriss et al., 2015), electrodermal recordings were obtained using AD Instruments (AD Instruments Ltd, Chalgrove, Oxfordshire) hardware and software. An ML138 Bio Amp connected to an ML870 PowerLab Unit Model 8/30 amplified the electrodermal signal, which was digitized through a 16-bit A/D converter at 1000 Hz**.** Electrodermal activity was measured during the scanning session with MRI-safe MLT117F Ag/AgCl bipolar finger electrodes filled with NaCl electrolyte paste (Mansfield R & D, St Albans, Vermont, USA) that were attached to the distal phalanges of the index and middle fingers of the left hand. A constant voltage of 22mVrms at 75 Hz was passed through the electrodes, which were connected to a ML116 GSR Amp.

Skin conductance responses (SCR) were scored when there was an increase of skin conductance level exceeding 0.01 microSiemens. The amplitude of each SCR was scored as the difference between the baseline (1 second average pre cue onset) and the maximum deflection (0.5-9 second post cue onset). Trials with no discernible SCRs were scored as zero. SCR magnitudes were calculated from remaining trials by averaging SCR values for each condition (Threat, Safe). Due to

recording errors, 2 participants did not have SCR data, leaving 40 participants with SCR data.

2.7 Ratings and SCR analysis

We conducted a 2 Condition (Threat, Safe) x IU ANCOVA for arousal ratings, valence ratings and SCR to the cues, where IU was entered as a continuous predictor variable. Any interaction with IU was followed up with pairwise comparisons of the means between the conditions for IU estimated at the specific values of + or -1 SD of mean IU. This type of analysis with IU has been previously published elsewhere (Morriss et al., 2015, 2016).

We performed hierarchical regression analyses on the rating/SCR difference score measures that showed an effect with IU. This analysis served to assess IU-specific effects over and above shared variance with trait anxiety (STAI). We entered STAI in the first step and then IU in the second step.

2.8 MRI

Participants were scanned with a 3T Siemens Trio using a 12 channel head coil (Siemens Inc., Erlangen, Germany). T2*-weighted gradient-echo, echo planar imaging (EPI) functional scans were acquired for the threat of shock task consisting of 281 volumes (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 192 × 192 mm, 3 × 3 mm voxels, slice thickness 3 mm with an interslice gap of 1 mm, 30 axial slices, interleaved acquisition).

Following completion of the functional scan, structural and fieldmap scans were acquired, which comprised of a high-resolution T1-weighted anatomical scan

(MP-RAGE, TR = 2020 ms, TE = 2.52 ms, flip angle = 90°, FOV = 256 × 256 mm, 1 x 1 x 1 mm voxels, slice thickness 1 mm, sagittal slices) and fieldmap (TR = 488 ms, TE 1 = 4.98 ms, TE 2 = 7.38 ms, flip angle = 60°, FOV = 256 × 256 mm, slice thickness 4 mm with an interslice gap of 4 mm, 30 axial slices).

2.9 fMRI analysis

FMRI analyses were carried out in Feat version 5.98 as part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Brains were extracted from their respective T1 images by using the FSL Brain Extraction Tool (BET) (Smith, 2002). Distortion, slice timing and motion correction were applied to all extracted EPI volumes using FUGUE and MCFLIRT tools. Gaussian smoothing (FWHM 5mm) and a 50 second high pass temporal filter were applied.

A first-level GLM analysis was carried out for each functional scan. Separate regressors were specified for the experimental conditions of primary interest (Threat/Safety Cues) by convolving a binary boxcar function with an ideal haemodynamic response (HR), which corresponded to the length of each cue (1 second) or the entire trial period (9 seconds). Regressors for the end of trial period with and without shock and six motion parameters were included to model out brain activity that was unrelated to the conditions of interest.

