

**EXAMINING THE UNIQUE CONTRIBUTION OF PARENTAL ANXIETY
SENSITIVITY ON ADOLESCENT NEURAL RESPONSES DURING AN
EMOTION REGULATION TASK**

by

Leah D. Church

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science in Psychological and Brain Sciences

Spring 2024

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ACKNOWLEDGMENTS

I wish to thank my advisor, Dr. Jeffrey M. Spielberg, for his guidance, mentorship, and unwavering support. I would also like to thank Dr. Nadia Bounoua, not only for her incredible mentorship but also for her friendship, which has been instrumental during my graduate career. This work was supported by the National Science Foundation (2021317035), the National Institute of General Medical Sciences (P20GM103653 9030), and the National Institute of Mental Health (1R01MH123470). I would also like to thank the members of the Connectomics of Anxiety and Depression Lab for their work collecting and cleaning data for the present study. Additionally, I am extremely grateful to my friends, family, and Colin Fitzgerald for their constant support.

This manuscript is dedicated to my parents, Jill and Steve Church, who have always believed in me, been patient with me, and encouraged me to pursue my dreams for as long as I can remember.

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ABSTRACT

Anxiety sensitivity and emotion *dys*regulation are transdiagnostic risk factors for anxiety pathology. Theoretical and empirical work also highlight the influence of parents on their adolescent's capacity for emotion regulation. We tested whether parental anxiety sensitivity uniquely moderated brain activation during emotion regulation in their adolescents. One hundred and forty-seven adolescents ($M/SD_{age} = 12.07/.90$; 50.3% female) and their parents (99.3% mothers) completed a measure of anxiety sensitivity. Adolescents completed an fMRI emotion regulation task that required youth to either *regulate* or *react* (regulation factor) to *negative* or *neutral* stimuli (valence factor). Analyses examined whether parental anxiety sensitivity moderated adolescent neural activation related to regulation demands and stimuli valence. Importantly, child anxiety sensitivity was included as a covariate, such that the findings reflect only the unique associations with parental anxiety sensitivity. Results revealed that parental anxiety sensitivity moderated neural responses to regulatory demands in several brain regions. Further exploration of the findings revealed that parental anxiety sensitivity was associated with greater activation in the inferior frontal gyrus (IFG), anterior cingulate cortex, and middle frontal gyrus (MFG) during *react* trials (p 's = .003-.02) and with decreased activation in a different region of right IFG/MFG during *regulate* trials ($p = .048$). Results suggest that parental anxiety sensitivity impacts their children's emotion regulation at a neurobiological level. Together, our results provide novel insight into the

impact of parental anxiety sensitivity on their child's emotion regulation-related brain activation, over and above adolescent anxiety sensitivity.

Keywords: anxiety sensitivity, emotion regulation, parents, adolescence, fMRI

Chapter 1

INTRODUCTION

Early adolescence is marked by a range of significant social, emotional, and neural changes and is the most common onset time for a range of pathology, including anxiety (Kessler, et al. 2007). Anxiety disorders are the most common mental health diagnosis in adolescence, with estimates ranging from 15-30% (Beesdo et al., 2009; Merikangas et al., 2010). The increased prevalence of anxiety in adolescence is highly linked to the maturational profile of emotion regulation capacity, which is the ability to implement psychological and behavioral strategies to manage emotions (Gross, 2002; Mathews et al., 2014). Specifically, emotion regulation capacity is inversely related to anxiety levels: both anxiety and emotion *dys*regulation increase during the transition *into* adolescence, and both decrease during the transition *out of* adolescence. This is consistent with work suggesting that emotion regulation disturbances play a critical role in the development of anxiety pathology (Cisler et al., 2010; Gross, 2002), along with more general outcomes, including academic performance and interpersonal functioning (Eisenberg et al., 2010; McLaughlin et al., 2011). In addition, meta-analytic evidence suggests that changes in emotion regulation during adolescence are linked to differences

in the development of both the prefrontal cortex (PFC) (Pozzi et al., 2021) and amygdala (Ashworth et al., 2021). This overlaps with activation differences observed in anxious adolescents, which also occur in PFC and amygdala (Ashworth et al., 2021; Xie et al., 2021). Thus, examining the manner in which the neural circuits instantiating emotion regulation function during adolescence may provide key insights into the development of pathological anxiety.

A key vulnerability factor for anxiety development is the level of parental anxiety present in the home (Cole & Deater-Deckard, 2009; McRae et al., 2018). The children of parents with anxiety pathology are over three times more likely to develop anxiety themselves, relative to the children without such parental pathology (Hirshfeld-Becker et al., 2008; Micco et al., 2009). Although genetic heritability accounts for 30-40% of this relationship, environmental influences also account for a significant portion of such developmental risk (Eley, 2001; Gross & Hen, 2004). Parents provide an environment in which unique, anxiety-related learning experiences may contribute to their children's development (Fisak & Grills-Taquechel, 2007). A recent model by Perlman and colleagues (2022) highlights the importance of dyadic social processes in parent-child anxiety transmission. They proposed that emotion modeling is a mechanism in the intergenerational transfer of anxiety. For example, parents may express physical (e.g., shaking) or verbal (e.g., ruminating out loud) manifestations of anxiety in front of their children, and children may subsequently model or up-regulate these behaviors in times of

emotional stress. Anxious parents also engage in avoidance behaviors (Aktar et al., 2022; Emerson et al., 2019), which may influence the strategies that their children employ to regulate their own emotions. Together, evidence suggests that parents' own anxiety-related pathology contributes to the development of maladaptive emotion regulation strategies in their offspring.

Although a mounting body of work has examined the impact of parental behavior on adolescent anxiety development (Garcia et al., 2014; Gross & Hen, 2004), little is known about the intervening mechanisms by which parental anxiety impacts their adolescent's anxiety. As mentioned above, emotion (dys)regulation in adolescents appears to be a prime candidate for such a mechanism, and this has prompted theoretical work positing that parental anxiety contributes to worse child emotion regulation, which in turn increases risk for child anxiety (Nolte et al., 2011; Perlman et al., 2022). Although relatively sparse and non-specific, existing research is consistent with these ideas. For example, parents' internalizing symptoms prospectively predict worse youth emotion regulation capacity (Hare et al., 2022). Moreover, Suveg and colleagues (2011) found that children's emotion regulation capacity mediated the relationship between general parental psychopathology and their children's internalizing symptoms. Although promising, this body of work has lacked specificity, for example, examining general psychopathology or internalizing, rather than anxiety in particular. Thus, this work can only support models of clinical-level risk transference, as opposed to the role of anxiety-

related symptoms and traits.

