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ARTICLE



Selective neural sensitivity to familial threat in adolescents with weak family bonds

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ABSTRACT

Familial stressors, such as weak familial connectedness, are associated with the development of maladaptive threat processing, yet little is known regarding how weak familial bonds impinge on biological mechanisms of threat processing. The present study leveraged multivoxel pattern analysis of fMRI data to compare the neural encoding of familial and nonfamilial threatening and non-threatening stimuli in adolescents who endorsed varying levels of connectedness to their families. Adolescents ($N = 22$, Mage = 14.38 years) reporting lower family connectedness 1 year earlier showed elevated sensitivity to familial threat, but not to nonfamilial threat in a neural network associated with threat processing, comprising left and right amygdala, and right inferior and middle temporal gyri. Results suggest that a learning history about one's social environment may shape neural mechanisms of threat processing by sensitizing them to risk-relevant stimuli. Such findings advance our understanding of how familial stressors contribute to disordered threat processing in adolescence.

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KEYWORDS

Threat; MVPA; family stressor; amygdala; fMRI

Introduction

Although the majority of youth benefit from rapid biological, psychological and social changes during adolescence, this “tipping point” in life is when many adolescents are initially diagnosed with various psychiatric diagnoses and begin to engage in high-risk, life-threatening behaviors (Dahl & Hariri, 2005). Threat processing is one such process that can go awry in adolescence (Spielberg et al., 2013), which when blunted can impair an adolescent's ability to perceive and avert real dangers, and when hyperactive can produce situationally-inappropriate states of high anxiety and panic. As adolescents inevitably face myriad, unprecedented social and academic challenges, especially during the transition from middle school to high school (e.g., Jackson & Schulenberg, 2013), familial support can be a vital buffer against such heightened stress (Hazel, Oppenheimer, Technow, Young, & Hankin, 2014). Despite recent advances in understanding how neural mechanisms of threat processing are affected by genetic differences (Demers, Conley, Bogdan, & Hariri, 2016; Gunduz-Cinar et al., 2013), little is known regarding how social influences serve to shape threat processing mechanisms. The present study examined how feeling disconnected from one's family may be

associated with sensitivity to threatening familial cues in neural mechanisms of threat processing.

The bonds forged between children and caregivers are vital to the child's developing biology and mental health by shaping how neural mechanisms of threat processing are sensitized to environmental threats. In rodent, non-human primate, and human studies, the formation of strong bonds between mother and child affects the development of the child's limbic circuitry (Moriceau & Sullivan, 2006; Tottenham, 2014) involved in emotion regulation and adaptive threat processing (Olsavsky et al., 2013). In adolescence, self-reported family connectedness (Ackard, Neumark-Sztainer, Story, & Perry, 2006; Delaney, 1996) and attachment style (Bögels & Brechman-Toussaint, 2006) are related to concurrent and longitudinal increases in anxiety. Biologically, adolescents endorsing weak family connectedness display hypersensitivity to threat in the amygdala (Van Harmelen et al., 2012). Moreover, those with an extreme form of weak familial connectedness, early maternal deprivation, show reduced habituation in the amygdala to facial stimuli (Olsavsky et al., 2013). This comports with the idea that those with weak family connectedness have greater sensitivity (do not habituate as much) to familial threats.

Strong parent-child bonds are typified by emotionally supportive parents, whereas weak bonds are

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associated with a lack of such support (e.g., Riggio, 2004). Extant work has demonstrated how the presence of empathic support, especially during times of navigating conflicts that arise between parents and adolescents, facilitates an adolescent's developing identity and health (Moretti & Peled, 2004). Because weakly bonded adolescents may incur greater stress during times of conflict with their parents, weakly bonded adolescents are likely sensitized to threatening familial cues, which serve as conditioned stimuli for such stress. Although we know from extant rodent and human research that a lack of adequate maternal support affects broad aspects of stress-responding in neuroendocrine systems (Hostinar, Sullivan, & Gunnar, 2014), we know little about how familial stressors may have more specific effects on the functioning of neural mechanisms of threat processing. Thus, in the present study, we sought to test if those with weak bonds to their families would be sensitized to cues of maternal threat (i.e. angry faces) above and beyond stranger threat. We hypothesized that when presented with threatening familial cues, weakly bonded adolescents would encode threatening maternal images more distinctly from stranger faces in threat-processing regions. Sensitivity in the present study thus refers to how distinct the neural encoding is of a given stimulus category.

