Sex differences in neural mechanisms of social and non-social threat monitoring

Tessa Clarkson [a],[*],[1], Yvette Karvay [b], Megan Quarmley [a], Johanna M. Jarcho [a]

[a] Temple University, Department of Psychology, USA
[b] Fordham University, Department of Psychology, USA

ABSTRACT

Adolescent males and females differ in their responses to social threat. Yet, threat processing is often probed in non-social contexts using the error-related negativity (ERN; Flanker EEG Task), which does not yield sex-specific outcomes. fMRI studies show inconsistent patterns of sex-specific neural engagement during threat processing. Thus, the relation between threat processing in non-social and social contexts across sexes and the effects perceived level of threat on brain function are unclear. We tested the interactive effect of non-social threat-vigilance (ERN), sex (N = 69; Male=34; 11–14-year-olds), and perceived social threat on brain function while anticipating feedback from 'unpredictable', 'nice', or 'mean' purported peers (fMRI; Virtual School Paradigm). Whole-brain analyses revealed differential engagement of precentral and inferior frontal gyri, putamen, anterior cingulate cortex, and insula. Among males with more threat-vigilant ERNs, greater social threat was associated with increased activation when anticipating unpredictable feedback. Region of interest analyses revealed this same relation in females in the amygdala and anterior hippocampus when anticipating mean feedback. Thus, non-social threat vigilance relates to neural engagement depending on perceived social threat, but peer-based social contexts and brain regions engaged, differ across sexes. This may partially explain divergent psychosocial outcomes in adolescence.

1. Introduction

Adolescent social interactions often result in bullying and peer victimization. In fact, social threat in the form of peer victimization becomes more common during adolescence (Troop-Gordon, 2017). Greater exposure to social threat is associated with long-term negative outcomes such as higher levels of social avoidance and emotional distress (Boivin et al., 1995; Buhs et al., 2006; Nishina et al., 2005), loneliness, social dissatisfaction, risk for internalizing problems, and social anxiety (Hawker and Boulton, 2000; Sentse et al., 2017; Takizawa et al., 2014). Additionally, experiences of social threat vary across sexes. For example, girls tend to experience more relational victimization, while boys tend to experience more physical victimization (Carbone-Lopez et al., 2010; Zimmer-Gembeck et al., 2005). Moreover, the link between exposure to social threat and long-term psychopathology differs across sex (Sentse et al., 2017). Differences in how males and females process and respond to social threats may impact their behavior during subsequent social interactions, thereby increasing risk for further

victimization and negative long-term psychosocial outcomes. Thus, mapping how threat processing differs across sex is imperative for understanding sexually dimorphic long-term outcomes.

Hypervigilance to social threat exacerbates the experience of being victimized (Dandeneau and Baldwin, 2004), increases subsequent rejection bias (Dandeneau et al., 2007), and potentiates interpretations of negative social interactions as intentional (Burgess et al., 2006). Furthermore, the hypervigilance for social threat hypothesis (HSTH), argues that rejection sensitivity contributes to social withdrawal and undermines the opportunity to develop and maintain positive social relationships (Cacioppo and Hawkley, 2009). One potential process underlying the HSTH may be that individuals who have greater predisposed risk to react to non-social threat experience heightened responsivity to social threat during social interactions (i.e. heightened brain activation and self-reports of perceived social threat). In turn, both hypervigilance to non-social threat and heightened responsivity to social threat may promote maladaptive patterns of cognition and behavior in subsequent social interactions, which could differ between sexes

(Buzzell et al., 2017a; Clarkson et al., 2019a, 2019b; Filippi et al., 2019; Nelson et al., 2016).

The difference in hypervigilance to threat between sexes may be particularly powerful during adolescence, as peer relationships become more important, salient, and complex, at the same time that neural networks implicated in social processing undergo critical developmental changes (Blakemore, 2008; Nelson et al., 2016, 2005). Yet, it is unclear if hypervigilance to non-social threat is associated with greater threat responses in social situations, or across measurement techniques (i.e. EEG, fMRI, self-report). Tests of correspondence between measures of hypervigilance to non-social and social threat are essential for elucidating more complex relations whereby hypervigilance to non-social threat may promote sex-related differences in long-term psychosocial problems (Clarkson et al., 2019a, 2019b).

Although commonly implicated in error monitoring, the Flanker-elicited ERN has also emerged as an index of hypervigilance to non-social threat (Chiu and Deldin, 2007; Ganushchak and Schiller, 2008; Hajcak et al., 2005; Kujawa et al., 2016; Meyer and Gawlowska, 2017; Riesel et al., 2012; Weinberg et al., 2012) and predicts emergence of social anxiety symptoms in adolescence (Buzzell et al., 2017b; Filippi et al., 2019). The ERN is generated in the anterior cingulate cortex (ACC; Carter et al., 1998) and is measured using electroencephalography (EEG). The Flanker task requires participants to monitor for the direction of a center arrow flanked by other arrows. The ERN is measured by subtracting the average electrophysiological response to trials in which participants correctly select the direction of the center arrow from the average neural response to trials in which participants make an error. The ERN has good internal (Olvet and Hajcak, 2009; Larson et al., 2010) and test-retest reliability (Olvet and Hajcak, 2009; Weinberg and Hajcak, 2011). More negative ERNs are indicative of greater vigilance to non-social threat (Hajcak et al., 2005; Moser et al., 2013), index magnitude of unexpected threat (Frank et al., 2005), and moderate the link between early childhood avoidance and subsequent onset of social anxiety (Buzzell et al., 2017b; Filippi et al., 2019). Additionally, the ERN is potentiated by higher levels of threat (Chiu and Deldin, 2007; Ganushchak and Schiller, 2008; Meyer and Gawlowska, 2017; Riesel et al., 2012), and is attenuated when attention to non-social threat is reduced via intervention (Nelson et al., 2015, 2017).

Between ages 12 and 17, the ERN becomes dramatically more negative (Davies et al., 2004), suggesting that greater threat-vigilance emerges in adolescence. These age-related changes in the ERN coincide with the development and maturation of the prefrontal cortex (Downes et al., 2017) and sex differences in the onset of social anxiety symptoms (Beesdo et al., 2007; DeWit et al., 2005). Despite the ERN's relation to the development of social anxiety, the experimental paradigm commonly used to elicit the ERN, the Flanker Task (Eriksen and Eriksen, 1974), does not resemble real-world social threat, nor does it yield sex differences (but see (Larson et al., 2011). This is surprising given marked sex differences in the incidence rate of social anxiety in adolescence (DeWit et al., 2005). Thus, hypervigilance to non-social threat measured via the ERN alone cannot explain differences in social behavior and negative psychosocial outcomes between sexes. Moreover, its applicability to understanding sex differences in socially-threatening situations, such as bullying, are unknown. One possibility is that basic sensitivity to non-social threat, as indexed by the Flanker-elicited ERN, may contribute to sex-related differences in processing social threat. Thus, it is important to examine relations between threat hypervigilant ERNs and social threat measures to better understand differences in psychosocial outcomes by sex.