In order to characterize the pathways by which parents influence their adolescents, a growing body of research has sought potential neural mechanisms by which this may occur (Pozzi et al., 2021). For example, negative parenting styles have been associated with altered activation of regions involved in emotional salience (e.g., anterior insula) in older children and adolescents (Marusak et al., 2017). Similarly, higher maternal warmth was related to lower activation in the amygdala, insula, and anterior cingulate cortex in adolescents (Butterfield et al., 2020). Although these studies support the idea that parental behavior impacts key circuitry implicated in both emotion regulation and anxiety, they do not speak to anxiety transmission in particular. Only a few studies have directly examined the impact of parental anxiety-related processes on their child's brain development. For example, Donnici and colleagues (2021) showed that postpartum maternal anxiety was associated with differences in amygdala functional connectivity in young children. Given the amygdala's role in emotion regulation, differences in the manner in which amygdala communicates may be a mechanism through which parental anxiety influences their child's emotion regulation. In a different study, healthy adolescents with anxious parents showed altered amygdala and dorsolateral PFC (dlPFC) activation during fear conditioning, with greater activation to neutral cues than to cues predicting threat, whereas healthy adolescents without anxious parents evidenced the opposite pattern (Chauret et al., 2019). These findings are open to a

number of interpretations. On one hand, the fact that at-risk youth evidenced the opposite pattern as those at low risk could be evidence of disturbed fear learning. At the same time, the authors suggest that the specific pattern observed in the at-risk group is indicative of *more resilient* regulatory function (Chauret et al., 2019), which appears counterintuitive. If true, one potential explanation lies in the fact that the at-risk group consisted of adolescents ages 10-17 who had not developed anxiety pathology themselves. Given that the majority of such pathology typically onsets during this window, the at-risk youth may have actually been resilient against anxiety development, given that they likely would have done so by that point otherwise (at least the older adolescents). In summary, there is a dearth of research in this area to date, making this an area in great need of further study.

Although the studies discussed above have provided key information, they have primarily employed diagnostic groups or broad symptom checklists. However, the field has increasingly recognized that the use of dimensional measures of specific transdiagnostic factors can provide greater insight into distinct mechanisms (e.g., genetic, neurological, environmental) that contribute to the development of anxiety (Insel et al., 2010; Norton & Paulus, 2017). One such transdiagnostic factor is anxiety sensitivity, which is defined as the fear of anxiety-related physical symptoms (e.g., rapid heart rate, nausea) and the belief that these symptoms signal negative outcomes, including physical (e.g., heart attack), social (e.g., rejection), and psychological (e.g., “going crazy”)

consequences (Silverman et al., 1991; Taylor, S. 1999). Previous research has identified anxiety sensitivity as a key risk factor for the development of anxiety pathology in youth (Schmidt et al., 2010) and adults (Kaczurkin et al., 2018). Importantly, anxiety sensitivity is not considered pathology itself, but rather is thought to be a potential causal mechanism for the later development of anxiety pathology (Olatunji & Wolitzky-Taylor, 2009). In support of this, anxiety sensitivity prospectively predicts the development of obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, and post-traumatic stress disorder (Calamari et al., 2008; Hayward et al., 2000; Marshall et al., 2010; Naragon-Gainey, 2010; Schmidt et al., 1997; Schmidt et al., 2010). Moreover, anxiety sensitivity is related to an array of related, yet distinct, anxiety-related factors such as worry, anxious arousal, fear of negative evaluation, and intolerance of uncertainty (Carlton et al., 2007; Floyd et al., 2005; Kashdan et al., 2007; Kemper et al., 2012). As well, anxiety sensitivity exists on a continuum of severity and, as such, is a useful indicator of risk for anxiety development in non-clinical samples.

Finally, research has evidenced key links between emotion regulation and anxiety sensitivity, including in the prediction of later anxiety (see Olatunji & Wolitzky-Taylor, 2009). Longitudinal, transactional relationships between anxiety sensitivity and emotion regulation have been established in adults (Church et al., in press), yet less is known about the possibility of such transactional relationships in adolescence. However, a recent study by Esmailian and colleagues (2021) found that emotion regulation mediated the

relationship between anxiety sensitivity and social anxiety in a sample of adolescents. Moreover, previous work in adolescents has also shown that anxiety sensitivity is associated with disturbances in emotion regulation-related neural activation (Church et al., under review). Although this work is highly suggestive that interactions between anxiety sensitivity and emotion regulation play a key role in the development of anxiety pathology, more work is needed to fully elucidate this potential pathway.

Present Study

As highlighted above, developmental models of youth anxiety highlight the impact of parents' own anxiety processes on their adolescent's development, which is hypothesized to be mediated by their child's emotion regulation capacity. The present study examines the role of anxiety sensitivity - a transdiagnostic anxiety-related construct - as it has been shown to be a robust lower-order dimension related to, and prospectively predictive of, trait anxiety (Olatunji & Wolitzky-Taylor, 2009). To our knowledge, no studies to date have explored the impact of parental anxiety sensitivity on adolescents' neural activation related to emotion regulation. The present study builds upon the dyadic social dynamic model proposed by Perlman and colleagues (2022) and addresses gaps in the literature by examining whether parental anxiety sensitivity uniquely moderates adolescent emotion regulation-related neural activation, after accounting for child anxiety sensitivity. The examination of the role of parental anxiety sensitivity, above and beyond adolescents' anxiety sensitivity, allows for a more nuanced understanding of the unique role of parental behavior on adolescents' emotion regulation capacity. In the present

study, adolescents completed an explicit emotion regulation task in which they were asked to either *regulate* or *react* to either *negative* or *neutral* stimuli. We hypothesized that adolescents of parents with greater anxiety sensitivity would show greater amygdala recruitment and weaker PFC recruitment when asked to *regulate* (vs. *react* to) responses to *negative* (vs. *neutral*) stimuli, compared to adolescents of parents with lower anxiety sensitivity.

Chapter 2

METHODS

Participants

Participants were recruited from Delaware and surrounding areas. Inclusion criteria were fluency in English, age 11-13 for females, and age 12-14 for males. The difference in ages by sex was due to the fact that females tend to enter puberty earlier than males (Brix et al., 2019; Tanner 1962), and changes in affective circuitry have been linked to pubertal processes (Blakemore et al., 2010; Ladouceur, 2012; Peper & Dahl, 2013). Thus, equating across biological sexes by approximate pubertal stage (vs. age) is more likely to equate the groups on the processes of interest. Exclusion criteria were: major medical or neurological illness, current psychosis, and/or any MRI contraindication (e.g., metal in body).

Self-report and MRI data were collected from 147 adolescents ($M/SD_{age} = 12.07/.90$; 50.3% female). Approximately 71% of the sample was White, 10% Black or African American, 2% Asian, 2% American Indian or Alaska Native, and 10% bi- or multi-racial, with approximately 7% of the sample identifying as Hispanic. Data on race and ethnicity was missing for 9 participants (6.1%) and 7 participants (4.8%), respectively. Parents ($M/SD_{age} = 41.58/6.12$) were 97.2% biological mothers. Parent educational attainment was as follows: 3.4% <12th grade, 20.4% High School/GED, 11.6% Associate's degree, 35.4% Bachelor's degree, 21.1% Master's degree, 6.8% Doctorate or professional degree. Educational attainment was missing for 2 participants (1.4%). Approximately 76% of parents reported a household income above \$50,000.

Self-Report Measures

The 18-item Childhood Anxiety Sensitivity Index (CASI; Silverman et al., 1991) was administered to assess adolescents' fear of arousal-related sensations (e.g., "*It scares me when I have trouble getting my breath*"). Participants were asked to rate the extent to which they agreed with each item from 1 ("*None*") to 3 ("*A lot*"). Items were summed to create total scores (M/SD=28.41/6.92).