In two separate general linear models, we defined two main effect contrasts to reveal phasic and sustained threat/safety related activity: (1) Threat vs. Safety across the 1 second cue period, and (2) Threat vs. Safety across the whole 9 second trial period. All contrasts were normalized and registered to MNI standard space using FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Second-level GLM

analysis consisted of regressors for the group mean and demeaned IU scores using FSL's OLS procedure. Whole-brain analysis was carried out using cluster thresholding with a $z = 2.3$ and a corrected $p < 0.05$ (see supplementary material).

We performed hierarchical regression analyses on the resulting significant clusters that showed an association with IU. We extracted % BOLD signal change difference scores from the relevant clusters and correlated these with the anxiety measures to test for IU-specific effects, by using STAI in the first step and then IU in the second step of hierarchical regression models.

3. Results

3.1 Ratings

Participants rated the threat cues as more negative ($M = 4.78$, $SD = 1.77$) and more arousing ($M = 5.78$, $SD = 1.68$) than the safe cue ($M = 6.78$, $SD = 1.56$ for valence and $M = 2.90$, $SD = 2.11$ for arousal respectively) [Condition (Valence): $F(1,39) = 29.127$, $p < .001$; Condition (Arousal): $F(1,39) = 47.095$, $p < .001$]. Higher IU was associated with significantly more negative ratings of the threat cues compared to the safe cues, $p < .001$ [Condition (Valence) x IU interaction: $F(1,39) = 5.764$, $p = .021$].

For the valence rating difference score (Threat cue – Safe cue), STAI made no significant contribution to the model at the first step [R^2=.044, F=1.808], whilst adding IU improved the hierarchal model at trend in the second step [ΔR^2 =.086, $F(1,38)$=3.746, p=.06].

3.2 SCR

SCR was greater to threat (*M* = .29, *SD* = .11) vs. safe (*M* = .16, *SD* = .11) trials [Condition: $F(1,38) = 43.694$, $p < .001$]. No significant interactions between Condition and IU emerged for SCR [Condition x IU: $F(1,38) = 3.047$, $p = .089$].

3.3 fMRI

For all participants threat vs. safe cues induced greater activation in the bilateral amygdala, insula, frontal operculum, pre and postcentral gyrus, paracingulate, cingulate, supramarginal gyrus and middle frontal gyrus (for full list of brain regions see Table 1 & Figure 2). During threat vs. safe trial periods, activations were observed in the bilateral insula, caudate, putamen, orbital frontal cortex, supramarginal gyrus, middle frontal gyrus, thalamus, and brain stem (for full list of brain regions see Table 1 & Figure 3), The reverse contrast, safe vs. threat trial period, revealed greater activation in the bilateral hippocampus, medial cortex, superior frontal and middle frontal gyri, and precuneus (for full list of brain regions see Table 1 & Figure 3).

For threat vs. safe cues, high IU was associated with greater activation in the medial frontal cortex and rostral dorsomedial prefrontal cortex (split into two clusters, see Table 1 & Figure 4). No significant IU-related effects were observed for the safe vs. threat contrast for the cue period. In addition, no significant IU-related effects were found for the contrasts from the trial period.

For the medial prefrontal cortex cluster (Threat cue – Safe cue), STAI made a significant contribution to the model at the first step [R^2=.220, $F(1,40)$=11.301, p= .002], and adding IU in the second step improved the model significantly [ΔR^2 =.167,

$F(1,39)=10.610$, $p=.002$]. Similarly, for the rostral prefrontal cortex cluster (Threat cue – Safe cue), STAI made a significant contribution to the model at the first step [$R^2=.218$, $F(1,40)=11.171$, $p=.002$], whilst adding IU improved the model significantly in the second step [$\Delta R^2 =.163$, $F(1,39)=10.287$, $p=.003$].