Because family connectedness may be especially important during the middle-school to high-school transition, we measured family connectedness during middle school, and followed adolescents through the high school transition to measure neural processing of

threat in high school. Indeed, family connectedness has been shown to be stress-buffering (Moretti & Peled, 2004) and transitioning to high school imposes new stressors on adolescents related to peer adjustment (Isakson & Jarvis, 1999). For instance, it has been shown that transitioning to high school is associated with increases in incidence of major depression (Seidman & French, 2004), binge drinking (Jackson & Schulenberg, 2013) anxiety and loneliness (Benner and Graham, 2009). During an fMRI task, adolescents saw images of their mothers and strangers displaying different emotional expressions. We used multivoxel pattern analysis (MVPA) because we conceptualized threat encoding of social stimuli as a multidimensional process (Figure 1).

In particular, during the fMRI task in which adolescents were exposed to repeated presentations of maternal angry faces, it was hypothesized that adolescents would rapidly encode multiple dimensions comprising social threat-processing, including valence, current and prior familiarity, and relevant contents from autobiographical memory related to the given stimulus (Oosterwijk, Touroutoglou, & Lindquist, 2014).

The MVPA classifier was trained on the persistent signal across blocks of either unpredictable angry or happy maternal or stranger faces (embedded within neutral faces) at the whole brain level and in several regions of interest (ROI) associated with threat-detection. The ROI analysis focused on a network of brain regions frequently involved in threat detection, henceforth referred to as the "threat network" comprising the

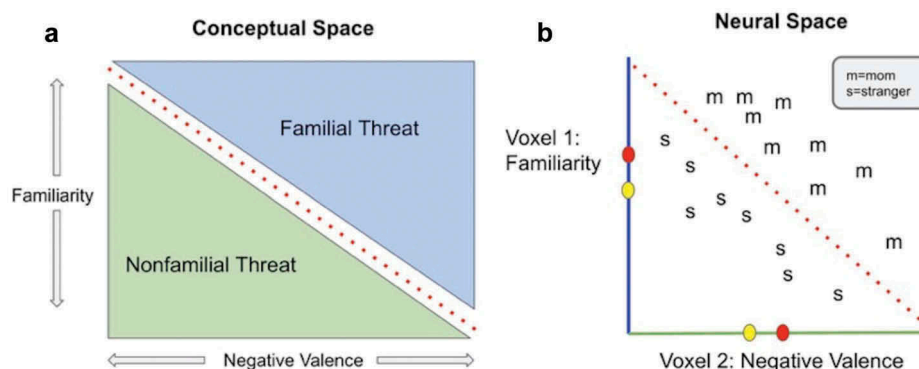


Figure 1. (a) Represents how we conceptualize social threat encoding as a multidimensional process, comprising two dimensions (non-exhaustive) of familiarity and valence. Holding valence constant, familial threat is always more familiar. Similarly, when holding familiarity constant, familial threat tends to elicit greater negative valence. However, the difference in either dimension may be minimal, which may be why it is difficult to distinguish these closely related cognitive representations using traditional univariate fMRI analyses. This conceptual structure may be implemented in neural systems associated with threat encoding as depicted in (b). Assume the 2 voxels in the axes comprise the entire amygdala. If one used traditional voxel-wise univariate analysis of fMRI data to test the hypothesis that voxels in the amygdala distinguish familial from nonfamilial threat, the mean voxel-wise activations for a given population for familial (red circles) and non-familial (yellow circles) stimuli may be insignificantly different from each other. Conversely, an MVPA algorithm that takes into account the distributed pattern of activity across voxels could estimate the red-dotted line that best distinguishes these types of stimuli.

