DOES NEURAL RESPONSE TO PARENTAL CRITICISM MEDIATE THE ASSOCIATION BETWEEN PARENTAL WARMTH AND ADOLESCENT DEPRESSION?

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Submitted to the Graduate Faculty of the

Kenneth P. Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

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September 1, 2017

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University of Pittsburgh, 2017

The risk for depression rises during adolescence, particularly in adolescents with a history of anxiety. Prior studies have shown that parenting factors, including warmth, indirectly affect depressive outcomes through their influence on adolescent development of emotion processing and regulation. Yet, it is not known whether the influences of parental warmth on depression are attributed to the effects of warmth on the functioning of underlying neural networks implicated in emotion processing and depression. Using a longitudinal and ecologically valid design, this study assessed whether the functioning of neural emotion processing and regulation networks in response to personalized parental criticism mediates the relationship between parental warmth and depressive symptoms in adolescents with a history of clinical anxiety. Parental criticism is considered a salient negative and socially relevant stimulus for adolescents, given the increased parent-child conflict during this period. 47 adolescents (M=13.43, SD=1.37) participated in a study assessing the effects of child anxiety treatment on the subsequent development of depressive symptoms. Immediately following anxiety treatment, adolescents and their parent participated in a worry discussion task. Observed positive and supportive parental affect was coded by trained observers. Adolescents also reported on perceptions of parental acceptance. Two years later, adolescents completed a functional neuroimaging assessment. During the neuroimaging task, adolescents were presented with auditory stimuli of pre-recorded parental criticism. Neutral, non-personalized statements were also presented. One year later, adolescents reported on depressive symptoms. Neither parental

warmth assessed behaviorally nor using self-report were related to adolescent depressive symptoms three years later. After controlling for multiple comparisons, higher adolescent-reported perceptions of parental warmth predicted lower neural activation in response to criticism, compared to neutral statements, in the left amygdala, bilateral insula, subgenual anterior cingulate, dorsal anterior cingulate, and right ventrolateral prefrontal cortex. Mediation hypotheses were not supported. Findings suggest that when adolescents perceive their parents as warmer, their brains are less activated in response to criticism two years later, in both affective salience and emotion regulation networks. These results may indicate that warm and accepting parenting behavior plays a key role in shaping how the adolescent brain perceives threat within interpersonal contexts and regulates associated emotion.

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1.0 INTRODUCTION

Adolescence is an important developmental period in which youth experience many major social and biological transitions that can trigger negative emotion (Sontag, Graber, & Clemans, 2011; Wigfield, Eccles, Iver, Reuman, & Midgley, 1991). The experience of negative emotion throughout these transitions is normative throughout the adolescent years, but can become detrimental to the psychological well-being of some adolescents. This is evidenced by the rise in depression rate from 3% in childhood to 14-20% during adolescence (Birmaher et al., 1996; Hankin, 2006). Further, girls and children with a history of clinical anxiety are particularly at risk, with a two- to six-fold chance for the development of depression compared to boys and non-anxious youth, respectively (Bittner et al., 2007; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Cyranowski, Frank, Young, & Shear, 2000). Factors contributing to this rise in depression during adolescence include pubertal maturation (Forbes, Phillips, Silk, Ryan, & Dahl, 2011), dysregulation of negative emotionality (Keenan & Hipwell, 2005; Zeman, Cassano, Perry-Parrish, & Stegall, 2006), and family-related environmental factors such as low perceived parental warmth and acceptance (Ackard, Neumark-Sztainer, Story, & Perry, 2006; Brennan, Le Brocque, & Hammen, 2003; Greenberger & Chen, 1996; Yap & Jorm, 2015; Yap, Pilkington, Ryan, & Jorm, 2014).

Conceptual models have postulated that dysregulated negative emotion, or the inability to effectively regulate one's negative emotions, plays an important role in adolescent depression.

Specifically, these models posit that individuals at higher risk for depression respond to negative events with higher levels of negative emotion and have difficulty regulating this response (Hofmann, Sawyer, Fang, & Asnaani, 2012; Yap, Allen, & Sheeber, 2007). Furthermore, research has found that vulnerability to frequent and intense negative emotion is especially pronounced for depressed individuals within the context of interpersonal relationships (e.g. social and familial) and socially evaluative events (e.g. events in which the individual could be judged by others) (Biglan et al., 1985; Monroe, Rohde, Seeley, & Lewinsohn, 1999; Shih, Eberhart, Hammen, & Brennan, 2006). This could be a particularly important factor to consider in the development of depression in adolescents because the social context becomes highly salient due to the convergence of social, neural, and hormonal changes during this developmental period (Larson & Richards, 1991; Nelson, Leibenluft, McClure, & Pine, 2005; Rudolph & Hammen, 1999; Silk, Davis, McMakin, Dahl, & Forbes, 2012). Additionally, this heightened sensitivity to social evaluation is also present in anxiety disorders, which may explain why history of anxiety exacerbates risk for depression in adolescents (Silk et al., 2012). Changes in the functioning of fronto-limbic neural circuitry supporting emotion reactivity and regulation are posited to underlie the heightened emotional salience and reactivity to socially relevant information during adolescence (Nelson et al., 2005; Silk et al., 2012). Therefore, although behavioral research has shown that salient environmental factors, such as the quality of the parent-child relationship, contribute to youth's ability to regulate emotional reactivity, it may be especially important to the prevention of adolescent depression to understand how these environmental factors influence the neural circuits underlying emotion (Steinberg, 2005; Yap et al., 2007).

1.1 ROLE OF PARENTING IN SOCIALIZING EMOTION REGULATION AND LINKS TO ADOLESCENT OUTCOMES

Gottman, Katz, and Hooven (1996) theorized that children learn effective emotion regulation through warm, responsive, and communicative parenting behavior in response to a child's negative emotion. Accordingly, studies have demonstrated that parents' warmth and responsiveness to their children's distress play a central role in socializing their children's ability to regulate negative emotions and decrease risk for internalizing symptoms (see reviews by Bariola, Gullone, & Hughes, 2011; A. S. Morris, Silk, Steinberg, Myers, & Robinson, 2007; Thompson, 1994). Though much of this research has focused on younger children, it is believed that parental factors likely continue to effect emotion regulation development through adolescence, since the neural substrates of emotion regulation are still developing (A. S. Morris, Silk, Steinberg, Myers, & Robinson, 2007). For example, one study showed that self-regulation skills between grades 5 and 11 were predicted by parents' high levels of warmth, monitoring, and school involvement during 5th grade (Bowers et al., 2011).

As posited by previous researchers (A. S. Morris et al., 2007; Silk et al., 2007; Yap et al., 2007; Yap & Jorm, 2015), studies have also shown that parenting factors indirectly affect depressive outcomes through their influence on youths' development of emotion regulation (ER). For example, in younger children, negative maternal emotional expressivity has been linked to child psychological adjustment through its effects on the child's regulatory skills (Eisenberg et al., 2001; Gottman, Katz, & Hooven, 1996; Greenberg et al., 1999). In adolescents, the ability to self-regulate mediated the longitudinal associations found between both nurturing-responsive and harsh-conflictual parenting and future psychological functioning, partially indicated by depressive symptomology (Brody & Ge, 2001). Adolescents' observed and self-reported use of

maladaptive ER strategies have also been reported to mediate the relationship between mothers' dampening and invalidating behaviors during positive interaction tasks and adolescent depressive symptoms (Yap, Allen, & Ladouceur, 2008; Yap, Schwartz, Byrne, Simmons, & Allen, 2010). From these studies, the current study hypothesizes that these indirect effects may be attributed to the possible role of parents' warmth and acceptance on the development and function of adolescent fronto-limbic brain regions underlying emotion processing and regulation.

1.2 NEURAL NETWORKS OF EMOTION REGULATION IN RESPONSE TO SOCIAL THREAT

It has been suggested that individuals who experience low levels of parental warmth are more emotionally labile when faced with stressful events and are more likely to perceive threat within interpersonal contexts (i.e. social threat), compared to those who experience high levels of warmth and acceptance (Rohner, 2004). Given the high emotional salience of social feedback that occurs during adolescence, and especially in youth with a history of anxiety (Silk et al., 2014) the current study assesses emotional reactivity and regulation that occurs in response to personally relevant, critical evaluation made by adolescents' parents. Two key brain networks believed to underlie emotion processing and regulation include an affective salience network and an emotion regulatory network (Casey, Jones, & Hare, 2008; Phillips, Drevets, Rauch, & Lane, 2003; Phillips, Ladouceur, & Drevets, (2008). As described below, although much research has been conducted to delineate the functional roles of these networks, not many studies have focused on their function in response to social threat during adolescence.

1.2.1 Affective salience network.

Within the affective salience network, key regions, including the amygdala, anterior insula, and subgenual cingulate (sgACC), are implicated in identifying, appraising, and experiencing emotion in response to negative events (Baird et al., 1999; Casey et al., 2008; Guyer et al., 2008; Mayberg et al., 1999; J. S. Morris et al., 1996; Phan, Wager, Taylor, & Liberzon, 2002; Phillips et al., 2003; Reiman et al., 1997; Vogt, 2005). In response to negatively valenced stimuli, these areas are found to be hyperactive in adults and adolescents with clinical and or at high risk for depression (Fales et al., 2008; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Mayberg et al., 1999; Monk et al., 2008; Perlman et al., 2012; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). For example, when depressed adolescents have been asked to rate how afraid they were of fearful faces, maintain their emotional response to negative images, or complete a facial-emotion matching task, they exhibit greater amygdala activation compared to healthy adolescents (Beesdo, Lau, Guyer, & et al., 2009; Perlman et al., 2012; Yang et al., 2010).

Most studies have used general negative stimuli, such as negative emotional faces, to examine the association between brain function and depression, but only a few have employed more salient and ecologically valid stimuli to examine neural response specific to negative social evaluative feedback and its link to depression in adolescents. For example, researchers have utilized tasks that simulate online interactions in which participants believe they are interacting with two same-aged peers in another location. Specifically, within the Cyberball Game (Masten et al., 2011) and the Chatroom Interact (Silk et al., 2014) tasks, participants experience peer exclusion and rejection when they are led to believe that two other “players” choose to toss a ball among themselves, excluding the participant from the game, or when two other “peers” choose to interact with each other about various topics, rejecting the participant. During the Cyberball

task, whole-brain analyses have found that greater sgACC activity in 13-year-olds during social exclusion, compared to inclusion, was related to more adolescent depressive symptoms reported by their parents one year later (Masten et al., 2011). In the Chatroom task, region-of-interest analyses found that clinically depressed adolescents, ages 11 to 17, exhibited exacerbated response to simulated peer social rejection in the amygdala, sgACC, and insula, compared to their healthy counterparts (Silk et al., 2014).

