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A multi-method assessment of error sensitivity and anxiety in childhood and adolescence

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Abstract of the Dissertation

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Anxiety disorders are the most frequent form of psychopathology in children and adolescents and often result in chronic impairment. Therefore, there is a critical need to identify markers that characterize normative versus anxious trajectories of development. One promising biomarker of anxiety is altered brain activity in response to errors, as reflected by the event-related potential (ERP), the error-related negativity (ERN). The ERN occurs around the time of error commission and is generated in the anterior cingulate cortex (ACC). An increased ERN has been consistently found in adults with anxiety disorders. Although the ERN is smaller in children and changes across development, some work has suggested that the ERN is increased in anxious children and that this relationship may differ as a function of developmental stage. The current study uses multiple neural measures to model error sensitivity and anxiety in a large sample of females spanning childhood and adolescence (8 – 14 years old). Using the ERN elicited during a flankers and Go/NoGo task, as well as error-related brain activity using fMRI, we modeled error sensitivity as a latent trait. The results from the current study suggest that anxiety symptoms increased during adolescence – and that these increases were better accounted for by puberty than age. Additionally, increased pubertal development was associated with increases in worry, social anxiety, and panic, but not separation anxiety. The ERN elicited by the flankers task was associated with increases in child anxiety - specifically related to increases in social anxiety symptoms. While error-related brain activity elicited by the Go/NoGo task related to increases in child anxiety, these associations were not as consistent as those observed using the flankers task. Consistent with previous work, we observed error-related ACC activity, which correlated with the Go/NoGo ERN. Error-related neural activity as measured during both the ERP tasks and in the scanner increased across development in a quadratic fashion, with a dip occurring around age 11. A model wherein error sensitivity, child anxiety, and development were modeled as latent traits showed excellent fit – suggesting that increased child anxiety related to increased error sensitivity, even when accounting for the impact of development.

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Introduction

Clinical anxiety affects between 15 – 20% of children and adolescents, making anxiety the most frequently diagnosed form of psychopathology among young people (Beesdo, Knappe, & Pine, 2009). Further, adult anxiety disorders commonly begin in childhood (Beesdo 2010; Kessler et al., 2005; Last, Perrin, Hersen, & Kazdin, 1996) and prospective-longitudinal studies in youth suggest anxiety disorders are stable over time and predict future anxiety and depressive disorders in adolescence and adulthood (Bittner et al., 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998; Wittchen, Lieb, Pfister, & Schuster, 2000). For example, one study found that 73% of children initially diagnosed with a specific phobia met criteria for an anxiety or depressive disorder at a 10 year follow-up (Emmelkamp & Wittchen, 2009). These studies suggest that anxiety disorders follow developmental trajectories that begin early in development and often result in chronic impairment, though the specific mechanisms and developmental pathways are not yet fully understood (Pine, 2007).

Given the chronic and impairing nature of anxiety, it is important to identify core neural systems implicated in the early etiopathogenesis of anxiety disorders. By pinpointing specific early-emerging biomarkers that appear relatively early in life and correlate to anxious versus normative trajectories of development, this work can shed light on specific neural mechanisms of risk. Understanding such mechanisms could suggest novel targets of treatment, help guide intervention and prevention strategies, improve our understanding of the etiopathogensis of these disorders, and increase our ability to find genetic correlates. To identify early-emerging biomarkers, one potentially fruitful approach may be to examine neural measures in children and adolescents that have previously been linked to anxiety disorders in adults (Pine, 2007).

An extensive amount of research in adults has linked an event-related potential (ERP) index of error processing to anxiety. The error-related negativity (ERN) is a response-locked negative deflection in the ERP at fronto-central sites approximately 50 ms after the commission of an error (see Figure 1) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN has been hypothesized to reflect the activation of a generic error detection system that becomes active across a range of response (Falkenstein et al., 1991) and stimulus modalities (Bernstein, Scheffers, & Coles, 1995; Holroyd, Dien, & Coles, 1998; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001).