bilateral amygdala and two regions in right temporal cortex that have been associated with threat detection and anxiety, the right inferior temporal gyrus (rITG) and right middle temporal gyrus (rMTG; Spielberg et al., 2013; Van den Bulk et al., 2014). We predicted that those with weak family connectedness would be hypersensitive only to familial threat (angry maternal faces), and not to nonfamilial threat (angry stranger faces) or familial and nonfamilial joy (happy maternal and stranger faces).

We used sensitivity scores derived from MVPA to operationalize neural sensitivity to types of social threats in order to test our hypothesis. Sensitivity in the present context refers to how differentiated the encoding is of a stimulus in the threat-detection system relative to similar stimuli. This is operationalized by sensitivity scores derived from MVPA classification, which indicate more correct classifications of a given stimulus type. In line with our hypothesis, we expected that those who had weak family bonds would be more sensitized in threat-processing circuitry to familial threat compared to non-familial threat, indicated by an elevated sensitivity score for that stimulus. Indeed, in the present study, more correct classifications of maternal threat is evidence that the neural code of maternal threat was more coherent and distinct from that of stranger threat for a given individual.

Importantly, we view sensitivity to maternal threat as an endophenotype of weak family connectedness, which may or may not result in manifest symptoms of anxiety. Although we predict that weak family connectedness should be anxiogenic in producing *state* anxiety in the presence of maternal threat, this may not be related to broader forms of trait anxiety that precede clinical diagnoses. However, to explore the degree of the relationship between family connectedness, maternal threat, and forms of anxiety, we collected a self-reported measure of trait anxiety at the time that neuroimaging was carried out and computed correlations among these three factors to inform inductive theorizing that may help future work in this area.

Methods

Participants

Twenty-four adolescents participated in the present study. Two participants were excluded due to missing and corrupted data. Our final sample included 22 adolescents (13 males). When participants were in the 8th grade (i.e., middle school; mean age = 14.38 years), they completed self-report measures of family connection. One year later, following the transition to high

school (mean age = 15.19 years), participants underwent a brain scan during which they completed a task depicting familial and stranger threat cues. Adolescent participants self-reported as White ($n = 14$), African-American ($n = 6$), Central-American ($n = 1$) or American ($n = 1$). All participants provided written assent and consent in accordance with the Institutional Review Board.

Measures

Self-reported family connectedness

In 8th grade, participants completed a family connectedness measure (Hardway & Fuligni, 2006) in which they answered 8 questions using a 5-point scale (1 = strongly disagree to 5 = strongly agree) to indicate how strongly connected they felt to their family (e.g., “I feel a sense that I personally belong in my family,” and “I do not feel like an important part of my family”). All items were summed to create an index of family connectedness ranging from 8–40 with higher scores indicating greater family connectedness ($\alpha = .87$). Family connectedness ranged from 21 to 40 in the present sample (Mean = 32.23, SD = 6.3). *Self-Reported Trait*

Anxiety

In 9th grade, participants filled out the Children’s Manifest Anxiety Scale (Reynolds and Richmond, 1978), in which they answered 28 questions on a 4-point scale (1 = Not at all, 4 = Very much) to indicate how often they felt anxious over the past 2 weeks. All items were summed to create an index of trait anxiety ranging from 28–112 with higher scores indicating greater anxiety ($\alpha = .96$). Trait anxiety ranged from 28 to 81 in the present sample (Mean = 48.72, SD = 16.6).

Procedure

Maternal vs. stranger go no-go task

In the 9th grade, one year after completing the self-report measure of familial connection, participants completed a brain scan during which they completed a Go No-Go task modified from prior work (Tottenham, Shapiro, Telzer, & Humphreys, 2012). Participants were instructed to press a button as quickly as possible during “go” trials and inhibit this response by not hitting any button during “no-go” trials (Figure 2).