Responses to social threat differ between the sexes across different measurement techniques. Although sex differences in the ERN are rarely identified, females exhibit greater social threat-vigilant responses, as indexed by behavior and subjective report (Cyranowski et al., 2000; Han et al., 2008; Hankin and Abramson, 2001; Nolen-Hoeksema and Girgus, 1994; Rudolph and Conley, 2005; Stroud et al., 2002; Zahn-Waxler et al., 2008). Sex differences in functional brain activation to social

threat have also been found in regions associated with aspects of threat-related processing (McClure et al., 2004; Shirao et al., 2005; Veroude et al., 2014). These regions include frontotemporal cortical areas such as the precentral gyrus, which is involved in social threat processing (Anderson et al., 2013; Kret et al., 2011; Sinke et al., 2010), the inferior frontal gyrus which is involved in self-focused threat processing, and the medial temporal gyrus which is involved in reward learning (Beckes et al., 2013). Subcortical regions are also implicated in social threat processing. For example, the putamen, is involved with evaluation, learning, and memory of threatening situations (Greenberg et al., 2005; Lago et al., 2017; Morin and Michaud, 2007), the amygdala is involved in threat detection (Nitschke, 2009), and the anterior hippocampus is involved in threat generalization (Bannerman et al., 2004; Straube et al., 2009) and harm avoidance (Yamasue et al., 2008). Some studies demonstrate that females have greater neural engagement to social threat (threatening faces: (McClure et al., 2004); viewing words about relationship conflict: (Shirao et al., 2005) in frontal and striatal regions. Yet, others demonstrate that males have greater neural engagement to social threat (social appraisals: (Veroude et al., 2014) in parietal and temporal regions. However, no study has examined how non-social threat vigilance might relate to social threat using the convergence of multiple measurement techniques to disentangle sex differences.

The VS Paradigm is an fMRI-based paradigm (Clarkson et al., 2019a, 2019b; Jarcho et al., 2013, 2016, 2019; Smith et al., 2020) that models real-world exposure to social threat as participants anticipant and receive social feedback from purported peers with reputations for being nice, mean or unpredictable. In our prior fMRI work using this ecologically-valid social interaction task, we demonstrated that while anticipating potentially threatening feedback from unpredictable peers, youth with hypervigilance to social threat (i.e. social reticence) have heightened engagement in brain regions associated with threat processing. Specifically, greater engagement of the ACC, where the ERN is localized, was associated with early childhood social reticence (Jarcho et al., 2016), a trait associated with the development of social anxiety later in life (Degnan et al., 2015). Moreover, like the Flanker-elicited ERN, engagement in this region mediated the relation between early social reticence and the development of social anxiety (Clarkson et al., 2019a, 2019b). Given the spatial overlap of the ERN and ACC, and shared relations to emerging social anxiety, it is possible that non-social threat vigilance (ERN) potentiates neural systems associated with social threat processing, and that these mechanisms may be distinct across sexes. Understanding relations between the hypervigilant responses to non-social threat and neural responses to social threat may help explain sex differences and their potential contribution to the emergence of psychosocial symptoms.

Sex may also impact how non-social threat vigilance (ERN) and perceived levels of current threat (self-report) alter brain activation during threatening situations with an added social component. For example, males and females who are hypervigilant to non-social threat exhibit different brain activation depending on the level of perceived threat, relative to those who are not hypervigilant (Maresh et al., 2013a). However, other evidence suggests females may experience greater neural engagement in striatal regions with greater perceived social threat (Guyer et al., 2009b; Lago et al., 2017). Still other studies show that males may have greater neural engagement to non-social threat cues in temporoparietal cortical regions, which also may be engaged during social situations (Han et al., 2008). Thus, it remains unclear if non-social and social threat processing have overlapping or distinct neural processes across sexes and if these relations are modulated by levels of perceived threat. Examining sex differences and the relations between these measures is needed to reconcile these discrepancies.

In this study we asked: do neural measures of hypervigilance to non-social threat relate to hypervigilance to social threat, and does this relation differ by sex and levels of perceived social threat? To answer

this question, we tested sex differences in relations between a well-established electrophysiological measure of non-social threat (ERN), perceived levels of VS-elicited social threat (self-report), and brain activation during the VS Paradigm (fMRI). We predict that males and females will have distinct mechanisms by which non-social threat processing and perceived levels of VS-elicited social threat relate to the brain's response to social threat. Specifically, we predict that threat-vigilant ERNs (ie. non-social threat) coupled with greater perceived VS-elicited social threat will result in heightened neural engagement, which may be regionally-distinct across sexes, during socially threatening interactions. Our results will reconcile the discrepancy between the lack of sex differences in non-social threat processing and observed sex differences in responses to social threat and negative outcomes.

2. Methods

2.1. Participants

A community sample of adolescents (N = 96, M_{age}=12.54, SD_{age}=1.11) without contraindications for fMRI (e.g., metal in their body, head injury, psychotropic medications, etc.), or existing medical or psychological disorders completed the VS Paradigm while undergoing fMRI (Clarkson et al., 2019a, 2019b; Jarcho et al., 2016, 2013; Smith et al., 2020), and an EEG-based Flanker Task (Eriksen and Eriksen, 1974). A subset of participants was excluded for technical difficulties (N = 7), motion censoring rates of > 1 mm for 15% or more repetition times (TRs; N = 10), lack of deception in the VS Paradigm (N = 5), or having a sibling who also completed the study (N = 5). Of the 69 participants with usable fMRI data, 65 also had usable (<66% errors, >6 trials; (Olvet and Hajcak, 2009) EEG-based Flanker data. The ERN for the remaining four subjects was imputed using predictive mean matching multiple imputations (Buuren and Groothuis-Oudshoorn, 2011), which maintains consistency on transformed data, like the ERN. Thus, 69 participants were included in fMRI analyses (see Table 1 for descriptive statistics).

2.2. Procedure

Participants attended two visits at Stony Brook University. Both child assent and parental consent were obtained for all participants on procedures approved by the Stony Brook University Internal Review Board.

2.2.1. Flanker task

During their first visit, participants completed a computerized version (Presentation software; Neurobehavioral Systems, Inc., Albany, CA) of the Flanker task (Eriksen and Eriksen, 1974) while undergoing EEG. While seated at a viewing distance of approximately 21.5 in. (54.5 cm), participants made responses using the right- and left-click of a mouse that indicated the direction of a center target arrow during randomly presented congruent, (50%; "<<<<<" or ">>>>>"), and incongruent (50%; "<<><<" or "><<>>") trials. All stimuli were presented for 200 ms followed by an inter-trial interval that varied randomly from 2300 to 2800 ms.

To be eligible to complete the experiment, participants were required to reach 80% accuracy on up to three blocks of 10 trials, to ensure understanding of the task and optimize the amount of errors. The experimental task consisted of 11 blocks of 30 trials (330 trials total). For optimal accuracy throughout the experiment, participants received feedback based on their performance at the end of each block. Those who made too many errors (75% correct or lower) were prompted to "Please try to be more accurate". Participants that made too few errors, which would prohibit analysis, (>90% correct) were prompted to "Please try to respond faster". If their performance was between 75% and 90% correct, the message "You're doing a great job" was displayed.

2.2.2. Virtual school paradigm

After completing the Flanker task, participants were told that at their next visit, they would be the "new kid" at a virtual school and would be interacting with sex-matched "other students" who had all previously participated in the study. As part of being the new kid, they were asked to create a computer-based avatar and profile describing their interests. Participants were told these items would be shown to the other students before the next visit so that they could chat with them about the content of their profile. In reality, there were no other students; all communications were computer-generated. Participants also completed questionnaires and a mock-scan simulation of a "recorded" session of the VS in order to practice making responses while in a scanner-like environment.