Researchers have also used negative parental feedback as social threat stimuli. During the Parental Expressed Emotion task, adults and adolescents listen to pre-recorded, critical statements from their own parent while undergoing the fMRI scan (Hooley et al., 2009). Using the Parental Expressed Emotion task, formerly depressed adult women were found to respond to maternal criticism with greater amygdala activation than never depressed women in a region of interest analysis (Hooley et al., 2009). In healthy adolescents, a whole-brain analysis showed that greater activation in the insula was elicited during maternal criticism, compared to neutral statements (Lee, Siegle, Dahl, Hooley, & Silk, 2014). Furthermore, in a whole-brain analysis, differences in neural activation to maternal criticism have been found between healthy and depressed adolescents in an area related to emotional memory encoding, the parahippocampal gyrus (Silk et al., 2017). Lastly, region of interest analyses showed that higher levels of depressive symptoms in low-SES, adolescent girls were associated with greater activation in the right amygdala while listening to maternal criticism (Aupperle et al., 2016). These studies have shown that healthy, at-risk, and depressed adolescents show greater activation of affective salience brain regions in response to social threat.

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1.2.2 Emotion regulatory network.

Several regions of the prefrontal cortex, including the dorsolateral and ventrolateral regions (DLPFC; VLPFC), as well as the dorsal anterior cingulate (dACC), are postulated to underlie cognitive processes involved in regulating negative emotions (Casey et al., 2008; Goldin, McRae, Ramel, & Gross, 2008; Nelson & Guyer, 2011; Ochsner & Gross, 2005, 2008; Phan et al., 2002; Phillips et al., 2003; Phillips et al., 2008). Reduced activation in the DLPFC, VLPFC, and dACC have been found in healthy adults when intense sadness is induced during neuroimaging, suggesting that decreased regulatory control may be typical in the initial experience of sadness (Mayberg et al., 1999). However, when asked to actively regulate sadness or ignore negatively salient stimuli, both adults and adolescents typically exhibit increased activation in these regulatory regions (Fales et al., 2008; Goldin et al., 2008; Lévesque et al., 2004; Price, Paul, Schneider, & Siegle, 2013), supporting this network's engagement in emotion regulation processes. Most researchers conclude that, in response to negative emotionally salient stimuli and cognitive tasks, depressed adults and adolescents show reduced activity in cognitive regulatory brain regions compared to healthy populations (Diler et al., 2013; Fitzgerald, Laird, Maller, & Daskalakis, 2008; Halari et al., 2009; Ho et al., 2014; Holmes & Pizzagalli, 2008; Joormann, Cooney, Henry, & Gotlib, 2012; Siegle et al., 2007), although the adolescent research has been more mixed (Kerestes et al., 2014).

Especially relevant to the proposed project are prior studies assessing adolescents' response to social threat in relation to depression. In response to peer rejection, prolonged activation in the dACC was found in depressed adolescents using whole-brain analyses (Silk et al., 2014). Using the Parental Expressed Emotion task, healthy, 11-to-17 year old male and female adolescents, whole-brain analyses showed less sustained activation in the DLPFC and

caudal ACC while listening to parental criticism, relative to neutral feedback (Lee et al., 2014). Conversely, formerly depressed adult women exhibited lower response in the DLPFC and ACC to maternal criticism, compared to healthy women, in a region-of-interest analysis (Hooley et al., 2009). Using maternal criticism stimuli, these results have not been replicated using whole brain analyses in depressed adolescents, and were not a focus in region-of-interest analyses within at-risk girls (Aupperle et al., 2016; Silk et al., 2017). As shown, the current literature assessing neural response to parental criticism in adolescents with or at-risk for depression is very preliminary. Therefore, study hypotheses are based on the larger literature on emotion regulation suggesting that depression is associated with lower regulatory region activation.

1.3 POTENTIAL ROLE OF PARENTING IN FUNCTIONING OF NEURAL NETWORKS OF EMOTION REGULATION

Although limited, research has shown that both the affective salience and emotion regulatory networks play a role in processing and regulating response to threat and depression in adolescents. Even fewer studies to date have focused on understanding how parenting might affect the functioning of these networks during adolescence. Pertinent to the current study, only three studies to my knowledge have reported associations between parenting and adolescent neural response to threat in fronto-limbic regions (Elliott et al., Under Review; Guyer et al., 2015; Romund et al., 2016). Using a region of interest approach, one study found that greater adolescent-reported maternal warmth was associated with less amygdala reactivity in response to negative emotional faces, compared to neutral faces, in healthy 13-to-16 year old adolescents (Romund et al., 2016). The current study's sample of youth was drawn from a larger study on

child anxiety treatment. Results from the larger study showed that when parents were observed using more positive socialization behaviors that encouraged youth to face challenges, healthy adolescents exhibited lower activation in the right anterior insula and perigenual cingulate (pgACC), while anxious adolescents showed higher bilateral anterior insula reactivity in response to threat words (Elliott et al., Under Review). The third study assessed the link between parenting and brain function using neural response specific to social threat in the Chatroom task (Guyer et al., 2015). Results showed that adolescents who exhibited a behaviorally inhibited (BI) temperament during infancy and toddlerhood had lower amygdala response to peer rejection, relative to acceptance, if they had mothers who reported higher levels of authoritative parenting, characterized by warmth, support, and involvement. In contrast, those adolescents who had mothers reporting higher levels of authoritarian parenting, characterized by harsh and punitive behaviors, showed lower VLPFC response to peer rejection, relative to baseline. These studies suggest that healthy adolescents show less threat-related affective salience activation to negative stimuli when they have warmer and more supportive parents. Findings from these studies are less clear regarding the emotion regulatory network, as regulatory neural network activations were shown to be lower in both healthy adolescents with parents who had harsher parenting styles and in healthy adolescents who had parents who used positive coping socialization practices. Mixed results could be due to the differences in measures of parenting (i.e. self-report vs. observations), in task stimuli, or the limitations of the task designs in their ability to directly test emotion regulation. Broadly, however, these studies support that adolescents may still be susceptible to or dependent on the influence of parenting socialization behaviors for the neurodevelopment of emotion processing network function, although this has not been tested in a prospective, longitudinal study.

1.4 THE PRESENT STUDY

The present study will examine whether neural activation in regions within affective salience and/or emotion regulatory networks mediate the relationship between parental warmth and the development of depressive symptoms over three years in a sample of adolescents at high-risk for depression due to their history of anxiety. Limited evidence suggests that parenting practices are associated with the neural response to threat, and only one study has utilized a social threat paradigm to assess this link. Furthermore, no study has tested a neurodevelopmental model indirectly linking parental warmth to adolescent depressive symptoms through social threat processing in the brain. The current study will test this model in a sample of adolescents with a history of anxiety, given their high sensitivity to social evaluation and high-risk for depression. Understanding these links could be instrumental in supporting the development of targeted, parenting-based treatment and prevention practices specific to youth with history of anxiety.

To assess the proposed model, adolescents will complete the Parental Expressed Emotion task in which they will listen to critical feedback from their own parent during their neuroimaging scan. During the adolescent years, parent-child conflict increases substantially (Laursen & Collins, 2009). Therefore, parental criticism is believed to be a salient, socially threatening stimuli, that has been found to contribute to adolescent depression (Frye & Garber, 2005). While findings using this task in previous samples of healthy and depressed adolescents support that adolescent neural circuitry is also sensitive to parental feedback, (Lee et al., 2014; Silk et al., 2017), the current study will address several limitations. The current study will

expand on this literature by assessing parental behaviors on neural responses in a longitudinal design, as the previous studies have been cross-sectional. Given the mixed findings in the literature, a region of interest approach will be used to specifically assess research aims within the emotion regulatory network regions, in addition to the affective salience regions. In addition, out of the three previous studies assessing parental effects on adolescent threat processing and regulation in the brain, only one previous study used observational data to assess parenting behaviors. More broadly, according to a 2014 meta-analysis, most longitudinal studies assessing the relationship between parental warmth and adolescent depression have relied on self-report questionnaires of perceived parenting (Yap et al., 2014). Given the status of the current literature, the present study will utilize both adolescent-reports and observational data to measure parental warmth behaviors. Some researchers have argued that utilizing observational data is more representative of everyday functioning and helps to strengthen the ecological validity of study findings (Furr & Funder, 2007).

Participants in this sample ranged between 11 and 16 years of age, encompassing a developmental period in which neural and hormonal changes are occurring as a consequence of pubertal maturation (Nelson et al., 2005). Therefore, effects of pubertal status on the proposed model were considered. Given that research has also shown that adolescent girls are at a higher risk for depression, parenting may be especially relevant for this portion of the youth population. Although we have a limited sample size, the present study probed for gender differences in the model. Finally, the youth in this sample previously received one of two psychotherapy interventions (i.e. cognitive behavioral therapy [CBT] or child-centered therapy [CCT]) for their anxiety as part of a larger study. Although effects of treatment modalities on brain function are currently unknown, treatment response was found to predict later depressive symptoms among

adolescents who received CBT but not CCT (Silk et al., Under Review). Therefore, treatment-type (CBT vs. CCT) was included as a covariate in the analyses.

The main research aim of this study is to investigate the extent to which parental warmth indirectly influences the development of depressive symptomatology through its effects on neural processing of negative feedback from parents. Based on the literature reviewed above, hypotheses are:

Hypothesis 1. Lower levels of parental warmth will predict greater levels of depressive symptoms three years later.

Hypothesis 2. Lower levels of parental warmth will predict neural activation in response to parental criticism (compared to neutral feedback) two years later. Specifically:

a. Lower levels of parental warmth will be associated with greater activation in three regions within the affective salience network (i.e. amygdala, sgACC, and insula) in response to parental criticism.
b. Lower levels of parental warmth will be associated with reduced activation in three regions within the emotion regulatory network (i.e. DLPFC, VLPFC, and dACC) in response to parental criticism.

Hypothesis 3. Neural response to parental criticism within regions of the affective salience and cognitive regulatory networks (see a & b below) will mediate the relationship between earlier parental warmth and the later development of depressive symptomatology (H1).

a. Lower levels of parental warmth will predict higher depressive symptoms three years later through heightened response in the three regions within the affective salience network (i.e. amygdala, sgACC, and insula) to parental criticism.

b. Lower levels of parental warmth will predict higher depressive symptoms three years later through reduced response in the three regions within the emotion regulatory network (i.e. DLPFC, VLPFC, and dACC) to parental criticism.