The task had five blocks each consisting of 80 trials, in which 75% of trials were “go” trials of neutral faces, intentionally outnumbering no-go trials in order to generate a prepotent response that is difficult to inhibit. The remaining “no-go” trials comprised emotional faces. Blocks consisted of (1) happy vs. neutral stranger

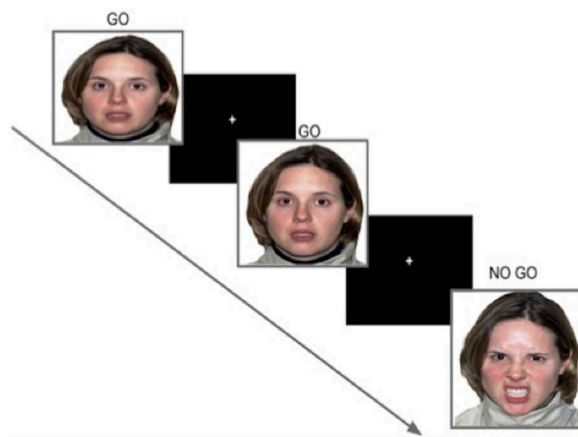


Figure 2. Mother vs. Stranger Go No-Go fMRI task.

faces, (2) angry vs. neutral stranger faces, (3) happy vs. neutral maternal faces, (4) angry vs. neutral maternal faces, and (5) blue vs. orange houses. Maternal images were taken on-site against a white background. Female strangers' faces were taken from the standardized NimStim stimuli (Tottenham et al., 2009). Importantly, stranger stimuli were matched to the race of maternal stimulus. Independent raters did not confirm that valence and intensity matched that of strangers.

Each stimulus was presented for 500 ms, followed by a fixation that was randomly jittered to vary the inter-stimulus interval increasing the experimental design efficiency. Each block included the same amount of TRs, followed by 7 TRs (14 seconds) of rest between blocks.

Data acquisition

Imaging data were collected using a 3 Tesla Siemens Trio MRI scanner. The Faces Go No-Go task included T2*-weighted echoplanar images (EPI) (slice thickness = 3mm; 38 slices; repetition time (TR) = 2s; echo time (TE) = 25ms; matrix = 92×92 ; FOV = 230mm; voxel size = $2.5 \times 2.5 \times 3 \text{ mm}^3$). Structural scans consisted of a T2*-weighted, matched-bandwidth (MBW), high-resolution, anatomical scan (TR = 4s; TE = 64ms; FOV = 230; matrix = 192×192 ; slice thickness = 3mm; 38 slices) and a T1* magnetization-prepared rapid-acquisition gradient echo (MPRAGE; TR = 1.9s; TE = 23ms; FOV = 230; matrix = 256×256 ; sagittal plane; slice thickness = 1 mm; 192 slices). The orientation for the MBW and EPI scans was oblique axial to maximize brain coverage.

MVPA data processing stream

Minimal preprocessing was done on NIFTI images in preparation for the MVPA analysis. FSL's MCFLIRT

(Jenkinson, Bannister, Brady, & Smith, 2002) with default settings was used for motion correction, followed by using FSL's FEAT to remove scanner drift using a high pass filter that eliminated frequencies below .01 Hz contributing to the BOLD signal (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0s). Smoothing was not used to avoid reducing the amount of information (by blurring distinct voxel-level signals) in the hypothesized multidimensional coding instantiated in small regions such as the amygdala (Pereira, Mitchell, & Botvinick, 2009).