The 18-item Anxiety Sensitivity Index (ASI; Taylor et al., 2007) was administered to assess parents' fear of arousal-related sensations (e.g., "*When I have trouble thinking clearly, I worry that there is something wrong with me*"). Participants were asked to rate the extent to which they agreed with each item from 0 ("*Very little*") to 4 ("*Very much*"). Items were summed to create total scores (M/SD=16.84/12.16).

fMRI Task

Adolescents completed an emotion regulation task during fMRI data collection, which has been previously validated in adolescent samples in multiple studies (Peirce, 2007; Silvers et al., 2012). The task presented negative and neutral social images and instructed participants to either embrace their natural responses (*react* condition) or to utilize cognitive reappraisal strategies (*regulate* condition). For each trial, a cue was presented for 2 seconds instructing participants whether to regulate or react during that trial, after which an image was presented for 8 seconds. Following some trials, participants were asked to rate their level of negative affect. Fixation crosses of variable duration were presented after the picture presentation and rating (when applicable). Trial order and fixation duration were created using a pseudo-genetic algorithm to optimize the

separability of effects. Participants were given task instructions prior to entering the scanner, including brief training in reappraisal and a practice administration, after which they completed three runs of the task within the scanner.

MRI Acquisition and Preprocessing

Data were collected via a Siemens 3T Magnetom Prisma scanner with a 64-channel head coil. Acquisition parameters were consistent with those used in the Human Connectome Project (HCP) (Van Essen et al., 2012) and Adolescent Brain Cognitive Development Study (Hagler et al., 2019). fMRI: 3 runs of multi-band EPI (MB-EPI) with a MB factor of 8 (TR=.829s, spatial resolution=2x2x2mm, and TE=40ms). For all participants, the 1st and 3rd runs were collected with anterior→posterior (AP) phase encoding. For 55 participants (37.4%), the 2nd run was collected with posterior→anterior (PA) phase encoding, whereas the remainder were collected AP. The change to all AP runs was made when we observed that, for some participants, regions of susceptibility (e.g., in orbitofrontal cortex) differed for AP and PA runs, such that moderately sized regions were excluded when only using voxels that contained data across all three runs. T1: Volume-navigated multi-echo MPRAGE (VNAV-T1) (1mm³, TI=1000ms, TR=2500ms, TEs=1.8ms, 3.6ms, 5.39ms, 7.18ms).

Using FSL and ANTS tools, data were motion and fieldmap corrected and spatially smoothed (FWHM=5mm). Next, motion-related components were estimated and removed via the ICA-AROMA tool, after which data were temporally high-pass filtered, and intensity-normalized. Finally, data were registered to MNI152 2009a space

via a two step process: (i) boundary-based registration implemented in FSL's FEAT and (ii) non-linear registration implemented in ANTS (Jenkinson et al., 2012). Finally, the two transformations were concatenated and applied to the relevant images using ANTS.

Bayesian hierarchical linear modeling was used to estimate an overall model that was nested within task run and participant. For each run, the fMRI timeseries were regressed on predictors modeling (i) the cue period (two predictors, modeling the *regulate* and *react* conditions), (ii) the image period (four predictors, modeling *regulate negative*, *regulate neutral*, *react negative*, *react neutral*), and (iii) the rating period (one predictor), all of which were convolved with a gamma function to account for the hemodynamic response. For each run, contrasts of the beta maps for the image period were created to model the three effects of interest: stimulus valence (*negative* vs. *neutral*, across regulation levels), regulation condition (*regulate* vs. *react*, across valence levels), and the valence X regulation interaction (*regulate* vs. *react* for *negative* stimuli contrasted against *regulate* vs. *react* for *neutral*). Within-participant second-level fixed-effects analyses were computed to estimate average effects for the three contrasts across the 3 runs, which were then carried up to the group level.

As mentioned above, some of the participants with a PA 2nd run had moderately sized regions excluded due to non-overlapping regions of susceptibility across AP and PA runs, despite the fact that at least two runs of data were available for a large percentage of the excluded areas. Thus, we developed a procedure to dually optimize both the reliability of the beta estimates (i.e., by averaging across as many runs as possible) and spatial coverage (i.e., by including voxels where at least two runs of usable

data were available). Specifically, for each participant, we computed four within-participant second-level fixed-effects analyses, namely the average of (i) all three runs, (ii) runs 1 and 2, (ii) runs 1 and 3, and (ii) runs 2 and 3. Next, we created an optimized beta map by (voxelwise) sequentially checking whether usable data was available for each of the four fixed analyses, moving through these fixed analyses in the order specified above, and stopping at the first fixed analysis to contain usable data in that voxel (if none did, a 0 was assigned to that voxel). For example, for a given voxel, our script first checked if usable data was available across all three runs. If so, the script copied the beta from the three-run fixed analysis into the optimized beta map. If not, the script next checked whether usable data was available for runs 1 and 2 and used that beta if usable data was present. This process continued through each of the fixed analyses until a usable beta was identified, and if none was found, a 0 was assigned for that voxel. Thus, this created a beta map where each voxel contained a beta estimated using data from (i) *at least* two runs and (ii) *all three* runs if available (or a 0).

Group Analyses

Between-participant third-level analyses were carried out in two ways. (i) Given that the susceptibility of amygdala to image artifacts will differ spatially across individuals, large portions of amygdala may be excluded when examining only those voxels that are present across *all* participants. Thus, the mean beta across amygdala voxels was extracted for each participant from the beta-maps for each image period condition, which were then entered into repeated-measures GLMs in SPSS with two

repeated factors (regulation and stimulus valence). One GLM was run to examine the main effect of parent ASI, controlling for adolescents' CASI scores. (ii) Using FSL's RANDOMISE tool (Winkler et al., 2014), voxel-wise GLM was carried out for the contrast of interest, with ASI as the predictor of interest in the model. Threshold-free cluster enhancement (Smith & Nichols, 2009) was used to avoid selecting a cluster-defining threshold while retaining the advantages of the information gained from the spatial structure. RANDOMISE uses non-parametric permutation-based methods (5000 permutations) to estimate the significance of each predictor in a voxel while controlling for the number of voxels under consideration. Voxels examined were limited to the prefrontal cortex (including anterior and mid-cingulate). To probe significant interactions, we extracted the mean beta across each identified cluster for the relevant conditions and used partial correlations to examine lower-level relationships (i.e., correlations within the regulation factor).

Chapter 3

RESULTS

Descriptive Statistics and Bivariate Correlations

Descriptive statistics and bivariate correlations of key study variables are provided in Table 1.

Parental Anxiety X Valence X Regulation Interaction

No significant effects were found in the prefrontal cortex or amygdala.

Parent Anxiety Sensitivity X Valence Interaction

No significant effects were found in the prefrontal cortex or amygdala.

Parent Anxiety Sensitivity X Regulation Interaction

Voxelwise analyses revealed a significant 2-way interaction between ASI and regulation level (e.g., *regulate* vs. *react*) in 6 clusters (see Table 2). Interactions were probed by extracting the mean beta across each cluster separately for each participant and condition, and these data were entered into repeated-measures general linear models in SPSS (V.28). Specifically, we split by levels of the regulation factor and computed partial correlations between parental ASI and fMRI activation within each level (controlling for child CASI).