Sensitivity Analyses: Sensitivity analyses will examine:

1) Whether the relationships described in Hypothesis 3 are maintained over and beyond:
    a. Anxiety symptoms at the time of the fMRI scan and one-year later
    b. Depressive symptoms at the time of the fMRI scan
2) Influences of adolescent pubertal status on neural response to criticism and depressive symptoms
3) Whether adolescent gender interacts with parental warmth to moderate mediation analyses

2.0 METHOD

2.1 PARTICIPANTS

Participants were 47 adolescents with a history of anxiety disorder and their primary caregivers, including 45 biological mothers and two fathers. Data were collected as part of the Child Anxiety Treatment Study (CATS) and the subsequent longitudinal Child Anxiety Treatment Study-Depression Follow-up (CATS-D) study. CATS was a randomized treatment study assessing predictors and correlates of treatment response to cognitive behavioral therapy (CBT) and child centered therapy (CCT) in anxious youths. Participants were recruited from the community through local media advertisements, referrals from pediatricians, school counselors, University mental health clinics, and other University research studies (Silk et al., 2013). At the original CATS assessment, 9-to-14-year-old anxious youth were required to meet DSM-IV criteria (American Psychiatric Association, 1994) for current generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and/or social phobia (SP). Youth were excluded if they received a primary diagnosis of major depressive disorder (MDD), obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), conduct disorder, substance abuse or dependence, or ADHD combined type or predominantly hyperactive-impulsive type. Exclusion criteria also included an IQ below 70 as assessed by the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999), or lifetime diagnoses of autism or Asperger's

syndrome, bipolar disorder, psychotic depression, schizophrenia, or schizoaffective disorder. Adolescents with metal braces or other metal objects in their body were also excluded due to participation in functional magnetic resonance imaging (fMRI) assessments. The study was approved by the University of Pittsburgh Institutional Review Board and informed consent and assent were obtained by participating youth and their primary caregivers.

A subset of participants from the CATS study were enrolled in the CATS-D study. The CATS-D study was designed to investigate risk factors for the onset of depression in youth with a history of anxiety. It involved annual psychiatric assessments for up to 4 years following the conclusion of treatment and a functional neuroimaging assessment two years after treatment. The present study includes the youth from the original CATS study that enrolled in CATS-D and completed the 2-year post-treatment fMRI scan.

Although, a total of 53 adolescents completed their 2-year fMRI assessment, six of these participants were removed from analyses due to fMRI task-related errors or participants falling asleep. Excluded adolescents did not differ from the included participants in age, gender, race, treatment type, anxious or depressive symptoms at 2-year fMRI assessment (*p's*>.05). At the time of the 2-year follow-up neuroimaging scan, which is the primary focus of the present study, these 47 adolescents ranged in age from 11- to 16-years-old (*M*=13.43, *SD*=1.37). The participants were equally distributed in gender (55.3% female) and were predominantly Caucasian (95.7%) (see Table 1 for demographics at all 3 time-points). Prior to treatment, all participants met criteria for at least one primary anxiety diagnosis. At 2-year, post-treatment, 61.7% (*n*=29) of the participants no longer met for any clinical diagnosis. The remaining participants (*n*=18) met for the following clinical diagnoses: at least one anxiety diagnosis

(*n*=14), ADHD (*n*=1), Tourette syndrome (*n*=1), and other (*n* =2) (see Table 1). Only one participant currently met for a comorbid diagnosis of depression (not otherwise specified).

Table 1. Participant characteristics

	T1 / Post-treatment	T2 / 2-year follow-up	T3 / 3-year follow-up
Child Age [M (SD)]	11.48 (1.38)	13.43 (1.37)	14.58 (1.32)
Gender [N (%) female]	26 (55.3)	26 (55.3)	26 (55.3)
Total Family Income ($10k's)	6.09 (3.17) [e]	6.35 (3.24) [i]	7.50 (2.64)
Head of Household Education [a]	5.85 (1.00)	5.87 (.99) [e]	6.07 (.96)
Race [N (%)]			
White, non-Hispanic	45 (95.7)	45 (95.7)	45 (95.7)
Black	1 (2.1)	1 (2.1)	1 (2.1)
Biracial	1 (2.1)	1 (2.1)	1 (2.1)
Treatment History [N (%)]			
CBT	28 (59.6)	28 (59.6)	28 (59.6)
CCT	18 (38.3)	18 (38.3)	18 (38.3)
Current DSM IV Diagnosis [N (%)]			
None	35 (74.5)	29 (61.7)	37 (78.7)
Anxiety disorder (1 or more)	10 (21.3)	14 (29.8)	8 (17.0)
GAD [1]	6 (12.8)	9 (19.2)	3 (6.4)
Social phobia	4 (8.5)	6 (12.8)	3 (6.4)
Specific phobia	2 (4.2)	6 (12.8)	1 (2.1)
Separation anxiety	3 (6.4)	1 (2.1)	1 (2.1)
ADHD	1 (2.1)	1 (2.1)	2 (4.2)
Tourette syndrome	0	1 (2.1)	1 (2.1)
Comorbid Depression NOS [2]	0	1 (2.1)	0
Enuresis	1 (2.1)	0	0
Other		2 (4.2)	0
Pubertal status [M (SD)] [b]	2.59 (1.17) [f]	3.18 (1.13)	3.77 (0.85) [j]
Anxiety symptoms, Child-report [M (SD)] [c]	18.22 (14.21) [g]	17.75 (10.84)	15.91 (11.44) [g]
Depressive symptoms, Child-report [M (SD)] [d]	8.82 (8.24) [h]	9.79 (9.75)	8.77 (9.81) [g]

[1] GAD=Generalized anxiety disorder; [2] NOS=Not otherwise specified; [a] Education levels (4=High School Graduate, 5=some college, 6=college degree, 7=graduate degree); [b] Pubertal symptoms=Pubertal Developmental Scale; [c] Anxiety symptoms=SCARED total score; [d] Depressive symptoms=MFQ total score; [e] n=45; [f] n=35, [g] n=44; [h] n=34; [i] n=46; [j] n=38

2.2 PROCEDURE

Prior to initial enrollment in the CATS Study, pre-screening phone interviews were completed with parents to determine eligibility. Participants and their parents were briefed on the details of the study and signed consent forms at their first laboratory visit. Caregivers and youth completed baseline questionnaires (including standard demographics) and were administered structured diagnostic interviews to confirm that they met DSM-IV criteria for current GAD, SAD, and/or SP disorder during their intake assessment. Participants were then randomized to participate in either a 16-week cognitive behavioral (CBT) or child centered (CCT) treatment (Silk et al., 2016). Participants randomized to the CBT treatment protocol (*n*=28) engaged in anxiety-management skill training, progressive muscle relaxation training, and anxiety-exposure sessions (Kendall & Hedtke, 2006). Participants randomized to the CCT treatment protocol (*n*=18) engaged in a non-directive therapy in which the therapist engaged in active listening, reflection, empathy, and encouragement to talk about feelings (CCT; Cohen, Deblinger, Mannarino, & Steer, 2004; Cohen, Mannarino, & Knudsen, 2005). Both protocols included parent participation in two sessions. Although, treatment response did not differ for youth treated with CBT compared to CCT at post-treatment, significantly more youth treated with CBT were still in recovery one year later (Silk et al., 2016). Type of treatment will be entered into statistical analyses as a covariate.

The current study will use data collected during post-treatment (T1), 2-year follow-up (T2), and 3-year follow-up assessments (T3) (see Figure 1). At the post-treatment visit, semi-structured diagnostic interviews were administered to primary caregivers and youth to assess the presence of any DSM-IV current or past psychiatric disorders. Primary caregivers and youth also completed questionnaires, including reports of caregiver's parental behaviors and symptoms of

anxiety and depression. Additionally, the dyad participated in parent-child behavioral observation tasks. Two years later, youth completed clinical interviews and symptom measures during a laboratory visit, and a functional magnetic resonance imaging (fMRI) assessment at a second visit (within approximately two to three weeks of their laboratory visit). One-year after the fMRI assessment, clinical interviews and anxiety and depression symptom questionnaires were completed.

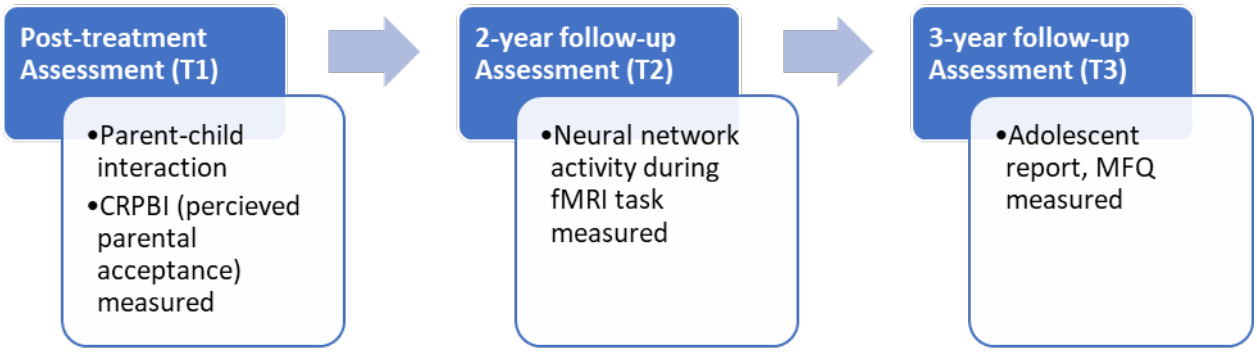

Figure 1: Timing of longitudinal assessments of study constructs

2.3 MEASURES

2.3.1 Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL)

The KSADS-PL (Kaufman et al., 1997) was completed at intake to confirm diagnosis for study eligibility and was repeated at all follow-up assessments. Trained bachelor's- and master's-level independent evaluators (IE's) interviewed parents and youth separately. Data from both informants were used to arrive at a preliminary diagnosis, and a child psychiatrist provided a

final diagnosis based on DSM-IV (American Psychiatric Association, 1994) criteria. Based on 20% of interviews, inter-rater reliability was high (κ=.89) for anxiety diagnoses.

2.3.2 Parent-child Interaction

Three parent-child behavioral observation tasks took place within the laboratory at post-treatment (T1). The worry conversation task will be used in the proposed analyses. The worry discussion task consisted of a five-minute conversation within which the dyad was asked to discuss a recent time when the child was worried (adapted from Suveg, Zeman, Flannery-Schroeder, & Cassano, 2005; Whaley, Pinto, & Sigman, 1999). This task was chosen as an ecologically valid paradigm selected specifically for its potential to induce emotionally salient responses from the participants.

The interaction task was video recorded. Parent and child behaviors were coded using an adapted version of the Living in Family Environments (LIFE) Coding System (Hops, 2007). This is an event-based coding system in which observers coded second-by-second speaker content from the video-recorded interaction. Parental warmth and acceptance was assessed using the "positive interpersonal" LIFE code. The "positive interpersonal" code focuses on warm, supportive, caring parental behavior delivered with positive affect. Relative duration of positive interpersonal behavior was calculated to reflect the proportion of time the parent spent displaying positive and caring affect and making approving or affirming statements (duration of positive interpersonal behavior/total duration of time the parent spent exhibiting all coded parental behaviors). Coding was conducted by extensively trained research staff who were blind to group and condition. Approximately 20% of the interactions were coded by a second observer to examine inter-rater reliability (κ=.76).