4. Discussion

We show that self-reported IU, a dispositional tendency to find uncertain situations negative, was associated with prefrontal neural recruitment during instructed threat of shock occurrence uncertainty (i.e. if a shock will occur or not). Specifically, we found individuals with high IU, relative to low IU to recruit greater medial prefrontal cortex and dorsomedial rostral prefrontal cortex to cues that signalled uncertainty of threat of shock vs. safety from shock. However, we did not observe individuals high in IU, relative to low IU to differentially recruit the amygdala or insula to cues that signalled uncertainty of threat of shock vs. safety from shock. Furthermore, IU-related effects were specific to the cue (phasic); we did not observe IU modulation of neural activity during the across the entire trial period (sustained). These findings suggest that IU may modulate neural circuitry to uncertain threat differently depending on the type of uncertainty (i.e. if, when and what). Furthermore, these results highlight the potential of self-reported IU in identifying mechanisms that may be related to conscious threat appraisal and anxiety disorder pathology.

In general, we found that participants recruited typical regions associated with instructed threat of shock tasks (Etkin et al., 2011; Grupe & Nitschke, 2013; Mechias et al., 2010; Morriss, Gell, et al., 2018). Participants recruited greater amygdala to threat vs safe cues (phasic), as well as greater putamen, caudate and insula during

threat vs. safe trial periods (cue + anticipation window). Moreover, participants recruited greater medial prefrontal cortex during safe vs. threat periods. As expected, greater SCR was observed to the threat vs. safe trials. Furthermore, participants rated threat cues as negative and moderately arousing, and safe cues as moderately positive and low in arousal.

The medial prefrontal cortex has been implicated in threat regulation and safety-signalling generally (Etkin et al., 2011; Milad & Quirk, 2012). In the context of instructed threat of shock, greater recruitment of the medial prefrontal cortex may reflect attempts to regulate. The modulation of activity in this area by IU is in line with prior work showing high IU individuals to recruit more medial prefrontal cortex during extinction of threat vs. safe cues (Morriss et al., 2015). Higher IU was also associated with greater dorsomedial rostral prefrontal cortex to cues signalling uncertainty of threat of shock vs. safety from shock. In a recent meta-analysis, the dorsomedial rostral prefrontal cortex has been suggested to underlie conscious threat appraisal during instructed threat conditioning (Mechias et al., 2010). Therefore, in the context of instructed threat of shock, greater engagement of the dorsomedial rostral prefrontal cortex may reflect conscious threat appraisal in individuals high in IU. Perhaps, individuals with higher IU were more 'consciously' engaged with the task because there was potential for uncertain threat outcomes. Alongside these neural findings, we also observed individuals with high IU, relative to low IU, to rate the uncertain threat cue as more aversive. The IU-related effects for the ratings provide further evidence that individuals with higher IU found the uncertain threat cue aversive, despite knowing that there was going to be uncertain threat.

We did not observe higher IU to differentially engage the amygdala or insula (across the cue or entire trial period), or display greater SCR to cues that signalled uncertainty of threat of shock vs. safety from shock. Whilst this is at odds with previous research (Morriss et al., 2015; Schienle et al., 2010; Shankman et al., 2014; Simmons et al., 2008; Somerville et al., 2013), there may be an explanation for these results. In the current study we only manipulated occurrence uncertainty of threat of shock (i.e. if a shock would occur or not), whereas in previous studies different types of uncertain threat were conflated (i.e. if, when and what type of aversive picture would be displayed). Many types of uncertainty in combination, compared to a single type of uncertainty, will probably be perceived as more arousing and threatening in general, but particularly by individuals who score higher in IU. Therefore, in a context where different types of uncertainty are combined, threat cues are more likely to engage circuitry such as the amygdala and insula, and arousal-based physiology such as SCR, in high IU to alert the individual to this particular situation of threat. Our results need to be further explored and replicated, in order to fully understand how IU modulates neural circuitry under different types of uncertain threat.