Using AFNI's 3dSVM algorithm (LaConte, Strother, Cherkassky, Anderson, & Hu, 2005), a linear classifier determined a decision boundary between the encoding of blocks of unpredictable familial threat from unpredictable non-familial (stranger) threat. 3dSVM implements a type of supervised learning, a support vector machine, to determine a hyper plane in high-dimensional space (each dimension representing a voxel within the region of interest (ROI)) that differentiates the encoding of experimental conditions. Each instance of the class (synonymous with block) that trained the classifier was a TR representing each time point of data collection in the 4D BOLD NIFTI file. Because these blocks contained unpredictable presentations of angry maternal or stranger faces, we operationalized the consistent signal across these blocks as unpredictable familial or non-familial threat. There is precedent for such modeling of protracted anxiety signals in univariate mixed block/event-related fMRI designs using unpredictable, threatening visual stimuli (Somerville et al., 2013).

The classifier was trained on the first half of the block and tested on the second half of the block. Stranger stimuli were used as a comparison to maternal stimuli (the MVPA models estimated a function that separates stranger from maternal threat) because their cognitive representations share characteristics (both are human faces and share similar valence). Hypersensitivity to a given stimulus class would result in more correct classifications. Thus, it was hypothesized that those with weak family bonds would show more correct classifications of maternal threat, reflecting neural sensitivity to such stimuli.

3dSVM was run on previously described preprocessed BOLD images. For each subject, 3dSVM was run on five different models a priori defined. Four ROIs were tested separately: (1) right and (2) left amygdala, (3) right inferior temporal gyrus (rITG) and (4) right middle temporal gyrus (rMTG). We also tested 3dSVM on a concatenation of all ROIs called the "threat network" (5th ROI). Each of these regions (amygdala and regions in anterior cortical temporal lobe) is part of a

putative functional network, the limbic system, which has been shown to have resting-state and task-based functional and structural connectivity (Oosterwijk et al., 2014; Yeo et al., 2011).¹ Each region was selected because of its association with various types of threat processing (measured by univariate fMRI), including negatively-valenced facial stimuli (Spielberg et al., 2013; Van den Bulk et al., 2014). ROIs were defined structurally using the Harvard Oxford atlas, and were transformed into subjects' BOLD space using FSL's linear, affine registration tool, FLIRT. The 1mm atlas space ROIs were transformed first to each subject's high-resolution T1-weighted structural image, and subsequently were transformed into native subject's BOLD space.

Lastly, we also tested 3dSVM at the whole-brain level to rule out the explanation that sensitivity increases as a function of more voxels used to train the classifier. To determine if the relationship between multivariate activity patterns in threat-processing neural regions and family connectedness was specific (as was hypothesized) to threatening stimuli, we also ran the same five MVPA models on blocks containing happy expressions for both maternal and stranger faces.

3dSVM computes a single, overall accuracy metric, which denotes in this study the percentage of correct classifications for both familial and non-familial faces. Since this number does not contain information about accuracy within each stimulus class, sensitivity analyses were conducted using an in-house written Python algorithm. Sensitivity is a metric from signal-detection theory that provides the fraction of correct classifications (true positives) of the total amount of opportunities to classify a specified type of true signal (true positives + false negatives).

The authors were in contact with a programmer who updates 3dSVM software, and this design was recommended given that our task only had one block per experimental condition (and thus could not be trained

and tested on separate blocks/runs). Cross-validation was not used to see how robust the classifier function was at predicting independent data (Etzel & Braver, 2013), because we expected the coding of familial threat to change over the course of the block and thus had a priori hypotheses of poor classifier performance for individuals with higher perceived family connectedness.

Results

MVPA test of sensitivity to unpredictable familial and stranger threat

To measure sensitivity to unpredictable familial threat (mothers angry faces), we conducted Pearson correlation tests between the MVPA-derived sensitivity metrics and all a priori defined ROIs and networks. Sensitivity of the entire "threat network" was inversely related to family connectedness (Figure 3) with the strongest effect size of all tests, followed by the left amygdala (see Table 1).