2.3.3 Child Report on Parental Behavior Instrument (CRPBI)

Adolescents completed a shortened version of the CRPBI (Schaefer, 1965; Schludermann & Schludermann, 1970) at their post-treatment assessment (T1). This 30-item, self-report questionnaire measures youth perceptions of their primary caregiver's behaviors on three constructs: acceptance, psychological control, and behavioral control. Parental acceptance is the construct of interest in the present study. This construct indicates child's perception of parental acceptance, warmth, and emotional support. Statements such as "My parent makes me feel better after talking over my worries with her," "…gives me a lot of care and attention," or "believes in showing her love for me" are rated as "not like", "somewhat like", or "a lot like" on a three-point Likert scale. This scale evidenced high internal consistency (α=.78) for the current sample.

2.3.4 Mood and Feelings Questionnaire (MFQ-C)

The Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988) is a 33-item self-report questionnaire assessing depressive symptoms in youth 8 to 18 years of age. Adolescents are asked to rate how true each item is of their mood and behavior within the past two-weeks on a three-point Likert scale (0 = "not true," 1 = "sometimes," 2 = "true"). Sample items include "I felt miserable or unhappy," "I cried a lot," "I slept a lot more than usual." The MFQ was administered at various points throughout the larger study. Adolescent-reported, total scores from the time of the scan (T2) will be used for sensitivity analyses. Adolescent-reported total scores from three-year follow-up assessment (T3) will be used as an outcome measure in the current project. If no assessment was available for participants at the three-year follow-up, their 2.5 year follow-up or 3.5 year follow-up (preferred) assessment was used. Using the two-year

follow-up assessment, high internal consistency (α=.96) has been established in the current sample. Higher total scores reflect greater symptomatology.

2.3.5 Screen for Childhood Related Anxiety Disorders (SCARED-C)

The Screen for Childhood Related Anxiety Disorders (SCARED-C; Birmaher et al., 1997) is a 41-item self-report questionnaire assessing symptoms of child and adolescent panic, separation anxiety, social phobia, generalized anxiety disorders and school refusal. It is validated for use in 8- to 18-year-old youth. Using the two-year follow-up assessment, high internal consistency (α=.92) has been established in the current sample. Sample items include "When I feel frightened, it is hard to breathe," "People tell me that I worry too much," "I worry about what is going to happen in the future." The SCARED-C was administered at various points throughout the larger study. Adolescent-reported, total scores from time of the scan (T2) and three-year follow-up assessment (T3) will be used to complete sensitivity analyses for the current project.

2.3.6 Pubertal Development Scale (PDS)

The Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) is a five item self-report that assesses physical development associated with pubertal changes. The current study used an adapted coding system (Shirtcliff, Dahl, & Pollak, 2009) that captures gonadal and adrenal hormonal signals of physical development on a 5-point scale. Pubic/body hair and skin changes were assessed in both boys and girls, as they are associated with adrenal hormones. Gonadal hormonal signals in girls are measured using questions about growth spurt, breast development, and menarche, whereas gonadal hormonal signals in boys are measured using

questions about growth spurt, deepening of voice, and facial hair growth. Total score from the PDS was used in sensitivity analyses for the current study.

2.4 FUNCTIONAL MAGNETIC RESONANCE IMAGING

2.4.1 Parental Expressed Emotion task

On the first day of the two-year follow-up assessment, primary caregivers were asked to create and record two 30-second clips describing aspects of their adolescents' behavior that bother them, two 30-second clips describing aspects of their adolescents' behavior that they especially like, and two 30-second neutral clips. Specifically, primary caregivers were asked to complete a worksheet in which they wrote down three ideas for each statement condition. They were then asked to choose two from each list, and with assistance from the experimenter, they recorded their statements into a computerized recording program. Each praise and critical statement began with a scripted introduction (i.e. "[Child's Name], one thing that I really like about you is…"; "[Child's Name], one thing that bothers me about you is..."). The neutral condition included primary caregivers' statements about the weather, or a trivial event that they felt the child would not be very interested in.

On the second day of the two-year follow-up assessment, youth underwent an fMRI assessment at a local brain imaging center. Participants were oriented to the scanner noises and were given time to practice the paradigms in a simulator machine. During the fMRI scan, participants completed a 10-minute structural scan, followed by a series of tasks including an adaptation of the Parental Expressed Emotion neuroimaging paradigm (Hooley et al., 2009;

Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005; Lee et al., 2014). During the scan, the primary caregiver's recorded clips were played over scanner-safe headphones in a block design. Specifically, there was a block (i.e. run) for each statement condition (praise, criticism, and neutral). Each block began with a 30.06 second rest period, followed by one 30.06 second statement presentation, a second rest period, the second statement presentation (same-condition), and a third rest period. Each run of the task followed this procedure and were each 2 minutes, 30 seconds long. The neutral block began the task for all participants, followed by either the praise and criticism blocks, which were counterbalanced across the sample. Following the fMRI assessment, participants were asked to read their parents' statements and rate their subjective emotions regarding each comment. Using a post-assessment valence and arousal form, they rated on a scale of 1 (not at all) to 10 (very) how positive and negative each comment was and how good and upset each comment made them feel.

2.4.2 Imaging Acquisition and Preprocessing

2.4.2.1 Apparatus Data were collected on a 3T Siemens Trio scanner. Thirty-two, 3.2mm slices were acquired parallel to the anterior-posterior commissure line using a T2* weighted reverse echo planar imaging pulse sequence (repetition time=1670 ms, echo time=29 ms, field of view=205 mm, flip angle=75). Scanning began at the first rest-period onset, and 18 scans were acquired per 30.06 second trial including both rest and stimulus types. Three conditions (criticism, praise, and neutral) were acquired during individual scan runs, lasting 2.5 minutes each. A total of 270 scans were acquired for the complete task (90 per session), in addition to high-resolution T1-weighted MPRAGE image (1mm, axial) for co-registration pre-processing procedures.

2.4.2.2 Preprocessing fMRI images were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Volumes were manually re-oriented to the AC-PC line, and slice timed. Images were next realigned to correct for head motion, segmented, and co-registered to a mean functional image. Realigned images were spatially normalized to a standard MNI template (Montreal Neurological Institute template) using a 12-parameter affine model. Normalized images were smoothed with a 6mm full-width at half-maximum Gaussian filter. Voxels were resampled during preprocessing to be $2mm^3$. Volumes with motion greater than 5mm/5º and global intensities more than 3 SD from the mean were detected using SPM ART toolbox. If no more than 25% of volumes per session were detected as outliers (n=0), volumes were repaired with interpolation using the ArtRepair toolbox. Repaired volumes were used for 1^{st} level analysis. Slow-drift motion correction was completed by including motion parameters as regressors in the GLM design in 1^{st} level analyses.

3.0 DATA ANALYTIC PLAN

3.1 FMRI

First-level analyses were conducted in SPM12 using repaired volumes from pre-processed data. All conditions from each run, including criticism, praise, neutral, and rest, along with six motion parameters, were included as regressors in the GLM design in 1st level analyses. All contrasts were created in the 1st level SPM designs. Two contrasts comparing criticism and neutral conditions to the average of all rest conditions throughout all three runs of the task (i.e. Criticism > RestAvg and Neutral > RestAvg), were used to confirm task-based condition effects. Using second-level analyses in SPM, BOLD activation in a whole-brain analysis at an uncorrected p-value of .005 was considered sufficient for the confirmation of task-based activation.

The contrast of interest for the current analyses was Criticism>Neutral. Group-level, one sample, t-test was completed in SPM using the 1st-level, Criticism>Neutral contrasts. The Marsbar toolbox was used to extract individual participant, mean activation data within a priori regions of interest (ROI) for Criticism>Neutral contrast. A priori regions of interest (ROI) were anatomically predefined by either Brodmann areas or the Automated Anatomical Labelling (AAL) atlas using the WFU PickAtlas Tool (v3.0.5). ROIs included the bilateral amygdala (AAL), bilateral anterior insula (AAL), sgACC (BA25), dACC (BA24/BA32), bilateral VLPFC (BA45/47), and bilateral DLPFC (BA8/BA9/BA46). Individual masks of each a priori ROI were

created for data extraction in Marsbar. If ROIs were divided into multiple sections in Marsbar, left sections and right sections were averaged to create a single left and right average, respectively, as needed for bilateral ROIs.

3.2 HYPOTHESES TESTING

Preliminary analyses in SPSS assessed bivariate correlations between sample characteristics including demographic information (age and gender) and T3 depressive symptoms (MFQ). If any significant relationships arose between descriptive variables and the T3 outcome measure ($p<.05$), they were included in the final analyses as covariates. Associations with race were not assessed due to a lack of data, as only two participants identified as non-White in the current sample. Treatment history (CBT vs CCT) was included in all analyses as a covariate, due to previous findings showing that depressive symptoms were predicted by treatment response within the CBT group (Silk et al., Under Review).

All final hypotheses were tested in SPSS, using the PROCESS macro (version 2.16.3; Hayes, A.F.). Individual PROCESS mediation models were completed to test hypotheses separately using individual, a priori ROIs (10). These models were run twice each, including one using observed parental warmth as the IV and the other using self-reported parental warmth/acceptance as the IV. F-test statistics for each path (i.e. total effect model, path a, path b) were used to determine significance of hypotheses. To account for multiple comparisons, p-values from individual path results for each ROI were entered into FDR correction analyses. This was completed separately for the two parenting measurement models. If the F-test survived FDR corrections ($p<.05$), the beta coefficient for parental warmth was used for interpretation.

Hypothesis 1, that T1 parental warmth would predict T3 depressive symptoms, was determined using the total effect, models. Hypotheses 2a and 2b, predicting that parental warmth at T1 would be associated with T2 neural response to parental criticism (versus neutral feedback), were determined by path a (i.e. IV to MED) models. Hypotheses 3a and 3b (i.e. indirect effect of T2 neural response to parental criticism on the relationship between T1 parental warmth and T3 depressive symptoms) were determined by indirect effect statistics, using the bootstrap (5000 samples) CI method. CBT/CCT was accounted for in all models. Models were re-run including pubertal status, T2 anxiety and depression symptoms, and T3 anxiety symptoms as co-variates for sensitivity analyses. The PROCESS macro does not allow the selection of specific variables to be co-varied from different model paths at one time. Therefore, all co-variates were accounted for across the full model in the sensitivity analyses. Moderated mediation models in PROCESS were used to assess gender effects.