Probing the interaction for Cluster 1 in right inferior frontal gyrus (IFG; Figure 1.A) showed that ASI was positively correlated with activation during *react* ($r=.23$, $p=.005$), but not *regulate* ($r=.03$, $p=.70$) trials (Figure 3). In Cluster 2 in right insula

(Figure 1.E), the correlation between ASI and activation was not significant in either condition (*react*: $r=.16$, $p=.06$ *regulate*: $r=-.06$, $p=.50$) (Figure 4). In Cluster 3 in right ACC, ASI was positively correlated with activation during *react* ($r=.20$, $p=.02$), but not *regulate* ($r=-.04$, $p=.67$) (Figure 5). In Cluster 4 in right IFG/MFG, ASI was negatively correlated with activation during *regulate* ($r=-.15$, $p=.048$), but not *react* ($r=.16$, $p=.055$) (Figure 6). In Cluster 5 in left IFG/MFG, ASI was positively correlated with activation during *react* ($r=.25$, $p=.003$), but not *regulate* ($r=-.05$, $p=.60$) (Figure 7). In Cluster 6, which was quite large and had its peak values in bilateral OFC, the correlation between ASI and activation was not significant for either condition (*react*: $r=.16$, $p=.053$; *regulate*: $r=-.01$, $p=.23$) (Figure 8).

Region of interest analyses in amygdala revealed no significant interaction between ASI and the regulation factor.

Chapter 4

DISCUSSION

Adolescence is a developmental period marked by alterations in emotion regulation capacity and is the typical onset time for anxiety pathology. Although it is well-established that parental functioning is an important influence on youth development, the factors driving these associations, particularly with regard to anxiety, are not well understood. The goal of the present study was to identify the impact of parental levels of a key transdiagnostic predictor of anxiety (anxiety sensitivity) on their adolescents' brain circuitry while these youth performed an explicit emotion regulation task. We found that parental anxiety sensitivity was related to differences in regulation-related activation in a number of regions of their child's brain, including inferior frontal gyrus (IFG), insula, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC). Taken together, this study advances prior work by identifying brain regions in which parental anxiety sensitivity impacts their children's emotion regulation. Below, we discuss each of the observed clusters in turn.

Contrary to our hypotheses, greater parental anxiety sensitivity was associated with increased activation of right IFG (BA 44; Figure 1A) during *react* trials (Figure 3). Aron and colleagues (2014) have proposed that this region of right IFG functions as a brake on prepotent response tendencies, suggesting that greater parental anxiety sensitivity may lead to increases in regulation when actively engaging with the emotional aspects of stimuli. However, this interpretation begs the question as to why similarly high levels of right IFG activation were not observed during the *regulate* condition, as this

would presumably require an equal, or greater, level of regulation. One possibility is that activation in this region of right IFG may reflect a more automatic form of regulation than is recruited during the explicit *regulate* condition. In other words, if reappraisal is successful in the *regulate* condition, there will only be a weak affective response, which will not recruit such automatic regulation. However, this would imply that reappraisal does not recruit this region of right IFG, which is inconsistent with meta-analytic work (Buhle et al., 2014). An alternative interpretation is provided by work suggesting that this region of right IFG is crucially involved in the detection of salient cues in the environment, whether or not this is followed by the inhibition of prepotent responses (Hampshire et al., 2010). Thus, greater activation in this region during *react* may reflect enhanced detection of salient cues when affective responses are unfettered, whereas such salience detection may occur less often if reappraisal is successful (i.e., during *regulate*). If accurate, this interpretation would indicate that higher parental anxiety sensitivity is associated with greater salience detection in their children when affective responses are encouraged. One method by which this may occur is that parents with greater anxiety sensitivity are more likely to model behaviors signaling their own heightened emotional reactivity. In turn, their adolescents may mirror the elevated reactivity to salient stimuli observed in their parents. Indeed, the role of modeling as a potential mechanism in the relationship between parental anxiety sensitivity and adolescent emotional behaviors (e.g., reactivity) is supported by the dyadic social dynamic framework proposed by Perlman and colleagues (2022). This interpretation is also supported by previous studies implicating the right IFG in imitation or mirror network systems (Carr et al., 2003; Lee et

al., 2006; Lee et al., 2008; Rizzolatti & Craighero, 2004) and is consistent with work on brain structure linking IFG with emotional reactivity in mid-childhood (Ewell et al., 2023).

At higher levels of parental anxiety sensitivity, adolescents evidenced greater activation in right insula (BA 13; Figure 1B) during *react* than *regulate*, and this relationship is absent at low levels of parental anxiety sensitivity (Figure 4). This pattern of activation is consistent with the interpretation described above suggesting that adolescents of parents with greater anxiety sensitivity exhibit relatively greater responses to salient cues, compared to the adolescents of parents with lower anxiety sensitivity. Indeed, extant work has linked insula activation to the detection of salient stimuli and to emotion generation (Morawetz et al., 2016; Morawetz et al., 2017). In adults with clinical levels of anxiety, insula hyperactivation has been linked to the experience of negative emotional responses (Etkin and Wager, 2007). The present findings add to this line of work by suggesting that parental anxiety sensitivity confers risk for heightened insula reactivity in response to emotionally salient stimuli in their adolescents.

Greater parental anxiety sensitivity was associated with increased right ACC (BA 24; Figure 1C) activation during *react* (Figure 5), but not *regulate*. Previous work has implicated this region of ACC in the appraisal of emotional stimuli (Etkin et al., 2011) and the up-regulation of emotion (Etkin et al., 2006), which is consistent with our interpretation that adolescents who have parents with greater anxiety sensitivity will exhibit heightened emotional responsivity to pertinent stimuli. Another possible interpretation of this finding is that adolescents' natural responses during *react* may

involve automatic emotion regulation strategies, as discussed above for the cluster in BA 44. This interpretation is supported by previous work linking ACC with self-regulation and assessing the salience of emotional stimuli (Bush et al., 2011; Posner et al., 2007). Anxiety sensitivity can be interpreted as an anxiety amplifier (Taylor et al., 2007), as it involves heightened assessment of stimuli or sensations for possible negative consequences. Therefore, elevated activation of ACC during *react* trials in adolescents of parents with heightened anxiety sensitivity may reflect parental modeling of heightened assessment of salient stimuli.

Consistent with our hypothesis, greater parental anxiety sensitivity was associated with decreased activation in right posterior IFG/MFG (BA 11/47; Figure 1D) during *regulate* (Figure 6). In the context of past research, which has emphasized the role of this region in inhibitory control (Beauchamp et al., 2016; Liu et al., 2020), there are several possible interpretations of this finding. For example, parents with more anxiety sensitivity may generally exert more control over their children's lives, reducing the child's need to inhibit their own emotions or behaviors, because their parent is guiding them away from situations likely to produce aversive outcomes. Indeed, distinct types of parental control have been associated with externalizing behaviors (e.g., aggression; Barber et al., 1994), which are often associated with impaired cognitive control (Karlsgodt et al., 2018). Alternatively, decreased activation in such regulation-related regions might indicate that parents with greater anxiety sensitivity have children with greater impulsivity. This interpretation seems less likely given the significant correlation between parent and child anxiety sensitivity, yet more work examining the relationship

between parental anxiety sensitivity and impulsivity would be needed to further support this notion.