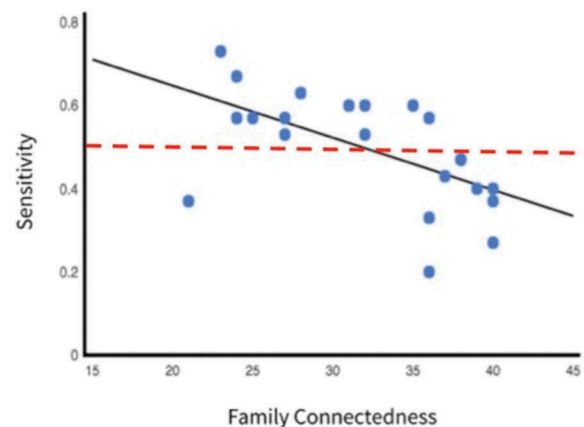


Figure 3. Family connectedness and sensitivity to unpredictable, familial threat in the threat network. The red-dotted line represents chance levels (50% accurate) for a 2-class classifier.

Table 1. MVPA results linking family connectedness with familial and nonfamilial threat and joy.

| Condition | "Threat Network" | left Amygdala | right Amygdala | right ITG | right MTG | Whole Brain |
|--------------------|------------------|---------------|----------------|-----------|-----------|-------------|
| Familial Threat | -.590** | -.474* | -.257 | -.377 | -.371 | -.479* |
| Nonfamilial Threat | -.075 | .091 | .052 | .061 | -.171 | .050 |
| Familial Joy | .354 | .196 | .355 | .366 | .262 | .302 |
| Nonfamilial Joy | .053 | .178 | .113 | .071 | .211 | .237 |

Each column denotes a brain region, and each row denotes the stimulus condition. Correlation values refer to the relationship between (1) neural sensitivity of a given brain region to a stimulus type and (2) family connectedness. The first correlation in the top left refers to the correlation between (1) neural sensitivity to familial threat in the "threat network" of brain regions and (2) family connectedness. * <.05 ** <.01

¹Although neuroscience has amassed a wealth of knowledge of associations between cognitive functions and brain activity/structure, meta-analyses using large databases such as NeuroSynth have revealed how functionally diverse brain regions (regardless of how finely-grained such regions are defined) are the rule rather than the exception (Anderson, 2014; Poldrack & Yarkoni, 2016). Thus, discussions of associations between a priori defined neural regions and threat processing do not imply that such regions are selective for threat processing, but rather, tend to be involved, and may be necessary (although the latter is a stronger claim).

Additionally, family connectedness correlated inversely with sensitivity at the whole brain-level, albeit with a lower effect size than the “threat network”. Next, we ran sensitivity analyses of the same five models for unpredictable nonfamilial threat (stranger angry faces). No significant correlations were found (see Table 1).

Comparison between familial and nonfamilial threat

To test if adolescents low in family connectedness were hypersensitive to familial relative to nonfamilial threat, we tested if the effect size of family connectedness and sensitivity to familial threat is significantly greater than the effect size of family connectedness and sensitivity to nonfamilial threat. To statistically compare such effect sizes, we leveraged Steiger’s Z-test for comparing bivariate correlations (Lee & Preacher, 2013). Results show that there is a significant difference in effect size between the aforementioned Pearson correlation coefficients ($z = -2.142$, $p = .03$). Taken together, as family connectedness decreases, individuals show hypersensitivity in limbic circuitry to familial threat relative to nonfamilial threat.

Sensitivity to unpredictable, familial and stranger joy

We tested the same 5 ROIs on blocks containing unpredictable familial or nonfamilial joy (i.e., happy faces) in order to rule out that those with low family connectedness had higher sensitivity to familial faces regardless of valence. Correlations were insignificant and in the opposite direction as the relationships supported by sensitivity to unpredictable threat (see Table 1). The reversal of the sign of the correlation is supported by extant evidence, which shows that those with high attachment security show enhanced amygdala responsiveness to maternal happy stimuli compared to stranger happy stimuli in childhood and adolescence (Tottenham et al., 2012). Finally, in terms of sensitivity to nonfamilial joy and family connectedness, correlations were not significant (see Table 1).