During their second visit, which occurred within one week of the first visit, participants were introduced to purported peers via yelp-like reviews left by previous participants. To enhance deception and the salience of the social interactions, they were also told that they would later get to Snapchat with each of the peers they interacted with in the VS. Prior to entering the VS, participants rated how nice or mean they thought each peer would be on a sliding scale from 1 to 10. Lower values corresponded to greater meanness ratings, higher values corresponded to greater niceness ratings, and a value of five signified that they were "unsure" how nice or mean a peer would be. These ratings were used to confirm that participants learned each peer's reputation.

Participants then underwent fMRI scanning while completing three nine-minute runs of the VS paradigm. The VS paradigm measures brain function as participants anticipate and receive social evaluation from two purported peers with reputations for being nice (100% positive evaluations), mean (100% negative evaluations), or unpredictable (50% positive 50% negative evaluations) (see Fig. S1 in the Supplemental Information; (Clarkson et al., 2019a, 2019b; Jarcho et al., 2016, 2019, 2013, for details). While in the scanner, participants engaged in 24 interactions with each peer type. After each interaction, participants made a person-based response ("You're Nice", "You're Mean"), situation-based response ("That's Nice", "That's Mean"), "no response" (active-avoidant response), or a sarcastic response ("Thanks… NOT!!!"). Deception was assessed after completion of the task during an interview in which participants were asked a series of increasingly specific questions about their experiences in the VS. This interview culminated in the examiner explicitly asking participants if they "interacted with other peers" in the VS (97% responded "yes"). Responses and reactions to the interview questions informed the experimenter's rating of the participant's deception on a scale of 0 (not at all) to 10 (very much). Only those with a deception rating > 8 were included in the sample (M=9.189, SD= 1.26).

In order to ensure that neural engagement elicited during the VS is a valid measure of social threat and is generalizable to real-world

Table 1
Descriptive statistics.

	N	Males M (SD)	Females M (SD)	Sex Differences p; d	Imputed Differences p
Sex (N)	69	34	35	–	0.47
Age (Years)	69	12.47 (1.11)	12.60 (1.12)	0.63; − 0.07	0.39
VS-elicited social threat	69	3.76 (2.69)	3.86 (2.44)	0.88; − 0.04	0.52
Real-world prior exposure to social threat	67	4.15 (6.02)	3.82 (4.67)	0.80; 0.06	0.07
ERN	69	-23.63 (29.67)	-30.95 (25.12)	0.26; 0.27	–

experiences of socially threatening situations, we compared VS-elicited social threat to real-world exposure of social threat. To measure real-world exposure to social threat, participants completed a modified child-based version of the Peer Victimization Questionnaire (PVQ). Questions assessing the experience of social threat were derived from Bradshaw et al. (2015), which synthesized previous versions of measures assessing bullying (Bradshaw et al., 2009; Nansel et al., 2001; Sawyer et al., 2008; Solberg and Olweus, 2003). However, to increase response range, each item was answered using a 5-point Likert scale ranging from 0, "it hasn't happened to me in the last couple months" to 4, "several times a week" (Olweus, 1996) rather than "yes" or "no" (Bradshaw et al., 2015). Self-reported real-world exposure of social threat was quantified as the sum of 11 items on the victimization sub-scale (Cronbach's alpha = 0.81).

2.3. VS-elicited social threat

After the study, but prior to debriefing, participants were interviewed to characterize their experience of feeling threatened in the VS. Specifically, they were asked "how bullied did you feel while in the Virtual School" on a scale of 0 (not at all) to 10 (very much). Ratings were used to measure social threat experienced during the paradigm.

2.4. Data acquisition

2.4.1. EEG data acquisition

EEG data were recorded using an elastic cap with 34 sintered Ag/AgCl electrode sites placed according to the 10/20 system. Electrooculogram recorded eye-movements using four additional facial electrodes: three electrodes were placed around the right eye (one above, one below, and one on the outer canthus) and one electrode was placed on the outer canthus of the left eye. Data were recorded using the Active Two BioSemi system (BioSemi, Amsterdam, Netherlands). EEG was digitized with a sampling rate of 1024 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz. A common mode sense electrode producing a monopolar (non-differential) channel was the acquisition reference.

2.4.2. fMRI data acquisition

Data were acquired on a Siemens MAGNETOM Prisma 3-Tesla whole-body MRI scanner. Each functional run included 251 functional image volumes with 37 contiguous axial slices (in-plane resolution=3.0 × 3.0 mm) obtained with a T2 * -weighted echo-planar sequence (repetition time/echo time ([TR/TE]= 2000/25 ms, flip= 45 ; field of view (FOV)= 240 mm, matrix= 96 × 96). A high-resolution structural scan was acquired (axial plane) with a T1-weighted magnetization-prepared spoiled gradient-recalled echo sequence (echo time/inversion time (TE/TI)= 2.23/1000 ms, flip= 8 ; FOV= 224 mm, matrix= 256 × 256, in-plane resolution,.7 × 0.7 mm) for anatomical localization and co-registration of functional data.

2.5. Data analyses

2.5.1. VS Paradigm Validity & Generalizability: is VS-elicited social threat associated with more exposure to real-world social threat?

In order to ensure that neural engagement elicited during the VS is a valid measure of social threat and could be generalizable to real-world socially threatening situations, we compared VS-elicited social threat to self-reported real-world experiences of social threat using Pearson correlations.

2.5.2. Non-social Flanker task: EEG data analysis

BrainVision Recorder and Analyzer 2 software was used for recording, offline data processing, and analysis (Brain Products, Gilching, Germany). All data were offline bandpass filtered from 0.1 to 30 Hz and were re-referenced to the average of the mastoid sites. Eye blink and ocular corrections were conducted using a standard regression-based algorithm (Gratton et al., 1983). Channels with artifacts (e.g., eye- and body-movements, signal noise, drift, etc.) were identified using the following thresholds: a voltage step of more than 50.0 μV between sample points, a voltage difference of 200.0 μV within a 400 ms sliding window, and a minimum voltage difference of 0.50 μV within a 100 ms interval. Data from channels with artifacts were interpolated using equally balanced information from surrounding channels. The recorded EEG activity was segmented relative to both error and correct responses during the Flanker Task, beginning 500 ms before a response and continuing 1000 ms following a response (i.e., 1500 ms epochs with time zero at the subject's response). Data were baseline-corrected using mean activity from a 200 ms window between − 500 and − 300 ms prior to participant's response. Participants were included if they had > 6 artifact-free trials for both error and correct trials, the minimum needed for a stable ERN (Olvet and Hajcak, 2009). On average, our sample had 36 ($SD = 20$) artifact-free error trials and 273 ($SD = 42$) artifact-free correct trials.

To better isolate the ERN components, we applied a current source density (CSD) transform (order of splines = 4, maximal degree of Legendre polynomial = 10; λ smoothing parameter = 10−5), which improves spatial localization of sources of the ERP by computing an estimate of the surface Laplacian based on the EEG voltage across the scalp electrodes. Laplacian data are reasonably free from signal originating from remote sources and attenuate the distortions of volume conduction (Vidal et al., 2003, 2000). As a result of this transformation, EEG voltage is described in units of uV/m^2 rather than uV. The CSD transformed ERN waveform and scalp distribution can be found in Supplemental Fig. S2. For completeness, the non-transformed ERN waveform and scalp distribution are also provided in Supplemental Fig. S3. Following the CSD transform, a negative deflection was observable after both error and correct trials (i.e., the CRN). Deflections for error and correct trials were then separately averaged. The error response was quantified on error trials as the mean activity between − 25 and 75 ms after the response at scalp site FCz, where error-related brain activity was maximal (Meyer et al., 2014). The ERN was then calculated by taking the error response minus CRN in order to disentangle the neural response to errors from generic response monitoring processes (Simons, 2010). More negative ERN values are indicative of greater threat-vigilant responses.