The study did have a few shortcomings. Firstly, the generality of these findings should be tested in future studies using aversive stimuli other than shocks and with different reinforcement rates of occurrence uncertainty (Chin, Nelson, Jackson, & Hajcak, 2016). Secondly, using different types of uncertain threat (i.e. if, when and what) – ideally in a single instructed threat of shock study - may elucidate if individuals high in IU are more sensitive to a particular type of uncertain threat (Bennett, Dickmann, & Larson, 2018; Davies & Craske, 2015). Lastly, the sample

contains only female participants, and future studies should include more diverse community or clinical samples.

Taken together, these results suggest that, during instructed threat of shock, IU is specifically related over STAI to activation in prefrontal cortical regions. These preliminary findings suggest that uncertainty-related biases may serve as a key candidate marker for maintenance of anxiety and stress disorders (Carleton, 2016a, 2016b; Grupe & Nitschke, 2013). Further research is needed to explore how individual differences in IU modulate different types of uncertain threat (i.e. if, when and what).

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Consent for publication: The authors give permission for publication.

Availability of data and material: For inquiries about access to the data, please contact Jayne Morriss.

Code availability: Not applicable.

Authors' Contributions: JM and TB carried out the study. NB developed the scripts for skin conductance extraction. JM performed the statistical analyses and drafted the manuscript. JM, TJ, and CvR designed the study. TB, TJ, and CvR revised the manuscript. All authors read and approved the final manuscript.

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Table 1

Regional activation patterns in response to stimuli presented in the threat of shock task

Task	Brain region	BA	Voxels (mm^3)	Max Z	Location of max Z		
					x	y	z
Threat of Shock (Cue Period)							
Threat > Safe	L amygdala, insula cortex, frontal operculum cortex, inferior frontal gyrus, frontal pole, middle frontal gyrus, supramarginal gyrus, postcentral gyrus, precentral gyrus	44/10/6/8/9/40/1/3	5722	4.35	-36	14	0
Threat > Safe	R amygdala, insula cortex, frontal operculum cortex, inferior frontal gyrus, frontal pole, middle frontal gyrus	44/6/8/9/40	4791	4.43	40	12	16
Threat > Safe	R parietal operculum cortex, middle temporal gyrus, supramarginal gyrus	21/40	3144	5.17	52	-42	6
Threat > Safe	Cingulate gyrus, paracingulate gyrus	24/32	1344	4.18	-8	2	40
Threat > Safe	Superior frontal gyrus	6/8	313	4.01	-6	40	54
Threat > Safe	Posterior cingulate gyrus	23	308	4.1	16	-18	38
Threat > Safe	R Superior frontal gyrus, precentral gyrus	6/8/4	282	3.58	16	0	66
Threat > Safe x IU	paracingulate gyrus, frontal medial cortex, frontal pole, superior frontal gyrus (medial prefrontal cortex)	32/10/9	894	4	2	58	30
Threat > Safe x IU	paracingulate gyrus, Frontal pole (rostral dorsomedial prefrontal cortex)	32/8	258	3.12	14	46	32
Threat of Shock (Cue and Anticipation Period)							