Activation in *left* IFG/MFG (BA 11/47; Figure 1E) showed a significant positive correlation with parental anxiety sensitivity during *react*. This pattern of activation is similar to that seen in the right IFG (BA 44) discussed above. Although a wealth of research (outlined above) has implicated *right* IFG as being more central to inhibitory control than left, a lesion study by Swick and colleagues (2008) suggested that left IFG is also critical for the implementation of inhibitory control. Thus, increased left IFG/MFG activation during *react* trials suggest that adolescents of parents with greater anxiety sensitivity may be attempting to engage in inhibitory control of emotional responses as an automatic response to emotional stimuli.

Finally, adolescents of parents with greater anxiety sensitivity evidenced greater activation for *react* than for *regulate* in a larger cluster that peaked in bilateral OFC (Figure 2), and this relationship was absent for adolescents of parents with lower levels of anxiety sensitivity (Figure 8). Although this cluster is large, and covers a number of regions, we focus our discussion here on the region with the strongest effect (OFC). OFC has been implicated in attention-related processes, including emotion-attention interactions (Mao et al., 2020; Perlman et al., 2014). Thus, parents with greater levels of anxiety sensitivity may be more likely to attend to stimuli that have the possibility to elicit anxiety-related sensations and subsequent negative interpretations. Together, a possible interpretation of this pattern of activation suggests that the adolescents of these parents may be copying their parents' increases in attention to environmental cues. More

work is needed to determine the role of neural development in this relationship, given that associations between the OFC and emotion-attention interactions are shown to be moderated by age (Perlman et al., 2014). As such, development of the OFC, including changes in functional connectivity with key structures (e.g., amygdala), may play a unique role in the development of emotion regulation-related attentional processes.

Integration Across Findings

Contrary to our hypotheses, greater parental anxiety sensitivity was associated with increased activation during *react* trials in a number of clusters. These regions have been implicated in various affective processes, including emotional reactivity (Etkin et al., 2015; Li et al., 2020; Morawetz et al. 2017). Despite a large emphasis on understanding the role of adaptive emotion regulation strategies (i.e., reappraisal), a growing literature suggests that up-regulation of emotion may serve as a maladaptive regulation strategy (Morawetz et al., 2017). Up-regulation of emotion refers to the process by which an individual increases the intensity of their emotional experience, thus, up-regulation of negative emotions serves to maladaptively increase or maintain such a negative emotional state (Morawetz et al., 2017).

Lateralization plays a key role in cognitive specialization (Craig et al., 2023), yet less is known about the developmental course of such specialization. Furthermore, down-regulation of emotions has been associated with greater right-lateralized neural activity (Morewetz et al., 2017), which is consistent with our results showing that IFG/MFG activation in the right hemisphere related to cognitive reappraisal was stronger in children

of parents with greater anxiety sensitivity. Together, results suggest that lateralization of the IFG/MFG is associated with specialization of emotion regulation processes. However, actual tests of lateralization are needed before any such conclusions can be drawn.

Clinical Implications

Broadly, the present findings flesh out the role of parental influence on the development of emotion regulation in youth. Our findings build upon the dyadic social dynamic model proposed by Perlman and colleagues (2022) by highlighting the role of parental anxiety sensitivity on adolescent emotion-related behaviors. The examination of anxiety sensitivity, a transdiagnostic factor thought to lead to anxiety pathology, is further aligned with the dyadic social dynamic model which emphasizes intervention implementation even in the absence of clinical diagnoses (for either parent or child). Present study findings extend this model by implicating the role parental influence into adolescence. Therefore, the parent-child dyad may be seen as a critical intervention target even in adolescence.

Findings from the present study also suggest potential targets for clinical interventions for children and parents experiencing anxiety symptoms. Specifically, findings underscore the important role that parental functioning has on adolescent emotion regulation, a transdiagnostic process implicated in anxiety disorders. Parents' own anxiety sensitivity may be a critical intervention target that promotes effective emotion regulation in their children. Indeed, parental anxiety management (plus child-focused cognitive behavioral therapy) has proven to be an effective treatment for

decreasing future anxiety diagnoses in children (Cobham et al., 1998; Cobham et al., 2010). Although a large portion of parent management training emphasizes behavioral strategies (Forgatch & Kjobli, 2016), it also promotes the use of parents' own emotion regulation skills in order to model effective regulation for their children (Khanna & Kendall, 2009). Similarly, interventions such as dialectical parenting promote emotion regulation skill acquisition for parents as a mechanism to promote co-regulation in times of heightened emotional reactivity and stress (Zalewski et al., 2020).

Strengths and Limitations

The present study addresses several significant gaps in previous work. First, the sample size is relatively large for a community developmental imaging study (n=147). Second, the present study utilizes an explicit emotion regulation task, allowing us to directly examine adolescents' reactivity and regulation-related alterations in neural activation. Third, the examination of parent characteristics (i.e., anxiety sensitivity) allows us to explore factors which may influence parenting practices and the emotional climate of the family, which have notable downstream effects on children's emotion regulation development. For example, a group-based approach does not leverage important heterogeneity *within* the groups and the use of arbitrary cutoffs leads to a number of difficulties (e.g., regression to the mean) (Preacher et al., 2005). This work on group differences can only inform us about the specific anxiety diagnoses examined and fails to elucidate processes in sub-clinical populations. Finally, the use of an early adolescent sample allows for the identification of neural mechanisms related to

alterations in transdiagnostic processes (e.g., emotion regulation) which have been shown to alter risk for psychopathology. The present study shows that parents, and their own anxiety, play a key role in their children's emotion regulatory processes despite adolescents' alleged decreased reliance on parents during this developmental period.

Despite several notable strengths, limitations must be considered when interpreting the present results. Although the sample size is relatively large, it is predominately white and non-Hispanic, making the generalizability of the findings to other sociodemographic groups less clear. The present study was also cross-sectional, limiting our ability to identify potential causal mechanisms in the relationship between parental anxiety sensitivity and child emotion regulation-related neural activation. The parent sample predominantly consisted of biological mothers, limiting our ability to understand the role biological fathers may play in their children's emotion regulation development. Finally, the focus on parental anxiety sensitivity in the present study is a strength in attempting to identify possible factors linking parent and child anxiety, but it is likely that there are additional parenting-relevant factors which warrant further study. For example, differences in parenting styles and parent-child relationship quality may be mechanisms which impact emotion regulation development in youth and should be examined in future research.

Future Directions

While the focus of the present study was to examine the relationship between parental anxiety sensitivity and neural mechanisms of children's emotion regulation, a

wealth of literature emphasizes the role of parenting style on children's emotional development (Morris et al., 2007). Future work examining the relationship between parental anxiety sensitivity and parenting styles would be an important next step to further understand the role of parents on their children's development of emotion regulatory capabilities. Advancing our understanding of the relationships between parents' emotion regulation and children's emotion regulation would allow us to parse the impact of both genetic and environmental factors on emotion regulation development. Further, given significant behavioral, affective, social, and neural changes across childhood and adolescence, future longitudinal research has the potential utility to critically inform etiological models of psychopathology. Implementing longitudinal research would also allow for the exploration of factors (i.e., adolescent emotion regulation) as potential mechanisms of parent-child transmission of anxiety (Perlman et al., 2022). Finally, examination of neural mechanisms of parents' emotion regulation may allow us to better explicate the role of genes vs. environment on children's emotion regulation development. Advanced imaging techniques such as hyperscanning (Nguyen et al., 2020; Nguyen et al., 2021) would provide unique insight into the impact of direct processes, such as modeling, by which risk for anxiety-related pathology may be passed from parents to their children. (Perlman et al., 2022; Reindl et al., 2018).