2.5.3. fMRI pre-processing

Standard preprocessing steps were implemented with afni_proc.py; these steps included slice timing, coregistration, smoothing to 6-mm full-width half maximum (FWHM), spatial normalizing to standard Talairach space, and resampling, which resulted in 2.5 mm^3 voxels AFNI software (Cox, 1996). Seven regressors of interest were modeled: three for anticipation of social evaluation (nice, mean, and unpredictable), and four for receipt of evaluation (positive evaluation from nice peers, positive evaluation from unpredictable peers, negative evaluation from mean peers, negative evaluation from unpredictable peers). An additional nine regressors of no-interest were also modeled: participants response and classroom selection events, six motion parameters, and linear drift. .

Individual-level regression analyses were carried out with AFNI's 3dDeconvolve function, in which regressors were time-locked to the onset of each event and convolved with a duration-modulated boxcar regressor. Temporally adjacent TRs with a euclidean-norm motion derivative > 1.0 mm were omitted from the model via censoring. This resulted in a β coefficient and t statistic for each voxel and regressor. Whole-brain percent signal-change maps were generated by dividing signal intensity at each voxel by the mean voxel intensity, and multiplying by 100.

2.5.4. Group level analyses

Analyses were conducted in AFNI's 3dMVM software (Chen et al.,

2014). Decomposition analyses were performed and plotted in RStudio (RStudio Team, 2016) using the "nlme" package for linear mixed effect models for interpretation purposes. Continuous variables (ERN, VS-based experience of social threat) were mean-split to facilitate interpretation of decompositions.

To avoid Type I errors in regions where signal dropout occurred, output maps were masked to include voxels within the gray cortical matter and where at least 90% of the participants had signal. A significance threshold was determined based on AFNI's 3dClustSim program. The spatial autocorrelation function (2-sided thresholding) was utilized to obtain accurate estimates of spatial smoothing across the brain (Cox et al., 2017). To achieve a voxel-wise probability threshold of $p < .005$ and family-wise error rate of $\alpha = 0.05$, cluster contiguity was set to 108 voxels. Significant clusters were extracted and plotted for descriptive purposes. One activation cluster spanned across numerous anatomically distinct areas, therefore a mask was created of the activation area and then separate activation clusters were extracted with the voxel-wise probability threshold of $p < .001$ and family-wise error rate of $\alpha = 0.05$, cluster contiguity was set to 10 voxels.

Exploratory region of interest (ROI) analyses were conducted to investigate potential activation in subcortical regions that would not survive strict whole brain cluster corrections due to their size. We applied an anatomical mask of the bilateral striatum, amygdala, and hippocampus to the group-level analyses to isolate activation clusters with the voxel-wise probability threshold of $p < .005$ and family-wise error rate of $\alpha = 0.05$. Cluster contiguity was set to 16 (striatum), 4 (amygdala), and 11 (hippocampus) voxels. For clusters that survived correction, the same decomposition procedures were implemented as described above.

2.5.5. Do neural measures of hypervigilance to non-social threat relate to hypervigilance to social threat, and does this differ by sex and levels of perceived social threat?

Primary analyses examined relations between non-social (i.e. EEG-based ERN) and social threat responses (i.e. VS-elicited social threat) and sex during both the anticipation and receipt of social feedback. Linear mixed effects models examined average activation during the anticipation and receipt of social feedback, separately, with the ERN, sex, and VS-elicited social threat as between-participants fixed-effects factors. Peer reputation (anticipation: nice, mean, unpredictable; feedback: nice, mean, unpredictable nice, unpredictable mean) was treated as a within-participants random-effects factor. Post-hoc power estimations (see Supplementary Materials) suggest the sample size was likely sufficient to detect small to medium size effects (Kumle et al., 2021). However, given the limitations in power analyses calculations for mixed-effects models, results should be replicated. Contrasts between reputations were compared using simultaneous tests for the general linear hypotheses, specifically, multiple comparisons of means -Tukey contrasts. Supplementary analyses were performed to test for task-related effects of reputation on brain function during anticipation and feedback (see Supplementary materials for methods and results).

In order to compare goodness of fit of each linear mixed model versus the null model, we used the log-likelihood ratio test. To do this, log-likelihood ratios were calculated comparing either the log likelihood of the task effects model or the primary analyses model to that of the null model. Large numbers indicated greater parameterized model fit, and rejection of the null model.

3. Results

3.1. Participants

There were no differences in age, VS-elicited social threat, real-world prior exposure to social threat, or ERN responses by sex ($p's > 0.26$, d's < 0.27; Table 1), between imputed vs. non-imputed participants, or between participants included vs. excluded on the basis of usable fMRI data or levels of deception ($p's > 0.06$).

3.2. VS Paradigm Validity & Generalizability: is VS-elicited social threat associated with more exposure to real-world social threat?

VS-based exposure to social threat and real-world exposure to social threat correlated ($r = 0.276$, $p = .023$; Fig. 1; Table 2), but were not related to the ERN ($r's < .10$, $p's > .41$; Table 2). In terms of real-world exposure to social threat, 30% of males and 28% of females endorsed experiences of some form of victimization at least "2–3 times a month" which is considered worthy of clinical intervention (Olweus, 1996). This is relatively high compared to a similar aged sample (11.1% males vs. 9.1% females: Olweus, 1996; 8–9% males vs. 8–16% females: Bradshaw et al., 2015). This suggests that the VS is a reasonable proxy of real-world exposure to social threat in the form of peer victimization.
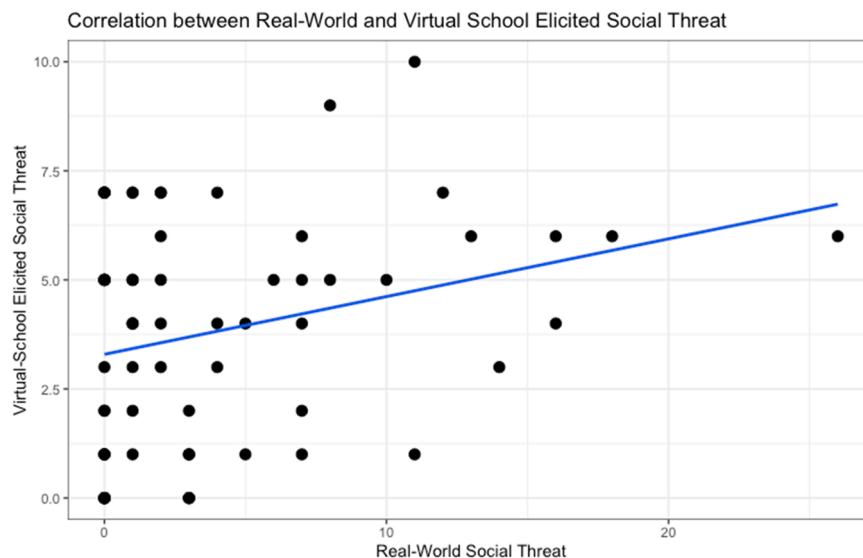

Fig. 1. Validity and generalizability check examining the correlation between real-world and VS-elicited social threat in the full sample. Higher values of both threat measures indicate greater incidence and perceived threat.