Threat > Safe	L insula cortex, frontal operculum cortex, inferior frontal gyrus, frontal pole, orobtial frontal cortex, putamen, caudate	47/45/44	3184	5.94	-32	22	12
Threat > Safe	R insula cortex, frontal operculum cortex, inferior frontal gyrus, frontal pole, orobtial frontal cortex, putamen, caudate	47/45/44	2979	5.24	34	24	-8
Threat > Safe	Cingulate, paracingulate, juxtapositional lobule cortex	24/32/4/6	2447	4.67	2	10	62
Threat > Safe	R supramarginal gyrus, parietal operculum cortex	40	1421	4.77	56	-42	40
Threat > Safe	L supramarginal gyrus, parietal operculum cortex	40	1359	4.66	-56	-24	18
Threat > Safe	Brain stem, thalamus		1292	4.44	2	-16	-10
Threat > Safe	Cerebellum		540	3.85	2	-50	-24
Threat > Safe	Occipital pole	17	393	4.45	34	-98	0
Threat > Safe	Precentral gyrus, middle frontal gyrus	4/6/8	338	3.96	42	4	52
Safe > Threat	posterior cingulate, precuneus cortex, occiptial pole, lingual gyrus, L hippocampus, R hippocampus	23/7/17/18/19	18491	6.11	10	-56	18
Safe > Threat	Subcallosal cortex, paracingulate gyrus, frontal medial cortex, frontal pole,	12/25/32/10	4671	6.44	4	48	-8
Safe > Threat	L superior frontal gyrus, middle frontal gyrus	6/8/9	924	4.27	-22	22	38
Safe > Threat	R superior frontal gyrus, middle frontal gyrus	6/8/9	727	4.74	24	32	44
Safe > Threat	L superior temporal gyrus, middle temporal gyrus	22/38	668	4.48	-64	-8	-14

Note: Corrected cluster for multiple comparisons at $p < 0.05$. BA = Brodmann Areas. Location of cluster's maximum Z are in MNI space. R = right; L = left.

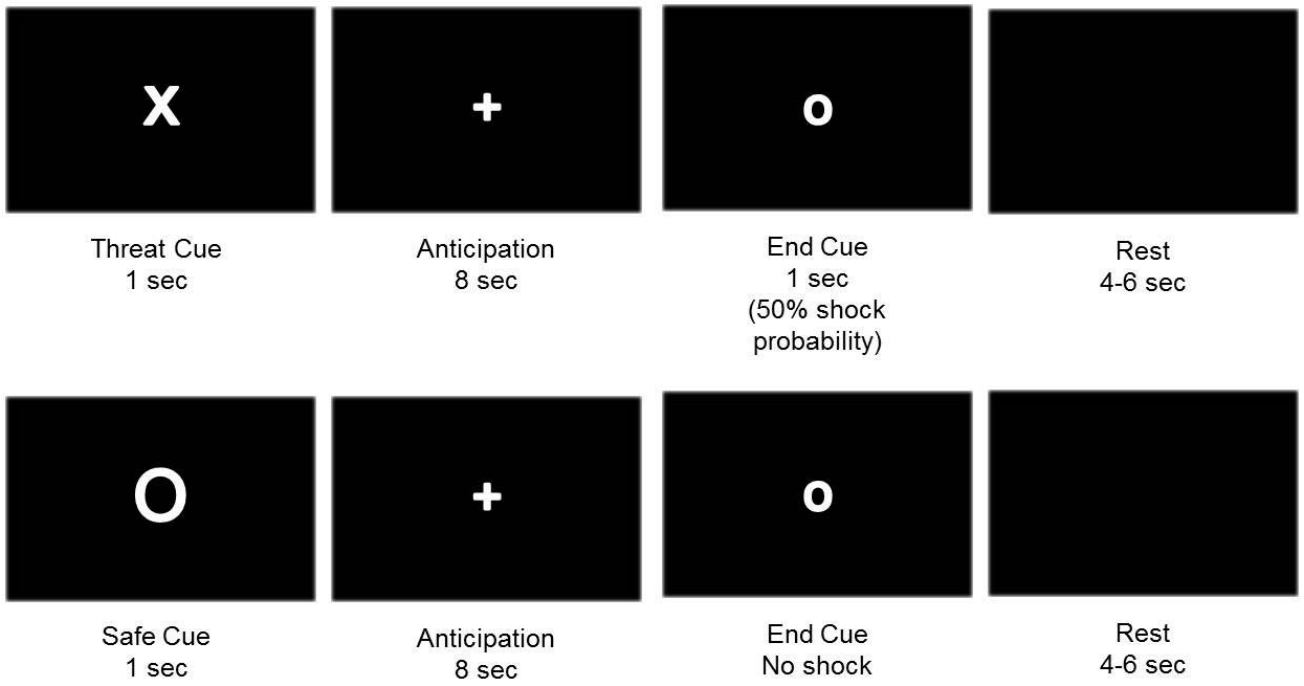

Figure 1: Image depicting instructed threat of shock task. Examples of threat (top row) and safe (bottom row) trial types. Participants were instructed on threat and safe contingencies before the start of the task.