4.0 RESULTS

4.1 PRELIMINARY RESULTS

Bivariate correlation analyses showed no significant associations between adolescent gender, T2 age, or T2 pubertal status and adolescent depressive symptoms at T3 (see Table 2 for associations). The sample of participants included only two non-White adolescents, therefore associations with race were not considered. T-tests showed no difference in T3 depressive symptoms between adolescents who completed CBT versus CCT anxiety treatments (t=.614, p=.542). Although no group differences were found between adolescents who completed the two therapy types in the current subsample, we previously found that treatment response predicted depressive symptoms in the CBT group, but not in the CCT group (Silk et al., Under Review), therefore therapy type (CBT vs. CCT) was included in all analyses as a covariate. Due to missing parenting data at T1 (observation data, n=10; self-report data, n=16) and/or missing T3 depressive symptom data (n=3), final model analyses will include subsamples of participants with full information available. Forty-four participants had available T3 depressive symptom assessments (i.e. 2.5-, 3.0-, or 3.5-year follow-ups). T3 depressive symptom outcomes were assessed approximately one year after the T2 fMRI assessment (M=12.53 months, SD=2.84). Models using observation data included 37 participants, and models using adolescent-report data included 31 participants.

Table 2. Correlation matrix of variables of interest

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16	17.	18.	19.	20.
1. Gender	1																			
2. Age	-.161	1																		
3. Pubertal status	.092	.669***	1																	
4. Therapy type	.304*	.237	.242	1																
5. Perceived warmth	-.165	-.201	-.107	.061	1															
6. Observed warmth	.030	.008	-.086	.061	.168	1														
7. DEP Sx (T2) [a, b]	.260	.247	.356*	.104	.078	-.314	1													
8. ANX Sx (T2) [a, c]	.338*	.097	.193	.323*	.166	-.103	.579***	1												
9. L Amygdala	.054	-.083	-.080	-.127	-.541***	-.271	-.103	-.255	1											
10. R Amygdala	.241	.036	-.101	-.018	-.280	-.248	.058	-.141	.711***	1										
11. L Anterior Insula	.101	-.023	-.118	.099	-.510***	-.131	-.098	-.247	.626***	.527***	1									
12. R Anterior Insula	.135	.016	-.097	.048	-.495***	-.202	-.026	-.164	.637***	.668***	.873***	1								
13. sgACC	.216	.116	.112	.094	-.516***	-.212	167	.108	.577***	.435***	.556***	.531***	1							
14. dACC	.166	-.154	-.145	.002	-.504***	-.129	.049	-.142	.680***	.516***	.725***	.726***	.714***	1						
15. L VLPFC	.127	-.075	-.173	.080	-.324	-.116	.012	-.121	.556***	.387***	.819***	.643***	.597***	.745***	1					
16. R VLPFC	.243	-.050	-.192	.083	-.478**	-.096	-.039	-.176	.467***	.403***	.712***	.729***	.568***	.736***	.736***	1				
17. L DLPFC	.062	-.245	-.289*	-.278	-.173	-.103	.033	-.175	.382**	.205	.293*	.278	.342*	.591***	.477***	.476***	1			
18. R DLPFC	.221	.002	.056	-.073	-.327	-.120	.372**	.006	.387**	.269	.345*	.404***	.465***	.695***	.500***	.605***	.554***	1		
19. DEP Sx (T3) [a, b, c]	.273	.199	.292	-.094	-.225	-.250	.562***	.353*	.023	.074	-.164	-.097	.164	-.002	-.074	-.013	-.119	.261	1	
20. ANX Sx (T3) [a, c, d]	.318*	.370*	.418***	.090	-.050	-.074	.530***	.546***	-.013	.113	-.233	-.144	.112	-.083	-.146	-.203	-.066	.112	.645***	1

*p<.05, **p<.010 ***p<.005; Note: L=left, R=right; [a] Sx=symptoms, [b] DEP=depressive, [c] ANX=anxiety, [d] n=44 for correlations with T3 Sx

4.2 HYPOTHESIS 1

The total effect models showed that neither T1 observed nor adolescent-reported parental warmth significantly predicted adolescent depressive symptoms at T3 (β=-.249, *B*=-30.920 (*SE*=20.694), *p*=.144; β=-.228, *B*=-.545 (*SE*=.441), *p*=.227).

4.3 HYPOTHESIS 2

4.3.1 Parental positive interpersonal observation

Parental positive interpersonal behavior at T1 did not significantly predict adolescent neural response to criticism at T2 in any of the ROIs within the affective salience network or within the cognitive regulatory network (see coefficients in Table 3 and Table 4, respectively). The overall model predicting variance in the left DLPFC was found to be significant (R^2=.434, F(2, 34)=3.937, $p_{\text{-uncorr}}$=.029). Model coefficients show that therapy treatment type was the significant predictor accounting for variance in left DLPFC activation. After family-wise FDR-threshold was applied to all ROI model statistics to account for multiple comparisons, the significant effect did not survive corrections for multiple comparisons (p_{FDR}=.290).

Table 3. T1 parental, positive interpersonal behavior (IV) and T3 adolescent depressive symptoms (DV) mediated by affective salience network ROIs (MED) (n=37)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c')	Indirect Effect (ab; β [bias-corrected CI])
L Amygdala	-	-.344 [1.202]		
Positive interpersonal behavior	-4.6230 [2.992]	-	-32.510 [21.703]	.013 [-.070, .164]
Therapy treatment type	-.607 [.518]	-.436 [3.704]		
R Amygdala	-	.234 [.848]		
Positive interpersonal behavior	-5.893 [4.241]	-	-29.538 [21.568]	-.011 [-.145, .063]
Therapy treatment type	-.485 [.734]	-.113 [3.655]		
L Anterior Insula	-	-1.827 [1.594]		
Positive interpersonal behavior	-1.332 [2.216]	-	-33.354 [20.708]	.020 [-.018, .132]
Therapy treatment type	-.251 [.384]	-.686 [3.588]		
R Anterior Insula	-	-1.217 [1.303]		
Positive interpersonal behavior	-2.877 [2.729]	-	-34.420 [21.069]	.028 [-.029, .180]
Therapy treatment type	-.384 [.472]	-.694 [3.624]		
Subgenual Cingulate	-	.757 [1.377]		
Positive interpersonal behavior	-3.137 [2.605]	-	-28.545 [21.351]	-.019 [-.160, .039]
Therapy treatment type	.126 [.451]	-.322 [3.624]		

$^{t}p<.100$, *p≤.050, **p≤.010, ***p≤.005; Note: analyses control for therapy treatment type

Table 4. T1 parental, positive interpersonal behavior (IV) and T3 adolescent depressive symptoms (DV) mediated by affective salience network ROIs (MED) (n=37)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c')	Indirect Effect (ab; β [bias-corrected CI])
Dorsal Anterior Cingulate	-	-.609 [1.690]		
Positive interpersonal behavior	-1.233 [2.128]	-	-31.671 [21.067]	.006 [-.032, .118]
Therapy treatment type	-.476 [.368]	-.517 [3.717]		
L VLPFC	-	-.748 [1.407]		
Positive interpersonal behavior	-1.293 [2.549]	-	-31.886 [20.994]	.008 [-.029, .131]
Therapy treatment type	-.434 [.441]	-.552 [3.672]		
R VLPFC	-	-.466 [1.578]		
Positive interpersonal behavior	-1.024 [2.280]	-	-31.397 [21.039]	.004 [-.026, .126]
Therapy treatment type	-.031 [.395]	-.241 [3.632]		
L DLPFC	-	-1.055 [1.050]		
Positive interpersonal behavior	-1.543 [3.380]	-	-32.547 [20.754]	.013 [-.019, .163]
Therapy treatment type	-1.593 [.585] **	-1.907 [3.953]		
R DLPFC	-	1.948 [1.175]		
Positive interpersonal behavior	-2.018 [2.946]	-	-26.990 [20.320]	-.032 [-.139, .010]
Therapy treatment type	-.587 [.510]	.917 [3.561]		

$^{t}p<.100$, *p≤.050, **p≤.010, ***p≤.005; Note: analyses control for therapy treatment type

4.3.2 Adolescent-reported parental warmth

Adolescent-reported parental warmth was significantly associated with neural activation in response to parental criticism in several ROI's within both the affective salience and cognitive control networks. Within the affective salience network, greater levels of reported warmth at T1 predicted less activation in the left amygdala, the bilateral insula, and the sgACC (see coefficients in Table 5). Within the cognitive control network, greater levels of reported acceptance at T1 predicted less activation in the dACC and right VLPFC (see coefficients in Table 6). Parental warmth did not predict activation in the right amygdala, left VLPFC, or bilateral DLPFC. To control for multiple comparisons, a family-wise FDR-threshold was applied to all ROI model statistics. Results after correction support that parental warmth and therapy type explained a significant proportion of variance in left amygdala (R^2=.307, F(2, 28)=6.203, p_{FDR}=.034), left insula (R^2=.274, F(2, 28)=5.277, p_{FDR}=.034), right insula (R^2=.265, F(2, 28)=5.039, p_{FDR}=.034), sgACC (R^2=.285, F(2, 28)=5.593, p_{FDR}=.034), dACC (R^2=.253, F(2, 28)=4.744, p_{FDR}=.034), and right VLPFC (R^2=.229, F(2, 28)=4.156, p_{FDR}=.043) activations. Model coefficients show that parental warmth was the significant predictor driving significant effects within all of the models. Models predicting right amygdala (R^2=.092), left VLPFC (R^2=.104), and bilateral DLPFC (L: R^2=.113; R: R^2=.121) activations did not pass FDR-thresholding ($p_{FDR} > .05$).