Relationship between family connectedness, neural sensitivity, and trait anxiety

Finally, we examined correlations between family connectedness, neural sensitivity to maternal threat, and trait anxiety. The relationship between family connectedness and trait anxiety was in the predicted direction, although not significant ($r = -.28$, $p = .22$), likely due to the low power in the present study. Moreover, the relationship between neural sensitivity to maternal

threat and trait anxiety was weaker and non-significant ($r = -.16$, $p = .47$).

Discussion

Although various forms of weak family connectedness are known to impinge on threat processing mechanisms, and confer risk for disorders of threat processing (Ackard et al., 2006), more work is needed to gain a better mechanistic understanding of the nature of dysfunction associated with familial stressors. Such understanding will advance theory regarding how familial stressors disrupt neural mechanisms and inform clinical applications designing more precise interventions for children and adolescents who are most impacted by feeling such disconnect from their families. The present study sought to contribute to this enterprise by testing the hypothesis that weak family connectedness would be associated with selective sensitivity to familial threat.

In a network of regions consistently involved in detecting threat, comprising key nodes of the limbic system, the coherence in the neural encoding of unpredictable, familial threat was related to weak family connectedness. To ensure that weak family connectedness was specific to threatening maternal stimuli, we also conducted several tests to rule out alternative explanations for our results. Null results of models that used positive familial and positive/negative nonfamilial stimuli ruled out the possibility that our main finding was driven by the familiarity of maternal stimuli and supported the conclusion that those low in family connectedness are uniquely sensitive to familial threats. Future work should endeavor to corroborate this conclusion by including familiar faces that are non-familial. Such an experimental paradigm could include faces of adolescents’ friends, for instance, as a contrast to family members.

Collectively, our findings reflect that feeling weakly bonded to one’s family may sensitize an adolescent to familial threats. That findings were specific to threatening stimuli suggests that weak family connectedness may result from adverse experiences between adolescents and their parents. A wealth of findings has demonstrated the amygdala’s role in facilitating learned associations between feared stimuli and anxiety responses (Tovote, Fadok, & Lüthi, 2015). Thus, unpredictable presentations of an angry maternal face may only induce state anxiety in individuals that have experienced unpredictable deleterious interactions with a parental figure. Future work should investigate this hypothesis by (1) testing potential mediators of the effects presented here, which could include insecure attachment styles and types of familial trauma

experienced by the adolescent (Sheridan & McLaughlin, 2014) and (2) associating sensitivity to threat as measured with MVPA to state measures of self-reported anxiety. More work is also needed to test the various ways in which trait anxiety, family connectedness, and neural sensitivity to familial threat are related. The present study found a moderate, albeit insignificant, correlation between family connectedness and trait anxiety, but found no evidence of a relationship between neural sensitivity to maternal threat and trait anxiety. Future work should use the methods in the present study with larger and clinically-diagnosed samples that are more optimized to evaluate such relationships.

Previous neuroscience studies of parent-child relations have likely been stymied by the constraints imposed on experimental findings by univariate fMRI analyses. For example, a recent investigation of how children and adolescents differentially encode maternal and stranger stimuli in amygdala failed to distinguish negatively-valenced maternal from stranger images (Todd, Evans, Morris, Lewis, & Taylor, 2011), which a subsequent study interpreted as meaning that negative valence dampens the amygdala response to maternal salience (Tottenham, 2013). A weakness of the aforementioned study is that it assumes the encoding of social stimuli is unidimensional. Although it may seem intuitive that threat-encoding should be instantiated unidimensionally, it assumes a very specific model of how neural systems give rise to psychological operations. An additional limitation is the reliance on self-report to glean measures of family connectedness. Future studies should endeavor to obtain more objective evidence of weak family connectedness, such as time spent with parents, history of conflict and abuse, etc.