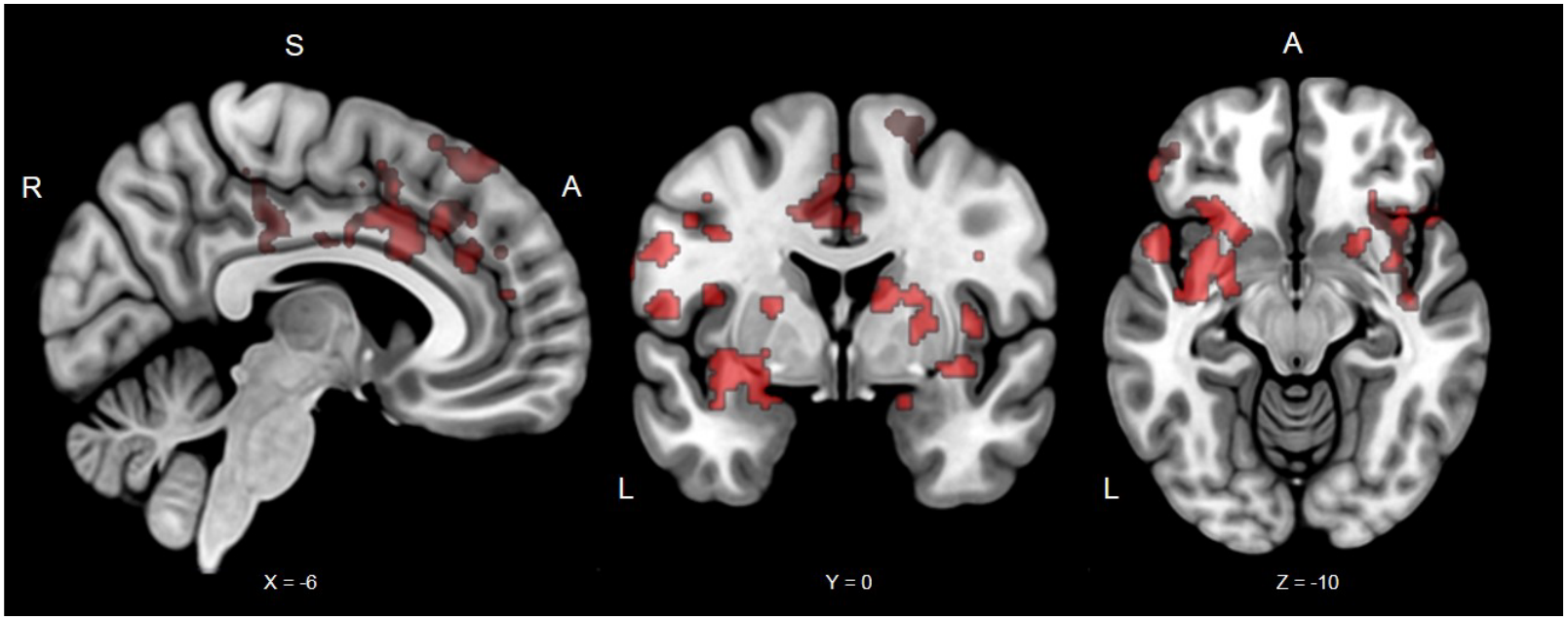

Figure 2: Significant clusters from the instructed threat of shock task for all participants during the cue period. Typical regions activated during threat and safety were observed. The red clusters are from the Threat > Safe contrast. Coordinates in MNI space; R, right; S, superior; A, Anterior.