Table 5. T1 adolescent-reported parental warmth (IV) and T3 adolescent depressive symptoms (DV) mediated by affective salience network ROIs (MED) (n=31)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c')	Indirect Effect (ab; β [bias-corrected CI])
L Amygdala	-	-.149 [1.461]		
Parental warmth	-.194 [.058] ***	-	-.516 [.530]	-.012 [-.264, .227]
Therapy treatment type	-.442 [.521]	.831 [4.079]		
R Amygdala	-	.268 [.910]		
Parental warmth	-.134 [093]	-	-.509 [.464]	-.015 [-.288, .047]
Therapy treatment type	-.623 [.835]	.932 [4.061]		
L Anterior Insula	-	-3.095 [2.020]		
Parental warmth	-.130 [.040] ***	-	-.946 [.504] ᵗ	.168 [-.046, .445]
Therapy treatment type	-.055 [.361]	.594 [3.865]		
R Anterior Insula	-	-1.384 [1.472]		
Parental warmth	-.171 [.057] ***	-	-.781 [.508]	.099 [-.093, .408]
Therapy treatment type	-.373 [.509]	.248 [4.002]		
Subgenual Cingulate	-	1.259 [1.533]		
Parental warmth	-.180 [.055] ***	-	-.318 [.522]	-.095 [-.322, .116]
Therapy treatment type	.406 [.491]	.254 [4.027]		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses control for therapy treatment type

Table 6. T1 adolescent-reported parental warmth (IV) and T3 adolescent depressive symptoms (DV) mediated by emotion regulatory network ROIs (MED) (n=31)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c')	Indirect Effect (ab; β [bias-corrected CI])
Dorsal Anterior Cingulate	-	-.938 [1.942]		
Parental warmth	-.132 [.044] ***	-	-.668 [.515]	.052 [-.159, .292]
Therapy treatment type	-.102 [.390]	.670 [4.016]		
L VLPFC	-	-.872 [1.611]		
Parental warmth	-.093 [.052] ᵗ	-	-.626 [.471]	.034 [-.060, .168]
Therapy treatment type	.183 [.470]	.925 [4.017]		
R VLPFC	-	-1.649 [2.032]		
Parental warmth	-.118 [.041] **	-	-.739 [.504]	.081 [-.073, .316]
Therapy treatment type	-.063 [.370]	.661 [3.982]		
L DLPFC	-	-2.209 [1.234] ᵗ		
Parental warmth	-.055 [.065]	-	-.666 [.430]	.051 [-.032, .285]
Therapy treatment type	-.943 [.583]	-1.317 [3.982]		
R DLPFC	-	1.150 [1.346]		
Parental warmth	-.117 [.062] ᵗ	-	-.411 [.470]	-.056 [-.257, .045]
Therapy treatment type	-.230 [.558]	1.030 [3.987]		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses control for therapy treatment type

4.4 HYPOTHESIS 3

Models showed that neither neural activity in any of the ROI's, nor observed parental warmth, significantly predicted adolescent depressive symptoms at T3 (paths b and c′, respectively). All indirect effects testing mediation were non-significant (Table 3: affective salience network; Table 4: cognitive regulatory network). Similarly, no significant effects were found with adolescent-reported parental warmth (Table 5: affective salience network; Table 6: cognitive regulatory network).

4.5 SENSITIVITY ANALYSES

Sensitivity analyses controlled for T2 pubertal status, T2 adolescent depressive symptoms and anxiety symptoms, and T3 anxiety symptoms.

4.5.1 Hypothesis 1

4.5.1.1 Parental positive interpersonal observation The total effect model results showed that neither therapy treatment type (*B*=-1.909 (*SE*=2.813), *p*=.503), T2 depressive symptoms (*B*=.228 (*SE*=.155), *p*=.153), T2 anxiety symptoms (*B*=-.088 (*SE*=.166), *p*=.600), nor T2 pubertal status (*B*=.071 (*SE*=1.270), *p*=.956) significantly predicted T3 depressive symptoms. Anxiety symptoms at T3 was the only significant predictor of T3 depressive symptoms (*B*=.594

(*SE*=.149), *p*=.000). Parental warmth did not predict T3 depressive symptoms (*B*=-15.712 (*SE*=15.228), *p*=.310).

4.5.1.2 Adolescent-reported parental warmth The total effect model results showed that neither therapy treatment type (*B*=-3.415 (*SE*=3.607), *p*=.353), T2 depressive symptoms (*B*=.392 (*SE*=.250), *p*=.129), T2 anxiety symptoms (*B*=-.086 (*SE*=.278), *p*=.759), nor T2 pubertal status (*B*=.536 (*SE*=1.693), *p*=.754) significantly predicted T3 depressive symptoms. Anxiety symptoms at T3 was the only significant predictor of T3 depressive symptoms (*B*=.419 (*SE*=.183), *p*=.031). Parental warmth did not predict T3 depressive symptoms (*B*=-.454 (*SE*=.373), *p*=.235).

4.5.2 Hypothesis 2

4.5.2.1 Parental positive interpersonal observation Controlling for T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status, parental positive interpersonal behavior at T1 still did not significantly predict adolescent neural response to criticism at T2 in any of the ROIs within the affective salience network or cognitive regulatory network (see coefficients in Table 7 and Table 8, respectively). After controlling for multiple comparisons, results of family-wise FDR-thresholding showed that models predicting neural activation were not significant (p's-$_{FDR} > .05$).

Table 7. Sensitivity Analyses: T1 parental, positive interpersonal behavior (IV) and T3 adolescent depressive symptoms (DV) mediated by affective salience network ROIs (MED) (n=37)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c′)	Indirect Effect (ab; β [bias-corrected CI])
L Amygdala	-	.332 [.915]		
Positive interpersonal behavior	-5.954 [3.084] ᵗ	-	-13.737 [16.385]	-.023 [-.205, .139]
Therapy treatment type	.079 [.570]	-1.935 [2.856]		
T2 depressive Sx	-.005 [.031]	.230 [.158]		
T2 anxious Sx	-.050 [.034]	-.071 [.174]		
T3 anxious Sx	.036 [.030]	.582 [.154] ***		
T2 pubertal status	-.518 [.257] ᵗ	.243 [1.373]		
R Amygdala	-	-.046 [.645]		
Positive interpersonal behavior	-5.950 [4.384]	-	-15.987 [15.955]	.003 [-.115, .158]
Therapy treatment type	.438 [.810]	-1.889 [2.875]		
T2 depressive Sx	.038 [.045]	.230 [.160]		
T2 anxious Sx	-.089 [.048] ᵗ	-.092 [.178]		
T3 anxious Sx	.067 [.043]	.597 [.157] ***		
T2 pubertal status	-.737 [.366] ᵗ	.037 [1.376]		
L Anterior Insula	-	-.338 [1.206]		
Positive interpersonal behavior	-1.179 [2.342]	-	-16.110 [15.532]	.005 [-.034, .110]
Therapy treatment type	.079 [.433]	-1.883 [2.859]		
T2 depressive Sx	.025 [.024]	.237 [.161]		
T2 anxious Sx	-.036 [.026]	-.100 [.174]		
T3 anxious Sx	-.012 [.023]	.590 [.152] ***		
T2 pubertal status	-.167 [.195]	.015 [1.305]		
R Anterior Insula	-	-.516 [.973]		
Positive interpersonal behavior	-2.753 [2.893]	-	-17.131 [15.644]	.017 [-.034, .162]
Therapy treatment type	.106 [.534]	-1.854 [2.849]		
T2 depressive Sx	.031 [.030]	.244 [.160]		
T2 anxious Sx	-.051 [.031]	-.114 [.175]		
T3 anxious Sx	.003 [.028]	.596 [.150] ***		
T2 pubertal status	-.303 [.241]	-.085 [1.319]		
Subgenual Cingulate	-	.382 [.966]		
Positive interpersonal behavior	-2.482 [2.919]	-	-14.763 [15.631]	-.011 [-.166, .053]
Therapy treatment type	.277 [.539]	-2.015 [2.866]		
T2 depressive Sx	.025 [.030]	.218 [.160]		
T2 anxious Sx	-.023 [.032]	-.079 [.170]		
T3 anxious Sx	.007 [.028]	.591 [.151] ***		
T2 pubertal status	-.111 [.243]	.114 [1.293]		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses controlling for therapy treatment type, T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status

Table 8. Sensitivity Analyses: T1 parental, positive interpersonal behavior (IV) and T3 adolescent depressive symptoms (DV) mediated by emotion regulatory network ROIs (MED) (n=37)

Mediating Variable	IV ⟶ MED (path a; B [SE])	MED ⟶ DV (path b; B [SE])	IV ⟶ DV (path c′)	Indirect Effect (ab; β [bias-corrected CI])
Dorsal Anterior Cingulate	-	-.786 [1.292]		
Positive interpersonal behavior	-.673 [2.176]	-	-16.241 [15.415]	.006 [-.033, .131]
Therapy treatment type	-.028 [.402]	-1.931 [2.843]		
T2 depressive Sx	.038 [.022] ᵗ	.258 [.164]		
T2 anxious Sx	-.039 [.024]	-.119 [.175]		
T3 anxious Sx	.013 [.021]	.604 [.151] ***		
T2 pubertal status	-.393 [.181] *	-.238 [1.380]		
L VLPFC	-	-.302 [1.028]		
Positive interpersonal behavior	-.810 [2.748]	-	-15.956 [15.488]	.003 [-.039, .120]
Therapy treatment type	-.099 [.508]	-1.939 [2.859]		
T2 depressive Sx	.032 [.028]	.238 [.161]		
T2 anxious Sx	-.018 [.030]	-.093 [.169]		
T3 anxious Sx	-.006 [.027]	.592 [.151] ***		
T2 pubertal status	-.343 [.229]	-.032 [1.337]		
R VLPFC	-	.391 [1.154]		
Positive interpersonal behavior	-.633 [2.445]	-	-15.464 [15.475]	-.003 [-.116, .032]
Therapy treatment type	.310 [.452]	-2.031 [2.878]		
T2 depressive Sx	.030 [.025]	.216 [.162]		
T2 anxious Sx	-.029 [.027]	-.076 [.172]		
T3 anxious Sx	-.005 [.024]	.596 [.151] ***		
T2 pubertal status	-.265 [.204]	.175 [1.325]		
L DLPFC	-	-1.209 [.731]		
Positive interpersonal behavior	-.509 [3.669]	-	-16.327 [14.810]	.007 [-.066, .166]
Therapy treatment type	-1.294 [.683] ᵗ	-3.474 [2.894]		
T2 depressive Sx	.045 [.038]	.282 [.155] ᵗ		
T2 anxious Sx	-.015 [.040]	-.106 [.162]		
T3 anxious Sx	-.004 [.036]	.589 [.144] ***		
T2 pubertal status	-.368 [.308]	-.374 [1.264]		
R DLPFC	-	.283 [1.005]		
Positive interpersonal behavior	.995 [2.810]	-	-15.993 [15.499]	.003 [-.020, .084]
Therapy treatment type	-.381 [.519]	-1.801 [2.883]		
T2 depressive Sx	.092 [.029] ***	.202 [.183]		
T2 anxious Sx	-.055 [.031] ᵗ	-.072 [.177]		
T3 anxious Sx	.019 [.027]	.589 [.152] ***		
T2 pubertal status	-.200 [.234]	.128 [1.305]		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses controlling for therapy treatment type, T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status

4.5.2.2 Adolescent-reported parental warmth Controlling for T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status, parental acceptance at T1 still significantly predicted adolescent neural response to criticism within the affective salience network (see coefficients in Table 9), including the left amygdala, bilateral insula, sgACC, and within the cognitive regulatory network (see coefficients in Table 10), including the dACC and right VLPFC. After controlling for multiple comparisons, results of family-wise FDR-thresholding showed that models predicting neural activation were no longer significant (*p's-$_{FDR}$* > .05). Given that none of these potentially confounding variables significantly contributed to variance in models, it is likely that the power to detect model effects was reduced.