Conclusion

In summary, parents' own anxiety sensitivity plays a key role in their adolescent children's emotion regulation, an influence that can be seen at a neural level. The

identified neural regions, such as the inferior frontal gyrus, insula, anterior cingulate cortex, and OFC, are implicated in emotional reactivity and regulation processes. Significant associations between parental anxiety sensitivity and adolescents' emotion-regulation related neural circuitry, above and beyond their own anxiety sensitivity, suggests parents' anxiety sensitivity may be a unique risk factor in youth emotion regulation development. Together, these results have the potential to inform etiological models of emotion regulation and anxiety and suggest parents may be a key intervention target or protective factor against emotion dysregulation in adolescence.

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Appendix A

TABLES

Table 1. Demographics Characteristics, Descriptive Statistics, and Bivariate Associations

Measure	Mean/%	Bivariate Associations		
		CASI	ASI	Sex
Child ASI (M/SD)	28.41 (6.92)			
Parent ASI (M/SD)	16.84 (12.16)	0.17*		
Child Sex (F) <i>N</i> %	74 (50.3%)	0.03	0.07	
Child Age (M/SD)	12.07 (.90)	-0.02	0.01	0.07

Note. *N* = 147; Sex: Male = 1, Female = 2; ASI = Anxiety Sensitivity Index; CASI = Child ASI; **p* < .05

Table 2. Regions of activation in adolescents related to parental Anxiety Sensitivity Index scores

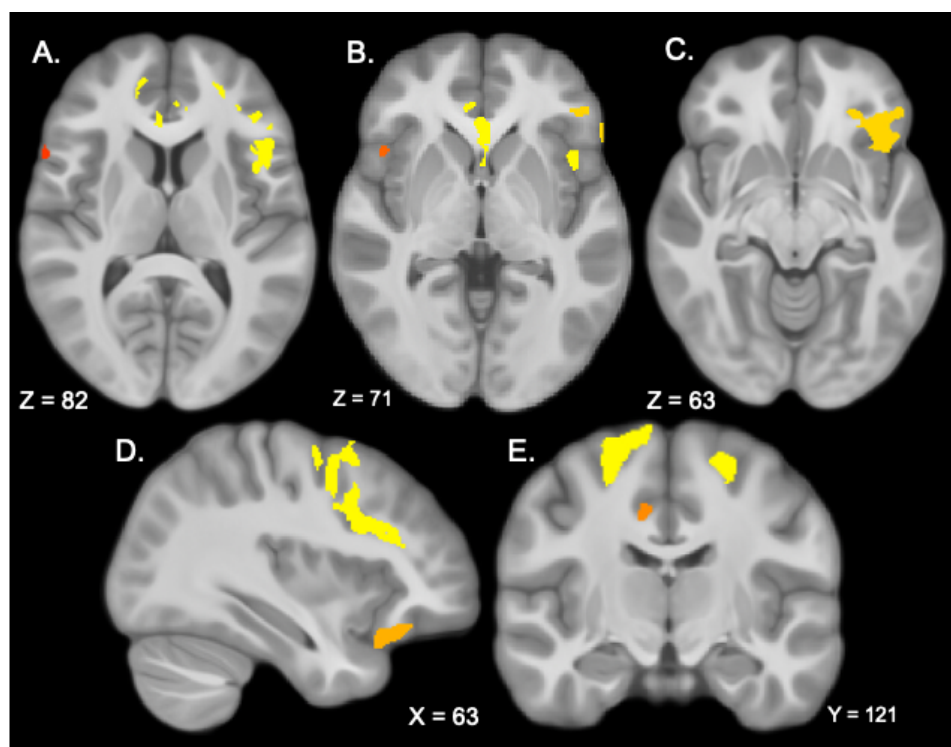
Cluster Number & Label	Size (mm³)	Center of Gravity MNI Coordinates (x,y,z)
ASI X Regulate vs. React		
1) Right IFG (BA 44)	61	59, 16, 9
2) Right Insula (BA 13)	62	46, 17, -1
3) Right ACC (BA 24)	119	11, -14, 43
4) Right IFG/MFG (BA 11 & 47)	2,084	43, 28, -21
5) Left IFG/MFG (BA 11 & 47)	4,577	-38, 40, -18
6) Peak in Bilateral OFC	38,444	8, 26, 20

Note. ASI = Anxiety Sensitivity Index; IFG = inferior frontal gyrus; ACC = anterior cingulate cortex; MFG = middle frontal gyrus; OFC = orbitofrontal cortex

Appendix B

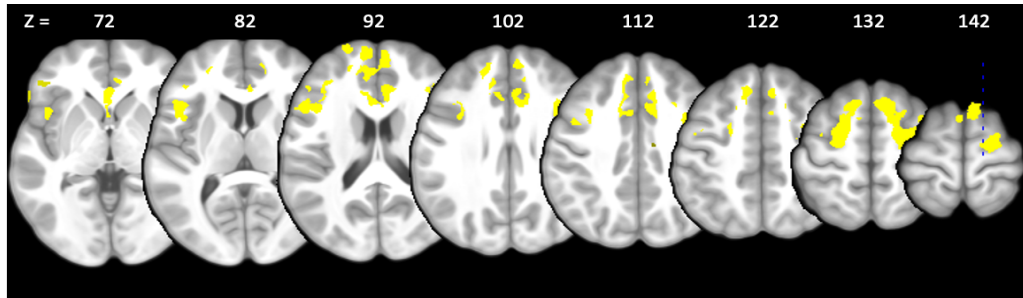
FIGURES

Figure 1. Clusters showing a 2-way interaction between parent and ASI and the regulation contrast