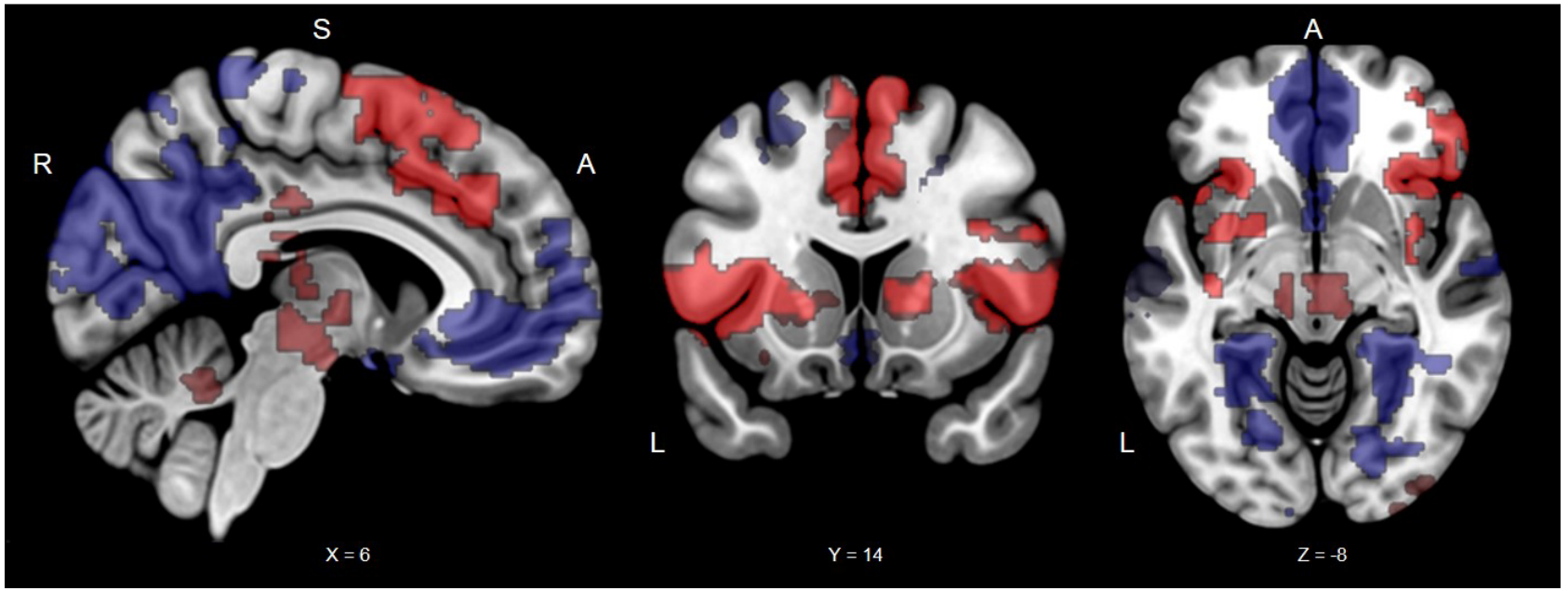

Figure 3: Significant clusters from the instructed threat of shock task for all participants during the cue and anticipation period. Typical regions activated during threat and safety were observed. The red clusters are from the Threat > Safe contrast and the blue clusters are from the Safe > Threat contrast. Coordinates in MNI space; R, right; S, superior; A, Anterior.