Table 2
Correlations between age, VS-elicited social threat, real-world prior exposure to social threat, and the ERN.

		1	2	3	4
Age (Years)	1				
VS-elicited social threat	2	0.172			
Real-world prior exposure to social threat	3	0.204	.276*		
ERN	4	0.015	-0.020	0.103	

3.3. Do neural measures of hypervigilance to non-social threat relate to hypervigilance to social threat, and does this differ by sex and levels of perceived social threat?

3.3.1. Anticipation

Whole-brain analyses revealed engagement of left precentral gyrus,

left medial temporal gyrus, and inferior frontal gyrus varied as a function of ERN, sex, VS-elicited social threat, and peer reputation (F's > 7.835, p's < .005; Table 3 & Fig. 2). Specifically, among males who had more threat-vigilant ERNs, the relation between VS-elicited social threat and brain activation in the left precentral gyrus significantly differed by reputation (mean-vs-nice: z = −0.048 p = 0.998 d=−0.006; unpredictable-vs-mean: z = −2.773 p = .015, d=−0.334; unpredictable-vs-nice: z = −2.691, p = .020, d=−0.324; Fig. 3A). Greater perceived social threat in the VS was associated with greater activation when anticipating feedback from unpredictable (r = .638, p = 0.007, but not nice (r = .161, p = 0.552 or mean (r = .111, p = 0.681 peers. This pattern failed to emerge among females. This same pattern emerged in the left perigenual ACC, inferior frontal gyrus, inferior parietal lobe, medial temporal gyrus, right insula, and medial frontal gyrus but did not reach statistical significance in decomposition

Table 3
Significant regions within the whole brain primary analyses: ERN by Sex by VS-based Exposure to Social Threat by Reputation during the anticipation period. *Indicates distinct anatomical sub-regions of the left medial temporal gyrus cluster identified using a threshold of Ke= 10 and p = .001. **Indicates exploratory analyses with clusters identified using anatomical masks of sub-cortical regions and a cluster threshold of Ke=amygdala: 4, anterior hippocampus: 11.5, and p = .005.

| Image Key	Brain Regions for Primary Analyses	MNI Coordinates			Cluster size (voxels)	F(2, 122)	Log Likelihood Ratio
		x	y	z			
1	Medial Temporal Gyrus	-54	-14	-20	667	13.467	274.323
	*Medial Temporal Gyrus	-54	-14	-120	86	16.933	263.215
	*Anterior Insula	-29	-6	11	82	11.352	272.755
	*Posterior Insula	-34	-16	1	40	8.949	278.337
	*Putamen	-21	-16	1	17	12.416	270.309
2	Precentral Gyrus	-29	-24	57	317	12.403	274.811
3	Perigenual Anterior Cingulate Cortex	-9	-40	14	315	9.355	256.293
4	Inferior Frontal Gyrus	-44	35	6	171	10.226	266.858
5	Medial Temporal Gyrus 2	-59	-52	-8	157	9.194	256.911
6	Inferior Parietal Lobe	-49	-33	24	139	10.861	276.632
7	Insula	34	-22	3	151	8.46	284.354
8	Posterior Cingulate	-11	-34	41	120	8.38	278.32
9	Medial Frontal Gyrus	6	-14	60	110	7.835	268.421
	**Amygdala	-24	-8	-20	15		
	**Anterior Hippocampus	-21	-11	-20	24		
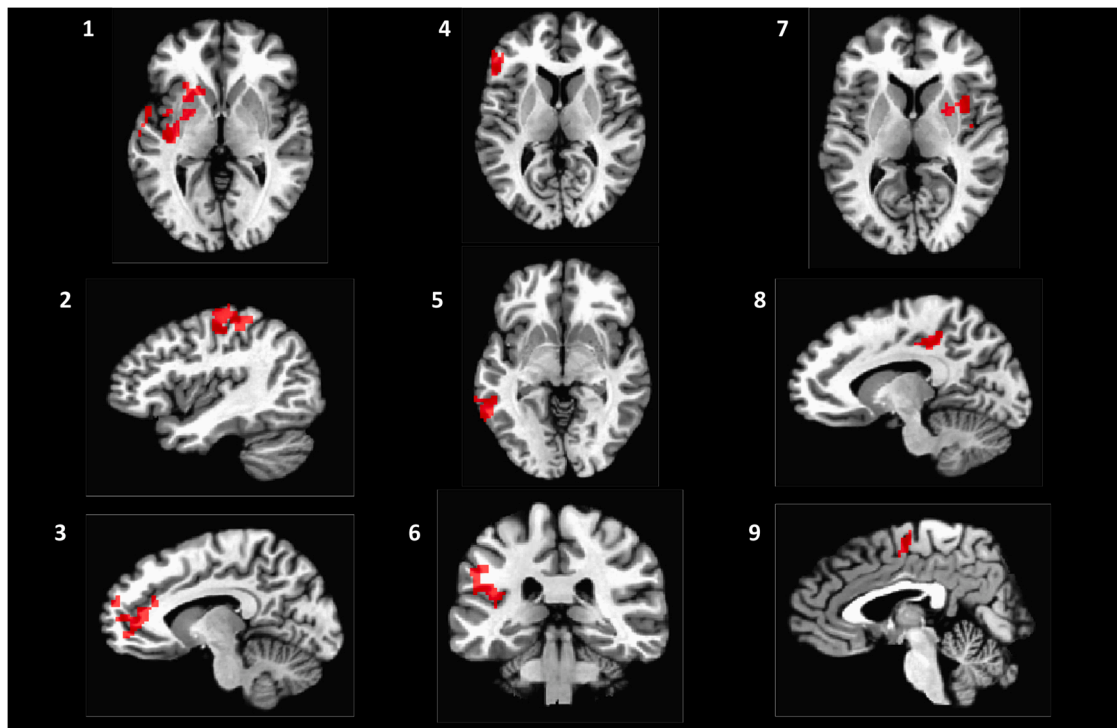
Fig. 2. Image key for whole brain primary analyses: ERN by sex by VS-elicited exposure to social threat by reputation during the anticipation period. The images map onto the extracted clusters from Table 3. Left equals left.
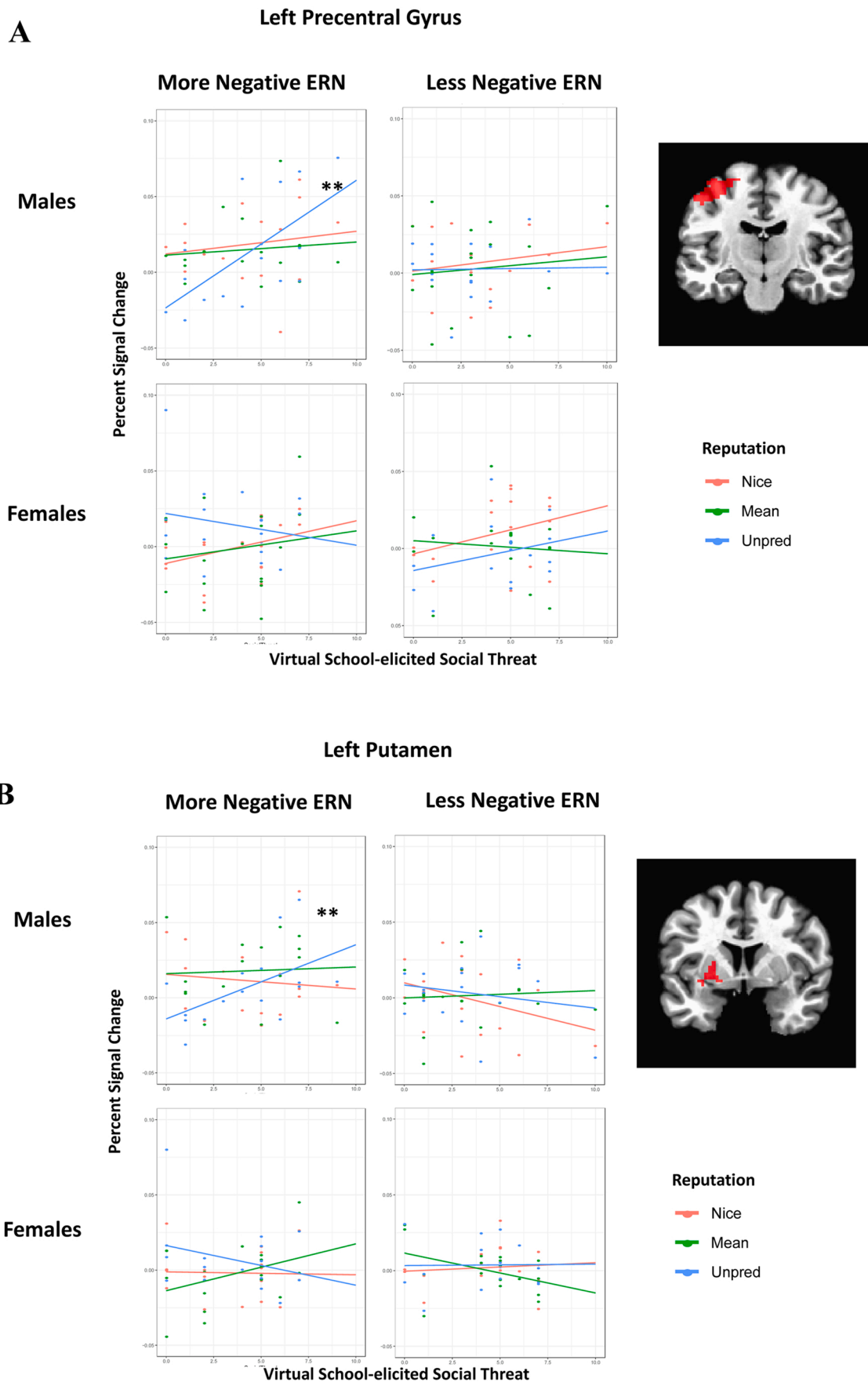
Fig. 3. Differences in average activation to unpredictable-vs-mean or nice peers in the A) left precentral gyrus (whole-brain cluster), and the B) left putamen (peak cluster within whole-brain left medial temporal gyrus cluster) for males who have more (left panel) -vs- less (right panel) negative ERNs.