Future work should examine how changes in family connectedness throughout adolescence impacts threat sensitivity to familial stimuli. Although the present study shows the predictive validity of measures of family connectedness taken before high school for neural markers of threat sensitivity to familial stimuli after entering high school, it may be the case that this relationship changes depending on when measures of family connectedness are gleaned. For instance, decreases in family connectedness after high school may be the result of factors unrelated to neural sensitivity to familial threat, as it is simply a normative factor associated with achieving more independence from

one's family. A recent longitudinal study of a large sample ($n = 821$) found that family connectedness decreases throughout the high school years, but rebounds as adolescents make the transition to young adulthood (Tsai, Telzer and Fuglini, 2013). However, it is unclear how significant these mean declines in family connectedness are for deleterious outcomes, such as psychopathology. The degree of decrease in connectedness is likely vital, as it has been shown that connectedness throughout adolescence is essential to adolescent health even when normative increases in familial conflict occur (Moretti & Peled, 2004). Indeed, some suggest that what may be most important throughout the adolescent years is relatedness between adolescents and parents (Allen, Moore, and Kuperminc, 1997). Thus, future work should seek to connect how transitions in family connectedness relate to both neural markers of threat processing as well as impacts on adolescent psychopathology.

It will be also be vital to test the hypotheses in the present study in larger datasets, as the field of human neuroimaging is moving towards big data projects with increased power. Indeed, the effect size reported here may be inflated due to the requirement of high power to meet statistical significance thresholds in the present small sample size (Ioannidis, 2005). However, although the effect size may decrease in a larger sample, it is the contention that with increased power, the effect would still be robust and worthy of further investigation.

Future research should also seek to understand how other neural systems contribute to present findings through use of functional connectomics approaches such as dynamic causal modeling (Friston, Harrison, & Penny, 2003; Sharp, Miller, & Heller, 2015). Extant theories suggest that memory structures formed by early adverse experience (e.g., parental neglect and abuse) influence psychopathological behavior (Lane, Ryan, Nadel, & Greenberg, 2015), which may be implemented in neural interactions between threat processing and memory systems.²

Additionally, future work should use complementary methods to linear classifiers, such as representational similarity analysis, which can describe how the multivariate patterns encoding types of social threats are related to each other (Kriegeskorte, Mur, & Bandettini, 2008). Such methods provide additional information above and beyond classification algorithms like SVM, and have been demonstrated to be more statistically sensitive to

²We do not mean to imply that amygdala and ROIs in lateral temporal cortex are not involved in memory processes. However, future experiments should assess how areas within hippocampi and frontal cortex are also involved in conscious and unconscious processing of risk-relevant learned associations, and how these mechanisms interact with amygdala networks involved in threat processing.

multivariate effects (Haxby, Connolly, & Guntupalli, 2014). Elucidating within- and between-subject quantitative descriptions of threat-encoding in multivoxel space may provide a better mechanistic understanding of how threat-processing regions function.

Conclusion

In conclusion, results suggest that familial stressors may impinge on threat processing neural mechanisms in a specific way such that those with weak family bonds show hypersensitivity to maternal threat in a neural “threat network”. Such selective sensitivity to familial threat in those weakly bonded to their families may confer risk for future psychopathology. The tendency to engage protracted threat processing in the presence of familial threats may predispose an individual to experience heightened anxiety in the context of familial conflict, which can become more frequent as adolescents assert their emotional and physical independence (Laursen & Collins, 2009). Cycles of familial conflict in this period of vulnerability may eventually erode mechanisms of threat processing to the point of producing clinically relevant anxiety symptoms. Moreover, heightened neural sensitivity to familial threat for those with familial stressors may be a biomarker that precedes clinical emergence of internalizing disorders. Thus, present findings may contribute to clinical interventions that target familial relationship quality as an antecedent to psychopathology, and prioritize familial interventions for children and adolescents with weak family connectedness.

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Disclosure statement

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