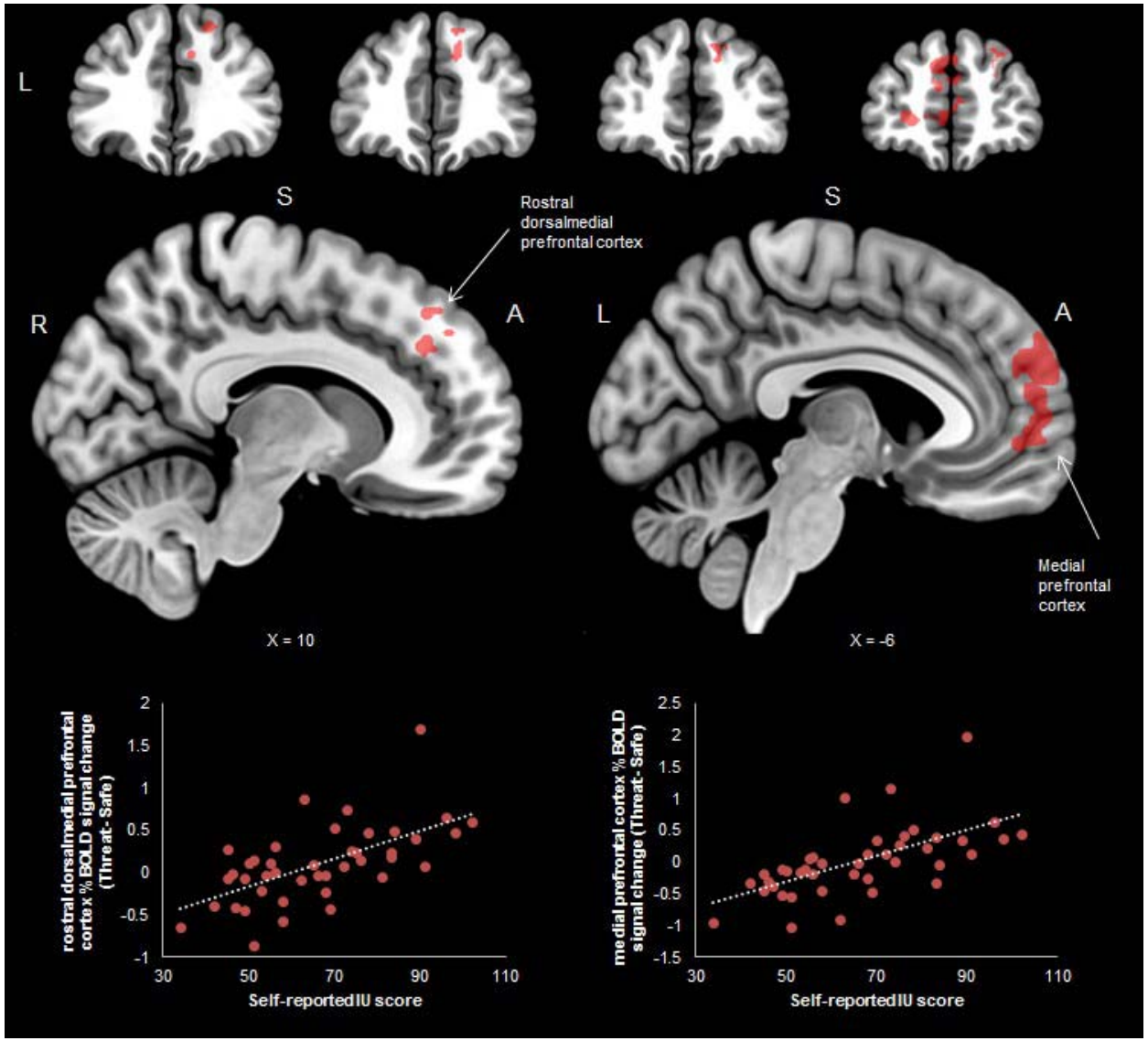

Figure 4: Significant clusters from the instructed threat of shock task during the cue period by individual differences in self-reported intolerance of uncertainty (IU). For threat vs. safe cues, high IU was associated with greater activation in the rostral dorsomedial prefrontal cortex and medial prefrontal cortex (see bottom of figure for correlations). Such prefrontal regions are thought to be related to regulation and conscious threat appraisal. Coordinates in MNI space; R, right; S, superior; A, Anterior.