Table 4

Significant low-order interactions for the whole brain primary analyses: ERN by Sex by VS-Elicited social threat by reputation during the anticipation period.

Significant Lower-Order Interactions	Brain Region	F	p
Sex x VS-Elicited Social Threat x Reputation	*Putamen	3.467	0.034
ERN x Sex	*Putamen:	10.481	0.002
Sex	*Putamen:	4.844	0.032
ERN x VS-Elicited Social Threat x Reputation	**Amygdala	3.516	0.033
ERN x VS-Elicited Social Threat	**Anterior Hippocampus	4.533	0.037

*Indicates distinct anatomical sub-regions of the left medial temporal gyrus cluster identified using a threshold of Ke=10 and p=.001. **Indicates clusters identified in exploratory ROI analyses.

analyses.

Within the large left medial temporal gyrus activation cluster, four anatomically distinct activation clusters emerged including the left medial temporal gyrus, anterior insula, posterior insula and putamen (Table 3; $p = .001$, $ke=10$). Putamen engagement varied as a function of ERN, sex, threat, and reputation ($F=12.416$, $p < .001$; Fig. 3B). Specifically, among males who had more threat-vigilant ERNs, the relation between VS-elicited social threat and brain activation significantly differed by reputation (mean-vs-nice: $z = .037$, $p = 0.999$ d= 0.004; unpredictable-vs-mean: $z = -2.834$, $p = .012$, d=0.341; unpredictable-vs-nice: $z = -3.231$, $p = .003$, d=−0.389; Fig. 1). Greater perceived VS-elicited social threat was associated with greater activation when anticipating feedback from unpredictable ($r = .537$, $p = 0.032$, but not nice ($r = .106$, $p = 0.697$ or mean ($r = .052$, $p = 0.850$ peers. This pattern was similar in the rest of the sub-regions including anterior and posterior insula, and medial temporal gyrus, but did not reach statistical significance in decomposition analyses. This pattern failed to emerge among females. Significant lower-order factorial interactions between each fixed and random effect as well as main effects are described in Table 4.

3.3.2. Exploratory subcortical analyses during anticipation

Exploratory analyses revealed engagement of left- striatum, amygdala and anterior hippocampus varied as a function of ERN, sex, VS-elicited social threat, and peer reputation (F's > 6.538, $p's < .002$; Table 3). The striatum cluster was the same as the one identified in the whole-brain analyses. Significant lower-order factorial interactions between each fixed and random effect as well as main effects are described in Table 4. Specifically, among females who had *greater* threat-vigilant ERNs, the relation between VS-elicited social threat and brain activation in the left amygdala (Fig. 4A) and anterior hippocampus (Fig. 4B) significantly differed by reputation, though the contrast decomposition analyses were not significant. Greater perceived social threat in the VS Paradigm was associated with *greater* activation when anticipating feedback from mean (amygdala: $r = 0.489$, $p = .0395$ and anterior hippocampus: $r = 0.5865$, $p = .0105$), but not nice (amygdala: $r = 0.373$, $p = .127$ and anterior hippocampus: $r = 0.456$, $p = .0574$) or unpredictable (amygdala: $r = −0.166$, $p = .509$ and anterior hippocampus: $r = 0.001$, $p = .995$) peers.

3.3.3. Feedback

Whole-brain and exploratory ROI analyses revealed no significant interaction between ERN, sex, reputation, and VS-elicited social threat, and brain function while participants received social feedback.

4. Discussion

This is the first study to demonstrate sex-specific relations linking neural measures of non-social and social threat processing to self-reported experiences of social threat. VS-elicited social threat

corresponded with real-world prior exposure to social threat in the form of peer victimization, suggesting results are generalizable to real-world experiences. In males, adolescents with hypervigilant neural responses to non-social threat that reported greater VS-elicited social threat exhibited greater brain activation anticipating unpredictable social interactions in temporoparietal and striatal regions. In females, adolescents with hypervigilant neural responses to non-social threat that reported greater VS-elicited social threat exhibited greater brain activation anticipating mean social interactions in the amygdala and anterior hippocampus. Our results help reconcile how hypervigilance to non-social threat relates to sex differences in neural response to social threat. This may help explain differences in social rejection behavior and psychosocial outcomes between sexes during adolescence. However, given our limited sample size, results should be replicated to confirm observed sex-specific relations in non-social and social threat.