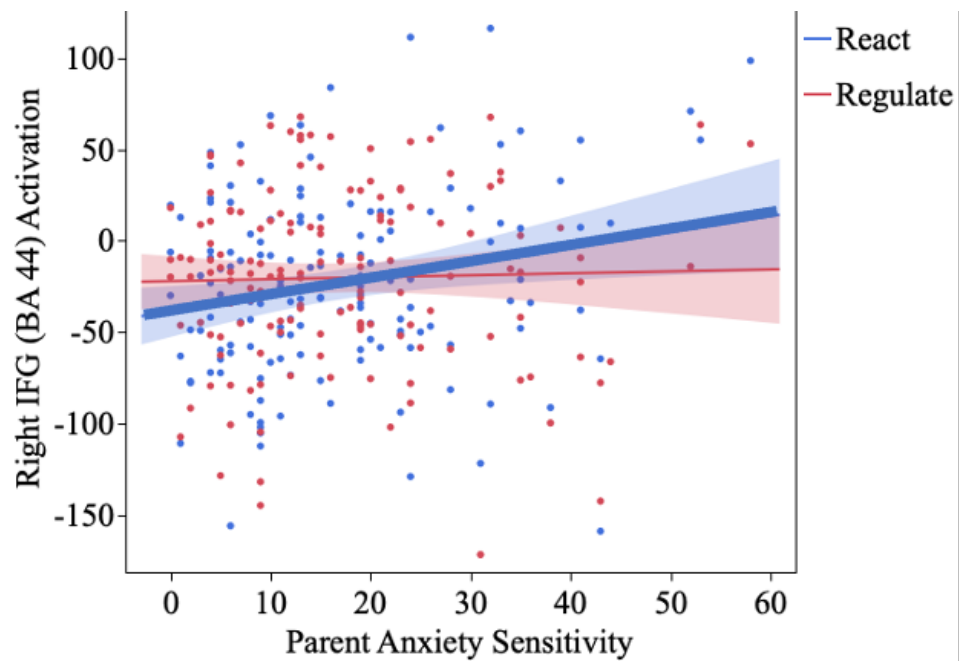
Note. IFG = inferior frontal gyrus; MFG = middle frontal gyrus; regulation contrast = *regulate* vs. *react*. Panels: (A) Cluster 1 in right IFG (red), (B) Cluster 2 in right insula (dark orange), (C) Cluster 5 in left IFG/MFG (medium yellow), (D) Cluster 4 in right IFG/MFG (light orange), (E) Cluster 3 in right ACC (medium orange). Cluster 6 (light yellow) is visible in all panels (see Figure 2 for a more comprehensive representation).

Figure 2. Cluster activation of the 2-way interaction between parent ASI and regulation level (regulate vs. react) peaking in bilateral OFC



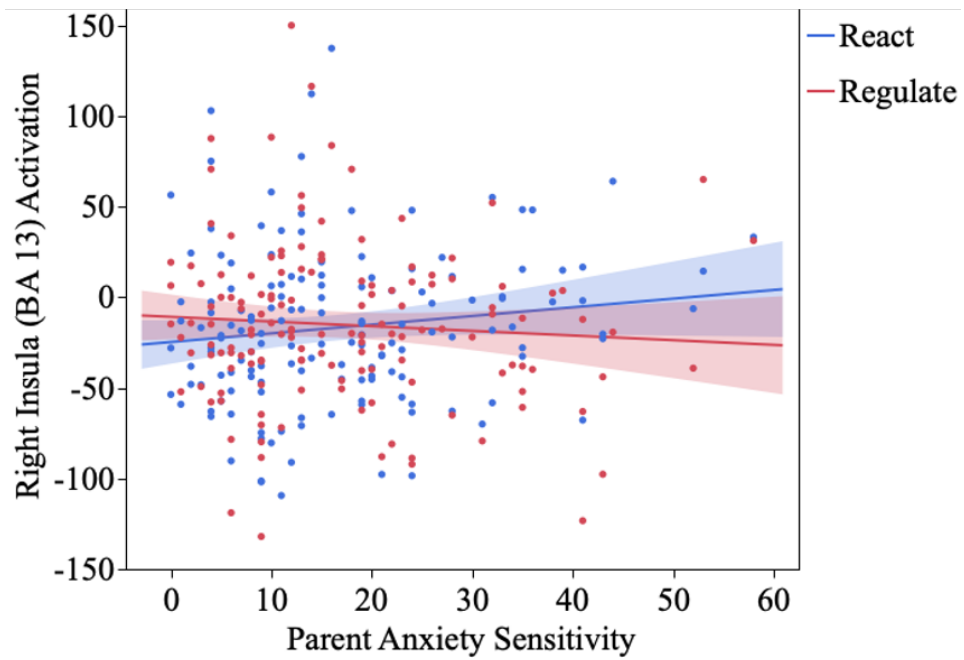
Note. OFC = orbitofrontal cortex

Figure 3. Interaction between right IFG activation and parental anxiety sensitivity



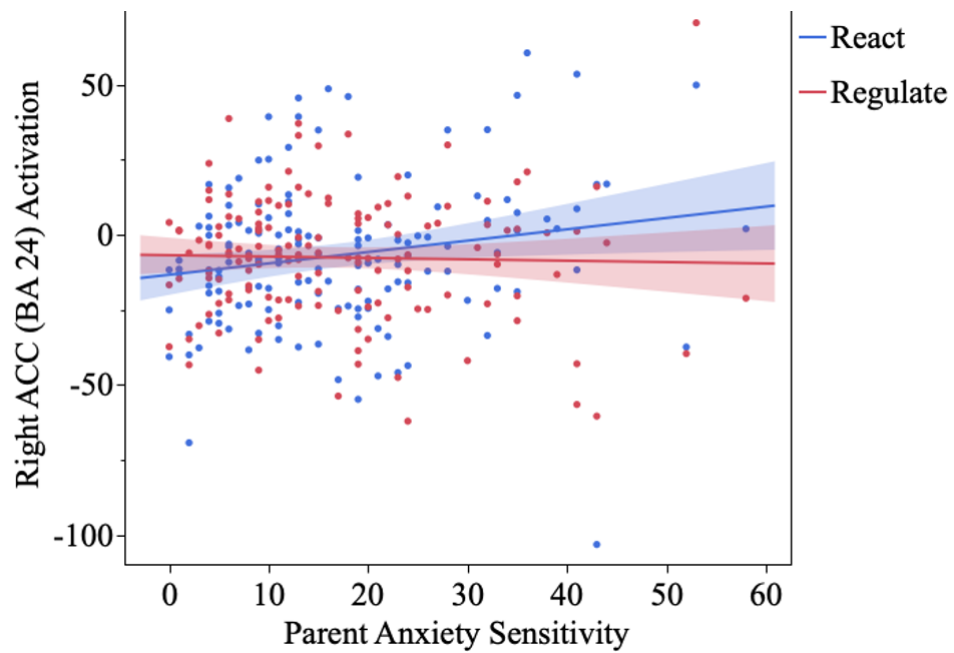
Note. IFG = inferior frontal gyrus; Parental anxiety sensitivity is positively associated with activation in the right IFG during *react* demands

Figure 4. Interaction between right insula and parental anxiety sensitivity



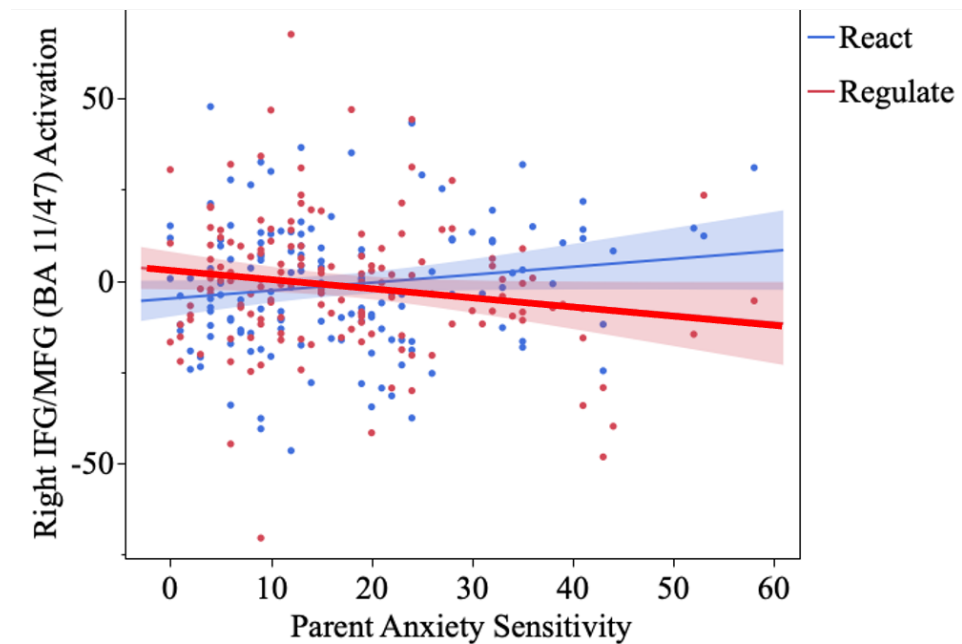
Note. Parental anxiety sensitivity trended toward a significant positive correlation with insula activation during *react* demands