Table 9. Sensitivity Analyses: T1 adolescent-reported parental warmth (IV) and T3 adolescent depressive symptoms (DV) mediated by affective salience network ROIs (MED) (n=31)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c′)	Indirect Effect (ab; β [bias-corrected CI])
L Amygdala	-	-.853 [1.211]		
Parental warmth	-.165 [.063] *	-	-.595 [.426]	.075 [-.166, .497]
Therapy treatment type	-.440 [.614]	-3.790 [3.684]		
T2 depressive Sx	.062 [.043]	.445 [.263]		
T2 anxious Sx	-.062 [.047]	-.139 [.291]		
T3 anxious Sx	.017 [.031]	.434 [.186] *		
T2 pubertal status	.210 [.288]	.715 [1.730]		
R Amygdala	-	-.461 [.787]		
Parental warmth	-.120 [.098]	-	-.509 [.389]	.029 [-.073, .438]
Therapy treatment type	-.394 [.949]	-3.596 [3.670]		
T2 depressive Sx	.128 [.066] ᵗ	.451 [.273]		
T2 anxious Sx	-.092 [.073]	-.129 [.291]		
T3 anxious Sx	.045 [.048]	.440 [.189] *		
T2 pubertal status	-.527 [.445]	.293 [1.766]		
L Anterior Insula	-	-1.901 [1.785]		
Parental warmth	-.134 [.043] ***	-	-.709 [.442]	.136 [-.135, .487]
Therapy treatment type	-.037 [.411]	-3.486 [3.597]		
T2 depressive Sx	.038 [.028]	.464 [.258] ᵗ		
T2 anxious Sx	-.012 [.032]	-.108 [.278]		
T3 anxious Sx	-.033 [.021]	.357 [.192] ᵗ		
T2 pubertal status	.019 [.193]	.573 [1.689]		
R Anterior Insula	-	-1.359 [1.257]		
Parental warmth	-.169 [.060] **	-	-.684 [.428]	.122 [-.083, .415]
Therapy treatment type	-.293 [.584]	-3.813 [3.613]		
T2 depressive Sx	.079 [.040] ᵗ	.500 [.268] ᵗ		
T2 anxious Sx	-.043 [.045]	-.144 [.282]		
T3 anxious Sx	-.020 [.030]	.391 [.184]		
T2 pubertal status	-.096 [.274]	.405 [1.691]		
Subgenual Cingulate	-	-.533 [1.341]		
Parental warmth	-.174 [.058] **	-	-.546 [.445]	.049 [-.250, .470]
Therapy treatment type	-.004 [.559]	-3.417 [3.672]		
T2 depressive Sx	.059 [.039]	.424 [.266]		
T2 anxious Sx	-.013 [.043]	-.093 [.283]		
T3 anxious Sx	-.003 [.028]	.417 [.187]		
T2 pubertal status	.240 [.262]	.663 [1.753] *		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses controlling for therapy treatment type, T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status

Table 10. Sensitivity Analyses: T1 adolescent-reported parental warmth (IV) and T3 adolescent depressive symptoms (DV) mediated by emotion regulatory network ROIs (MED) (n=31)

Mediating Variable	IV → MED (path a; B [SE])	MED → DV (path b; B [SE])	IV → DV (path c')	Indirect Effect (ab; β [bias-corrected CI])
Dorsal Anterior Cingulate	-	-1.574 [1.642]		
Parental warmth	-.114 [.046] *	-	-.633 [.417]	.095 [-.074, .355]
Therapy treatment type	-.035 [.449]	-3.470 [3.614]		
T2 depressive Sx	.061 [.031] ᵗ	.488 [.269] ᵗ		
T2 anxious Sx	-.053 [.035]	-.170 [.292]		
T3 anxious Sx	.000 [.023]	.419 [.183] *		
T2 pubertal status	.109 [.211]	.708 [1.705]		
L VLPFC	-	-1.091 [1.344]		
Parental warmth	-.094 [.057]	-	-.557 [.396]	.055 [-.031, .285]
Therapy treatment type	.062 [.552]	-3.347 [3.634]		
T2 depressive Sx	.061 [.038]	.459 [.265] ᵗ		
T2 anxious Sx	-.020 [.042]	-.108 [.281]		
T3 anxious Sx	-.025 [.028]	.392 [.187]		
T2 pubertal status	.062 [.259]	.603 [1.707] ᵗ		
R VLPFC	-	-.998 [1.785]		
Parental warmth	-.124 [.043] **	-	-.577 [.438]	.066 [-.132, .300]
Therapy treatment type	.030 [.419]	-3.386 [3.660]		
T2 depressive Sx	.053 [.029] ᵗ	.446 [.271]		
T2 anxious Sx	-.023 [.032]	-.109 [.285]		
T3 anxious Sx	-.020 [.021]	.399 [.189] *		
T2 pubertal status	-.176 [.196]	.360 [1.746]		
L DLPFC	-	-2.839 [.981] **		
Parental warmth	-.011 [.068]	-	-.485 [.326]	.017 [-.177, .200]
Therapy treatment type	-.511 [.657]	-4.865 [3.194]		
T2 depressive Sx	.086 [.045] ᵗ	.637 [.234] *		
T2 anxious Sx	-.115 [.051] *	-.413 [.268]		
T3 anxious Sx	.026 [.033]	.492 [.162] **		
T2 pubertal status	.079 [.308]	.759 [1.483]		
R DLPFC	-	-.273 [1.208]		
Parental warmth	-.101 [.064]	-	-.481 [.399]	.015 [-.111, .160]
Therapy treatment type	-.494 [.622]	-3.550 [3.729]		
T2 depressive Sx	.100 [.043] *	.420 [.282]		
T2 anxious Sx	-.051 [.048]	-.100 [.290]		
T3 anxious Sx	.003 [.032]	.420 [.187] *		
T2 pubertal status	.157 [.292]	.579 [1.738]		

ᵗp<.100, *p≤.050, **p≤.010, ***p≤.005; Note: analyses controlling for therapy treatment type, T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status

4.5.3 Hypothesis 3

4.5.3.1 Parental positive interpersonal observation Controlling for T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status, neither ROI neural activations nor parental acceptance significantly predicted adolescent depressive symptoms at T3 (paths b and c′, respectively). After family-wise FDR corrections, results showed that all models explained a significant amount of variance in T3 depressive symptoms: bilateral amygdala (L: R^2=.610, F(7, 29)=6.493, p_{FDR} < .001; R: R^2=.609, F(7, 29)=6.447, p_{FDR} < .001), bilateral insula (L: R^2=.610, F(7, 29)=6.474, p_{FDR} < .001; R: R^2=.612, F(7, 29)=6.548, p_{FDR} < .001), sgACC (R^2=.611, F(7, 29 =6.502, p_{FDR} < .001), dACC (R^2=.614, F(7, 29) = 6.581, p_{FDR} < .001), bilateral VLPFC (L: R^2 = .610, F(7, 29)=6.477, p_{FDR} < .001; R: R^2=.610, F(7, 29)=6.487, p_{FDR} < .001), bilateral DLPFC (L: R^2=.642, F(7, 29)=7.444, p_{FDR} < .001; R: R^2=.610, F(7, 29)=6.474, p_{FDR} < .001). Significant variance in these models was primarily driven by the effects of T3 anxious symptoms. All indirect effects testing mediation were non-significant [see coefficients in Table 7 (affective salience network) and Table 8 (cognitive regulatory network)].

4.5.3.2 Adolescent-reported parental warmth Controlling for T2 depressive and anxious symptoms, T3 anxious symptoms, and T2 pubertal status, neither ROI neural activations within the affective salience network nor parental acceptance significantly predicted adolescent depressive symptoms at T3 (paths b and c′, respectively; see Table 9). Results within the cognitive regulatory network showed that greater activation to parental criticism in the left DLPFC was a significant predictor of lower levels of adolescent depressive symptoms at T3. All other cognitive regulatory ROIs remained non-significant predictors of T3 depressive symptoms (i.e. path b). All direct effects of parental acceptance on T3 depressive symptoms (i.e. path c′)

also remained non-significant. After family-wise FDR corrections, results showed that all models did explain a significant amount of variance in T3 depressive symptoms: bilateral amygdala (L: R^2=.512, F(7, 23)=3.443, p_{FDR}=.014; R: R^2=.509, F(7, 23)=3.399, p_{FDR}=.014), bilateral insula (L: R^2=.525, F(7, 23)=3.626, p_{FDR}=.014; R: R^2=.525, F(7, 23)=3.636, p_{FDR}=.014), sgACC (R^2=.505, F(7, 23)=3.346, p_{FDR}=.014), dACC (R^2=.520, F(7, 23)=3.564, p_{FDR}=.014), bilateral VLPFC (L: R^2=.515, F(7, 23)=3.490, p_{FDR}=.014; R: R^2=.508, F(7, 23)=3.391, p_{FDR}=.014), bilateral DLPFC (L: R^2=.634, F(7, 23)=5.701, p_{FDR}=.010; R: R^2=.502, F(7, 23)=3.316, p_{FDR}=.014). Significant variance in these models was primarily driven by the effects of T3 anxious symptoms. All indirect effects testing mediation remained non-significant [see coefficients in Table 9 (affective salience network) and Table 10 (cognitive regulatory network)].

4.6 MODERATION EFFECTS OF GENDER ON MEDIATION MODELS

4.6.1 Parental positive interpersonal observation

Gender had a main effect on the right DLPFC (B=1.012 (SE=.483), t(32)=2.095, p=.044), such that girls had greater DLPFC activation to parental criticism than boys. Gender did not have a main effect on neural response to criticism in any other ROI (t's=.667-1.700, p's>.05). Gender did not moderate the relationship between parenting and neural response to criticism in any of the ROIs (t's=-.970-.758, p's>.05). No significant moderated mediation effects were found in affective salience ROI models (Index range = -.821 to 6.852, CI range [LLCI = -26.327 to -7.348, ULCI = 11.912 to 57.398]) or cognitive regulatory ROI models (Index range = -.374 to 4.988, CI range [LLCI = -25.652 to -9.293, ULCI = 13.839 to 74.087]).

4.6.2 Adolescent-reported parental warmth

Gender did not have a main effect on neural response to criticism in any ROI (*t's*=-.259-.923, *p's*>.05). Gender did not moderate the relationship between parenting and neural response to criticism in any of the ROIs (*t's*=-1.021-.237, *p's*>.05). No significant moderated mediation effects were found in affective salience ROI models (Index range = -.115 to .082, CI range [LLCI = -.908 to -.473, ULCI = .156 to 1.113]) or cognitive regulatory ROI models (Index range = -.033 to .066, CI range [LLCI = -1.651 to -.260, ULCI = .299 to 1.428]).