Ratings of perceived social threat during the VS Paradigm were associated with reports of peer victimization in real life. This finding underscores the ecological validity of the VS Paradigm in simulating real-world peer victimization, and thus, the generalizability of neural activation during realistic socially-threatening interactions. Moreover, consistent with previous studies of social threat processing (Guyer et al., 2009a; Han et al., 2008; Maresh et al., 2013b), perceived levels of VS-elicited social threat impacted neural activation. Specifically, we demonstrated that relations between non-social and social threat processing emerged when perceived social threat was high. This suggests shared neural systems are not simply a result of cognitive monitoring or detection, but are modulated by the salience of threat cues.

We found that while anticipating social feedback from unpredictable peers, males who had threat-vigilant ERNs, and reported feeling more socially threatened during the VS, had greater brain activation in temporoparietal and striatal regions. This finding is consistent with previous literature showing that males exhibit more threat-vigilant ERNs in more unpredictable non-social situations (Frank et al., 2005). Our results are also consistent with previous findings showing greater neural engagement in the ACC to unpredictable social threat (in the form of threatening pictures of faces) in males, but not females (McClure et al., 2004). Our work extends these findings by demonstrating that more threat-vigilant ERNs also correspond to greater brain activation in a broad threat processing network including the insula, inferior frontal gyrus, and striatum during unpredictable social situations when experienced social threat is high. The ACC has not only been linked to the ERN specifically (Carter et al., 1998), but is involved in monitoring and detecting threat responses (Bishop, 2008). Moreover, both the insula and inferior frontal gyrus (IFG; Perino et al., 2020) are part of the ventral attention network, which is involved in involuntary attention to threatening and salient cues (Miller, 2015). This is consistent with our previous findings demonstrating relations between social anxiety symptoms, which often precipitate feelings of social threat during social situations, and greater activation in the ACC and insula while anticipating unpredictable social feedback (Clarkson et al., 2019a, 2019b; Jarcho et al., 2016).

We found that males with more threat-vigilant ERNs who experienced more VS-elicited threat had greater activation in the left precentral gyrus and putamen while anticipating unpredictable social threats. The precentral gyrus has been linked to the detection, rather than evaluation, of social threat and is more reactive in males than females (Han et al., 2008). The putamen is involved in the evaluation of contexts, threats, and rewards while anticipating outcomes (Haruno and Kawato, 2006). Moreover, the putamen has also been implicated in fear conditioning in uncertain situations, wherein greater activity is associated with hypervigilant reactivity to threat (Lago et al., 2017; White, 2009).

Taken together, our results indicate enhanced activation in regions associated with detection and involuntary attention in males who are experiencing unpredictable social threat, and have a proclivity towards hypervigilance to non-social threat. This is further illustrated by the lack
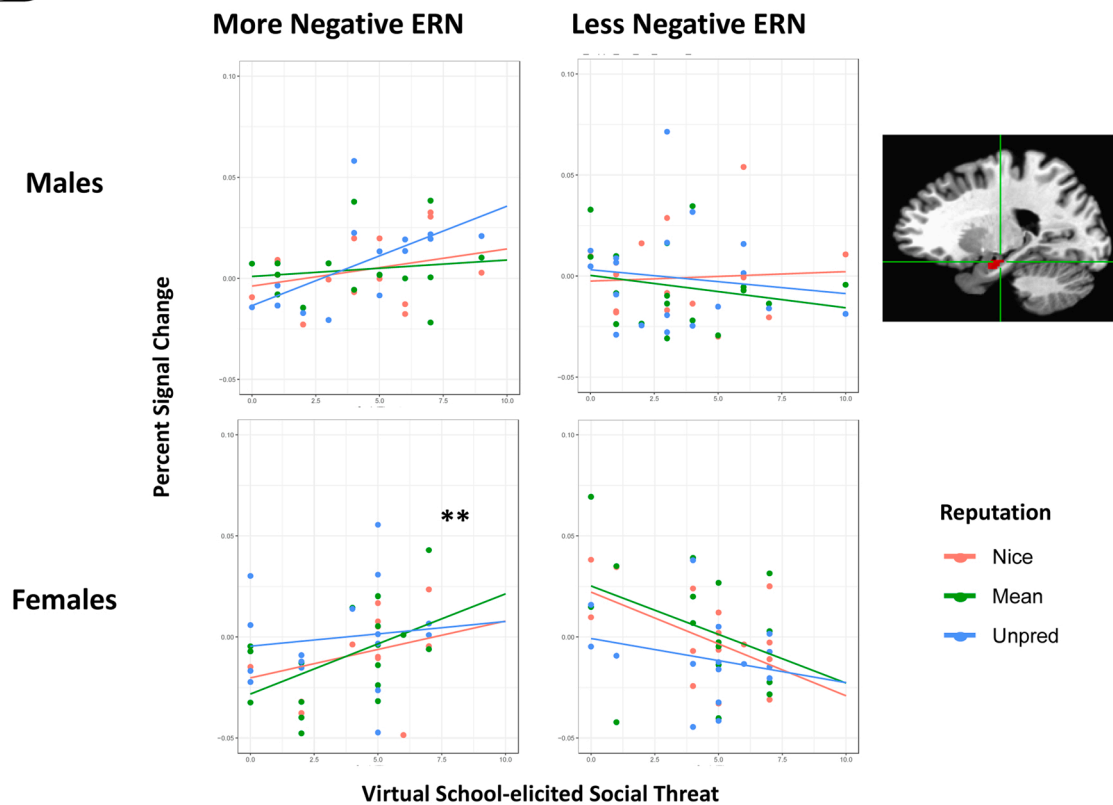
Left Amygdala

A
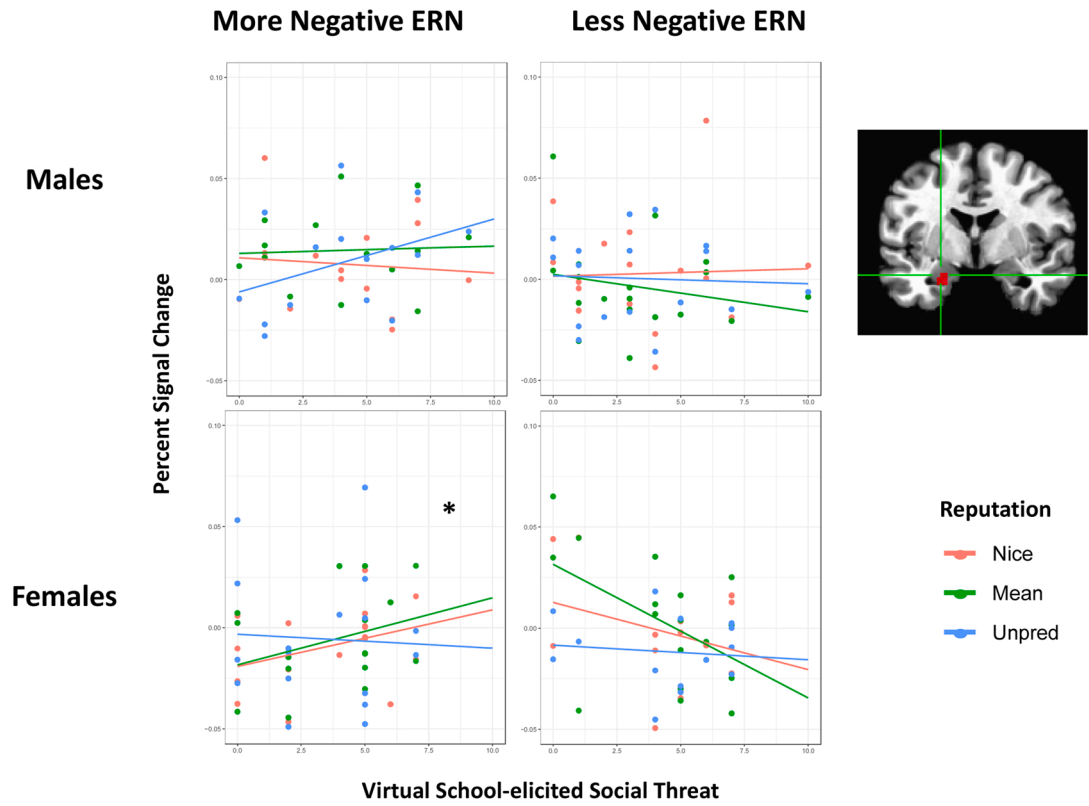
Fig. 4. Exploratory Analyses: Differences in average activation to unpredictable-vs-mean or nice peers in the A) left amygdala, and the B) left anterior hippocampus for males and females who have more (left panel) -vs- less (right panel) negative ERNs.