Figure 5. Interaction between right ACC and parental anxiety sensitivity



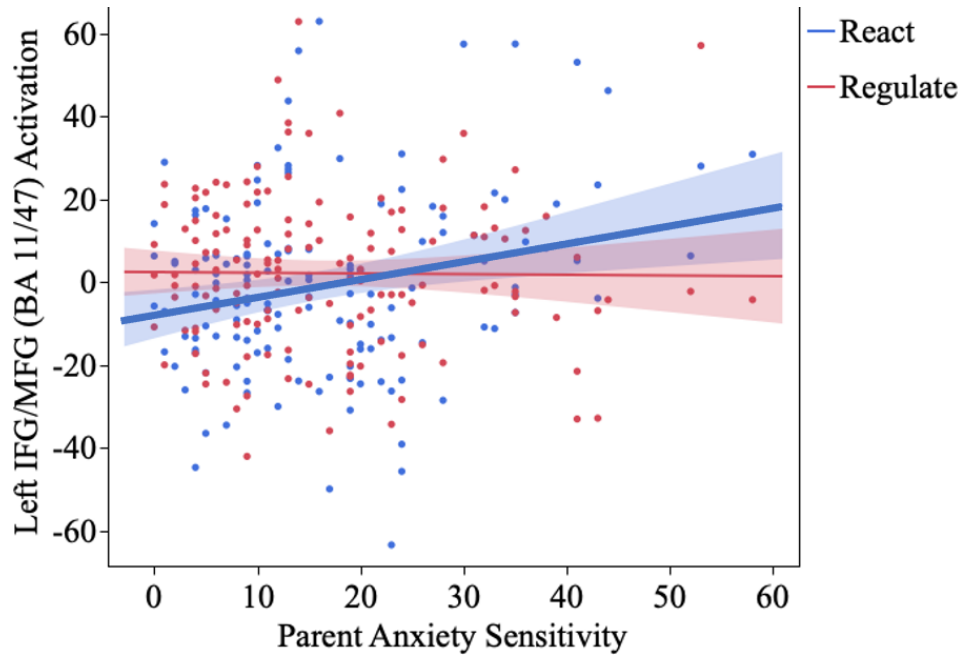
Note. ACC = anterior cingulate cortex; Parental anxiety sensitivity is positively associated with activation in the right ACC during react demands

Figure 6. Interaction between right IFG/MFG and parental anxiety sensitivity



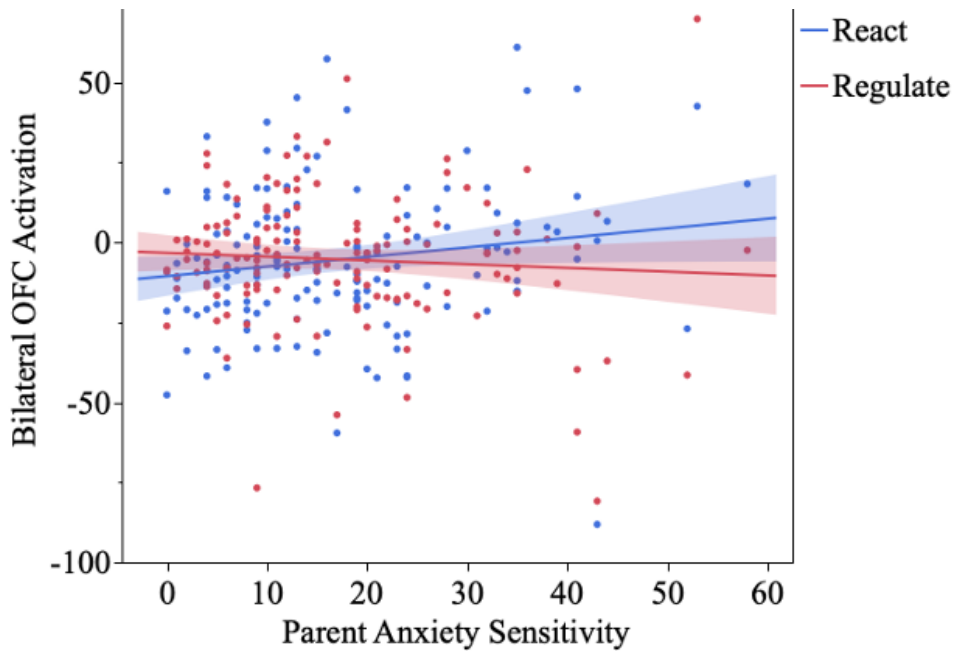
Note. IFG = inferior frontal gyrus; MFG = middle frontal gyrus; Parental anxiety sensitivity is negatively associated with activation in the right IFG/MFG during *regulate* demands

Figure 7. Interaction between left IFG/MFG and parental anxiety sensitivity



Note. IFG = inferior frontal gyrus; MFG = middle frontal gyrus; Parental anxiety sensitivity is positively associated with activation in the left IFG/MFG during *react* demand

Figure 8. Interaction between bilateral OFC and parental anxiety sensitivity



Appendix C

IRB APPROVAL LETTER OF DMECH



Institutional Review Board
210H HULLIHEN HALL
NEWARK, DE 19716
PHONE: 302-831-2137
FAX: 302-831-2828

DATE: August 7, 2019
TO: Jeffrey Spielberg
FROM: University of Delaware IRB
STUDY TITLE: [1464167-1] Testing a Dual Mechanism Model of Adolescent Anxiety & Related Sex Differences
SUBMISSION TYPE: New Project
ACTION: APPROVED
APPROVAL DATE: August 7, 2019
EXPIRATION DATE: July 16, 2020
REVIEW TYPE: Full Committee Review
REVIEW CATEGORY: Subpart D Determination- 45 CFR 46.404

Thank you for your New Project submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Full Committee Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on July 16, 2020. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix D

IRB APPROVAL LETTER OF RADARS



Institutional Review Board
210H Hulihan Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE: September 24, 2021
TO: Jeffrey Spielberg, Ph.D.
FROM: University of Delaware IRB
STUDY TITLE: [1784617-2] Testing a Dual Mechanism Model of Adolescent Anxiety
Development & Related Sex Differences
SUBMISSION TYPE: Revision
ACTION: APPROVED
APPROVAL DATE: September 24, 2021
EXPIRATION DATE: September 14, 2022
REVIEW TYPE: Full Committee Review

Thank you for your Revision submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Full Committee Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on September 14, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

INSTITUTIONAL REVIEW BOARD

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