5.0 DISCUSSION

Much of psychological research to-date has shown that parenting behaviors have important effects on child and adolescent outcomes, including emotion regulation abilities, psychosocial functioning, and the development of depressive symptoms (Bariola et al., 2011; A. S. Morris et al., 2007). However, very few studies have explored whether these behavioral effects can be attributed to parental influences on the function of underlying emotion processing networks. Findings from the present study suggest that the extent to which adolescents perceive their parents as warm is related to how their brain activates to personally relevant criticism from their parents two years later. Contrary to our hypotheses, results failed to show that parental warmth was directly or indirectly associated with depressive symptoms in previously anxious adolescents. However, findings do provide further evidence that parenting factors continue to play an influential role in brain processes that are still malleable during adolescence (A. S. Morris et al., 2007). Specifically, we found that greater perceived parental warmth predicted lower neural reactivity to parental criticism. These effects were widespread, occurring in both the affective salience network (i.e., left amygdala, bilateral insula, and sgACC), and emotion regulatory network (i.e. dACC and right VLPFC). Findings suggest that positive parental socialization behaviors occurring during early adolescence, as opposed to only in early childhood (Guyer et al., 2015), are still important in the development of emotion processing and regulation throughout adolescence.

As hypothesized, higher adolescent-reported parental warmth and acceptance was linked to lower left amygdala, bilateral insula, and sgACC activation in response to parental criticism two years later. These brain regions are considered part of the affective salience network that has been shown to underlie processes involved in identifying, appraising, and perceiving cues as salient (Phillips et al., 2003; 2008). Our findings are consistent with previous studies showing that adolescents with warmer and more supportive parents exhibit reduced hemodynamic response in the amygdala and insula to negative facial affect, threat words, and social rejection stimuli (Elliott et al., Under Review; Guyer et al., 2015; Romund et al., 2016). It is interesting to note that the patterns of activation found in this sample are consistent with the patterns found in prior studies with healthy adolescents. Considering that the current sample of adolescents was previously treated for anxiety, these results could suggest that treatment may have an effect on how adolescents process social threat information. Direct comparisons of treated and untreated anxious adolescents would be needed to test this theory, and would be a promising area for future research.

Contrary to hypotheses, the current study found that adolescents reporting higher levels of parental warmth and acceptance exhibited reduced activation in the dACC and right VLPFC to parental criticism. These regions are part of an emotion regulation brain network associated with the processing and regulation of negative emotion (Casey et al., 2008; Phillips et al., 2003). Although, adolescents were not given specific instructions to regulate their emotion to negative feedback, it was expected that higher parental warmth would be associated with more automatic activation in regulatory regions, suggesting a dampening effect on affective salience network reactivity. Our results were not consistent with prior research showing that lower adolescent VLPFC response to peer rejection was associated with harsh parenting styles (Guyer et al.,

2015). The opposite pattern found in the current study may be reflect more efficient regulatory processing in adolescents as a consequence of positive parental socialization factors such as warmth behaviors. It has also been established that projections between the affective salience and emotion regulation networks are bi-directional (Casey et al., 2008). Therefore, it may be that because adolescents with higher perceived parental warmth had lower affective salience activity in the amygdala, insula, and sgACC, there was less need for regulatory region activation.

However, the current findings are consistent with the a prior study showing that positive parental socialization behaviors are associated with lower pgACC activation in response to physical threat words in healthy adolescents (Elliott et al., Under Review). Interestingly, a recent review discusses literature showing that the neural substrates of social and physical pain are highly overlapping (Eisenberger, 2012). Social pain research has found that dACC activation (in addition to insula and sgACC activation) is not only associated with the experience of pain due to physical discomfort, but also with social exclusion during the Cyberball task in adults and adolescents (Eisenberger, 2012). Additionally, activation in the dACC has been related to greater subjective feelings of distress and disconnectedness following social exclusion experiences (Eisenberger, 2012). Together, these findings may indicate that greater parental warmth is related to lower levels of distress or negative affect that can result from perceived social and physical threat.

Hypotheses proposing that greater parental warmth would predict lower depressive symptoms in adolescents were not supported in the current study. This was unexpected, given the increased susceptibility to socially relevant feedback in youth with histories of anxiety and given the recent meta-analysis showing that parental warmth is a predictor of depressive symptoms in youth (Costello et al., 2003; Yap & Jorm, 2015). However, according to the meta-analysis, the

range of effect sizes found for this association are highly dependent on the study research design. Specifically, small to medium effects, ranging from -.202 to -.316, were largely found in cross-sectional or retrospective studies (n=95), whereas small effect sizes, ranging from -.159 to -.246, were found in the relatively small number of longitudinal studies (n=18). Results of the meta-analysis also found smaller effect sizes in longitudinal designs, with more years allowed between assessments. Accordingly, the current study found small standardized effects of parental warmth on adolescent depressive symptoms (observed parental warmth: β=-.249; adolescent-reported parental acceptance: β=-228). Therefore, it is likely that the study was not sufficiently powered to detect the effects of warm parenting on depressive symptoms.

Additionally, results showed that brain activation within the affective salience and emotion regulation networks did not mediate the association between parental warmth and adolescent depressive symptoms. These results were primarily due to the findings that adolescent neural activation did not predict depressive symptoms one year later. These findings are inconsistent with the literature on the neural correlates of depression in adults and adolescents (Hamilton et al., 2012; Kerestes et al., 2014). In addition to the current study, only two others have explored relations between neural activation in response to socially threatening stimuli and depression outcomes, (Pfeifer et al., 2011; Silk et al., 2014). These two studies utilized peer exclusion and rejection imaging tasks, whereas the current study utilized a parental criticism task. Therefore, it may be that the way in which neural emotion processing and regulation occur in response to parental criticism is not as salient to risk of depression as the way the brain responds to negative feedback by peers. Future research should assess whether neural emotion processing in response to peer-related threat mediates the link between parental warmth and future depression symptoms. Given that the current study results showed that parenting still plays

a role in neural emotion processing and regulation, it may be that the role of parenting on neural response to peer feedback would be a stronger predictor of risk for adolescent depression. In addition, prior research has found that lack of parental warmth contributes to risk for depression through its effects on other contributing risk factors, such as adolescent self-esteem or increased parent-adolescent conflict (i.e. poor relationship quality) (Baetens et al., 2015; Bolton, Barrowclough, & Calam, 2009; Sheeber, Hops, Alpert, Davis, & Andrews, 1997). Therefore, it is possible that neural response to parental criticism may be mediating a link between parental warmth and a more specific and proximal risk factor for depression, such as adolescent self-esteem or increased conflict with parents. This would be an important area for future exploration.

In addition to the main results, the current study explored the strength of these associations after accounting for potentially confounding factors that can also play a role in brain activation and depression outcomes. Findings from these sensitivity analyses showed that neither pubertal status, concurrent depressive symptoms, nor concurrent anxiety symptoms at the time of the scan contributed to the way adolescents' brains activated in response to parental criticism, or to the level of depressive symptoms reported one year later. Concurrent anxiety symptoms reported at the three-year follow-up was the only significant predictor of three-year follow-up depressive symptoms. Given that none of these variables significantly contributed to variance in models predicting adolescent brain activation, nor significantly reduced the effects of parental warmth on neural activation, results of the initial models were interpreted. Since risk for depression is nearly twice as high in girls, compared to boys, interaction effects of gender were considered next (Cyranowski et al., 2000). Researchers have posited that girls may be at higher risk for depression because they have been found to be more interpersonally sensitive than boys (Cyranowski et al., 2000). Therefore, it was hypothesized that the effects of parental warmth on

neural emotion processing and regulation would be stronger in girls, leading to larger and significant effects on depression symptom outcomes. However, this hypothesis was not supported by the results. Specifically, results indicated that parental warmth was similarly related to neural emotion processing similarly in boys and girls.

Interestingly, in contrast to the results found by Elliott et al. (Under Review) linking behavioral observations of parenting to neural correlates of threat processing, the current study failed to find associations of observed parenting with neural response to threat. In the present study, observed and adolescent-reported parenting measures were positively associated, although not significantly. In the prior study, the observed parenting variable assessed an emotion-specific parenting practice (encouragement of coping), as opposed to global observed warmth as in the current study. Therefore, it may be that observations of more specific parenting practices that serve to teach or model emotional responses have a stronger relation with emotional outcomes compared to more global aspects of parenting style. It also may be that, because adolescent self-report measures of warmth are generalized beyond a single interaction, they may better account for more historical and global perceptions of parental warmth across time. These global perceptions may have a stronger influence on the development of adolescent emotion processing and regulation.

The current study has many strengths, including the use of both self-reported and observed parental warmth, its prospective longitudinal design, and the use of a personalized, ecologically valid imaging task. Despite the study's strengths, there were some limitations. Due to the unavailability of parenting data for some youth, sample size was limited, influencing the ability to detect small effects. In addition, although the aims of the study were to better understand both emotion processing and regulation neural networks in relation to parenting and

depression, the Parental Expressed Emotion task did not directly instruct participants to actively regulate their emotional response to critical feedback. Therefore, it is possible that the task did not sufficiently engage regulatory region activation, which limits the interpretations of findings within the regulatory neural network. Furthermore, recent affective neuroscience research has focused on the associations between dampened neural response to positive stimuli, such as positive facial affect, peer acceptance, or monetary reward, and depression outcomes. Given the important role that anhedonia plays in depression, it may be that neural network functioning in response to parental praise is more directly associated with risk for depression, compared to parental criticism. The current study did not assess these associations, but future research should compare models using both positive and negative feedback. Finally, given the ethnically homogeneous and mostly college-educated sample, the effects of race and socioeconomic status (SES) were not explored. Therefore, the generalizability of the results is limited to Caucasian, middle-to-high socioeconomic status adolescent populations. There could be cultural differences based on ethnicity and/or SES in the way parents display warmth and how it contributes to brain function and depression. The results are also specific to adolescents who have been treated for anxiety. It is possible that the effects of treatment alter the role that parental warmth plays in the risk of future depression or on how adolescents' brains process social threat information. Therefore, future research should include a comparison group of adolescents who have a history of anxiety, but did not receive treatment.

Despite these limitations, the present study expands a limited, yet growing area of research assessing how parental factors continue to affect the functioning of brain networks that underlie emotion processing and regulation and associated depressive symptomatology throughout adolescence. The current study's results showed that neural reactivity within the

affective salience and emotion regulation networks when hearing criticism from parents is lower in adolescents if they perceive their parents to be warm and accepting. More broadly, these results support theories that youth learn how to adaptively process negative emotions and perceive less threat within interpersonal contexts as a function of warm, responsive, and communicative parenting behavior (Gottman et al., 1996; A. S. Morris et al., 2007; Rohner, 2004).

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