of these relations while males anticipated social feedback from mean peers, who would typically be characterized as socially threatening. This highlights the importance of uncertainty in social threat processing in males. Therefore, neural engagement of non-social threat processing is likely related to the detection and monitoring of social threat for males, and is heightened when anticipating more unpredictable social interactions.

Exploratory analyses also revealed that while anticipating social feedback from mean peers, females who had more threat-vigilant ERNs and reported feeling more socially threatened during the VS had greater activation in the left amygdala and anterior hippocampus. This finding is consistent with previous literature showing greater amygdala activation while anticipating non-social threat cues (Bannerman et al., 2004; Nitschke, 2009; Tye et al., 2011). Our results extend this work indicating one process by which the amygdala may detect social threats in females. This work aligns with some studies that shown elevated levels of oxytocin in females only are related to greater activation in the amygdala while viewing social and non-social threats (Lischke et al., 2012). Our work suggests that only females who have heightened non-social threat vigilance and report feeling socially threatened have increased amygdala responses to predictable social threats. This same pattern was observed in the anterior hippocampus in hypervigilant females. The anterior hippocampus involved in threat generalization, harm avoidance, and the development of anxiety symptoms (Parfitt et al., 2017; Yamasue et al., 2008). Previous work has shown that dysregulation in brain dynamics between the ACC and anterior hippocampus during non-social threat can lead to anxious behavior (Straube et al., 2009). Our work builds on this by relating the ERN, which is generated from non-social threat in the ACC, to heightened activation in the anterior hippocampus in females who are hypervigilant while anticipating socially-threatening situations. This may help explain the increased prevalence of social anxiety in females, despite similar base rates of hypervigilant non-social threat responses across the sexes. Over time, such a pattern of engagement may lead to the development of anxious behaviors through overgeneralizing social threats. As these results were exploratory in nature, future studies should replicate this relation in females to confirm our results.

By linking non-social and social threat processing, our results may help reconcile differences in behavioral reactions to social threat between the sexes. For example, it is known that males are more likely to engage in physical aggression in response to social threat (Carbone-Lopez et al., 2010). According to our results, one plausible explanation for this could be that males are more vigilant to detecting social threat when anticipating unpredictable social feedback, rather than after evaluating social threat once it's received. Thus, they are more likely to react prior to the receipt of social threat, or are more likely to detect and respond quickly to social threat. In contrast, females are more reactive to anticipating predictably mean social feedback, and may either over-generalize this feedback to promote anxiety symptoms, or effectively learn to avoid socially threatening situations. Indeed, previous studies suggest females are more likely to engage in evaluation of threat (Shirao et al., 2005), over-generalize during threat detection (Day et al., 2016), and be more reactive after receiving social feedback (Rudolph and Conley, 2005; Stroud et al., 2002).

Similar neural responses were engaged while anticipating peer feedback across reputations, as described in the supplement. Only when examining individual difference factors (sex, perceived social threat, and ERN) did we find differences in neural responses between reputations. This suggests that brain responses during anticipation of social interactions vary across individual difference factors and may be important for understanding observed sex differences in reactions to social threat.

In sum, our results help elucidate one way that non-social threat processes are linked to unpredictable social threat in males and predictable social threat in females. This may shed light on real-world experiences of social threat and observed sex differences in social behavior and negative psychosocial outcomes. Males who have hypervigilant responses to non-social threat engage in similar threat detection processing while anticipating unpredictable social situations when they are feeling threatened as they do when process non-social threat. This may lead to differential behavioral responses to unpredictable social situations and could help to explain increased proactive/impulsive aggressive response in males compared to females (Carbone-Lopez et al., 2010; Connor et al., 2003). Females who have hypervigilant responses to non-social threat engage in similar threat detection processing while anticipating predictably negative social situations when they are feeling threatened, in regions important for threat generalization, as they do when process non-social threat. This may explain the over-generalization of threat responses observed in females (Day et al., 2016).

4.1. Limitations and future directions

Though our results shed light on plausible neural systems by which social threat processing may influence reactions to social threat differently in males and females, we did not directly measure behavioral aggression (relational or physical), following social threat. Thus, future studies examining reactions to social threat in males and females should be conducted to examine relations between neural engagement of threat processing and behavior. We also did not find any shared relations between non-social threat processing and the feedback stage of the VS Paradigm. This could indicate overlap between non-social and social neural threat processes is primarily anticipatory. This is further supported by our task effects indicating an effect of reputation in the feedback portion of the task suggesting the manipulation was effective in eliciting differential neural responses to social feedback (see Supplemental Material results). Additionally, we were not able to measure trial-by-trial perceptions of social threat. Thus, it is unclear if greater perceived levels of social threat are isolated to the anticipation of unpredictable peer evaluation in males and mean peer evaluation in females, or if perceived threat levels are maintained through the task. Moreover, we found that perceived levels of social threat during the VS related to real-world reports of peer victimization. However, we cannot distinguish if hypervigilant threat processing in males and females observed in our study are a result of previous experiences of peer victimization or if these relations predispose males and females to experience more victimization as a result of their neural reactivity to various social threats. Thus, longitudinal studies examining shared mechanisms in relation to the occurrence of peer victimization are needed to tease apart the development of threat processing.

Additionally, threat processing is dynamic and informs predictions about subsequent interactions. Our study examined overall differences in brain activation across the task, however, it is important to understand how threat vigilance ultimately informs future vigilance, predictions, and reactions to the same peer in subsequent social interactions. Moreover, due to constraints of the study design, the non-social threat measure was always obtained first, within one-week of the social threat measure. Thus, responses to the flanker non-social threat task could have primed participants in the social threat task. However, since this protocol was consistent across subjects it is unlikely that this contributed to observed differences between sexes. Finally, although post-hoc power estimations based on previous studies suggests that the current sample size was sufficient to detect small to medium effects, future studies with a larger sample size are warranted given the

complexity of relations.

Despite these limitations, our results provide clear evidence that non-social and social threat processing engage similar neural systems, but these systems are distinct across sexes. Such results help elucidate sex-discrepant negative outcomes and behavioral responses to social situations and may provide novel sex-specific targets for the prevention and intervention of peer victimization and later emergence of social anxiety symptoms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data statement

De-identified data available upon request to the senior author, Dr. Johanna M. Jarcho

Acknowledgments

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2021.101038.

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