High-density EEG source localization studies of the ERN have been conducted in adults (Dehaene, Posner, & Don, 1994; Hermann, Ziegler, Birbaumer, & Flor, 2002; van Veen & Carter, 2002) and children (Ladouceur, Dahl, & Carter, 2007; Santesso & Segalowitz, 2008), as well as two magnetoencephalography (MEG) source localization studies (Keil, Weisz, Paul-Jordanov, & Wienbruch, 2010; Miltner et al., 2003). A recent analysis combining data from 15 such studies found a mean ERN source locus in the dorsal anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC) (Agam et al., 2011).

Intracranial recordings in human patients with epilepsy (Brázdil, Roman, Daniel, & Rektor, 2005; Brázdil et al., 2002) and single-unit recordings in monkeys (Godlove et al., 2011; Ito, Stuphorn, Brown, & Schall, 2003) have also found error related brain activity in the anterior cingulate cortex and medial frontal cortex. Furthermore, some intracranial recordings have implicated phasic theta bursts in the dorsal ACC, as well as local field potentials in the amygdala following error commission (Pourtois et al., 2010). Pourtois et al. (2010) also found coupling in the theta band between the dorsal ACC and amygdala, suggesting these regions are functionally

communicating during error detection. Other studies have also implicated the amygdala in error processing (Polli et al., 2008; Polli et al., 2009; Sagaspe, Schwartz, & Vuilleumier, 2011).

Consistent with source localization and intracranial recordings, functional magnetic resonance imaging (fMRI) studies have consistently found error activation in the dorsal ACC (Beckmann, Johansen-Berg, & Rushworth, 2009; Carter et al., 1998; Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Hester, Fassbender, & Garavan, 2004; Kiehl, Liddle, & Hopfinger, 2000; Mathalon, Whitfield, & Ford, 2003; Menon, Adleman, White, Glover, & Reiss, 2001). Debener et al. (2005) found that single-trial ERN magnitude predicted simultaneous fMRI activity in the rostral cingulate zone. Additionally, Agam et al. (2011) found that ERN magnitude correlated with activation of both the dorsal ACC and PCC, and that these two regions demonstrated coordinated activity based on functional connectivity. Another study found that the single-trial ERN correlated with the time course of activation in the anterior midcingulate cortex (caudal ACC), the presupplementary motor area, the insula, and parts of the basal ganglia (Huster et al., 2011). And, two studies using independent component analysis to combine electrophysiological and hemodynamic data have implicated the dorsal ACC and lateral prefrontal cortex in error processing (Donamayor, Heilbronner, & Münte, 2012; Edwards, Calhoun, & Kiehl, 2012). Taken together, these findings suggest that the ERN may be primarily generated in the ACC.

Early conceptualizations of the ERN and error-related ACC activity focused primarily on cognitive processes. One of the earliest theories regarding the ERN is the Mismatch Theory which suggests that a neural system compares the mental representations of the correct and actual response and that the “mismatch” between these representations elicits the ERN (Bernstein et al., 1995; Coles, Scheffers, & Holroyd, 2001; Falkenstein et al., 1991). In support

of this view, the degree of mismatch between the correct and actual response impacts the magnitude of the ERN; for example, responding with both an incorrect hand and incorrect finger, versus errors involving only an incorrect hand or finger, produces a larger error response (Bernstein et al., 1995; Falkenstein et al., 1991). Additionally, the ERN is increased when participants are more confident in having made an error (Scheffers & Coles, 2000). According to the Mismatch Theory, the error signal should be utilized to shape subsequent behavior (Coles et al., 2001; Gehring et al., 1993), and response time slowing following error trials supports this notion (Rabbitt, 1966). However, observations of a small ERN-like component even on correct trials (the correct-related negativity, i.e. the CRN) when no mismatch between the actual and intended response should exist, posed a challenge to this theory. To account for this, theorists proposed that the ERN and CRN may reflect the response checking process itself, and the increased negativity on error trials may reflect an additional error signal (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000).

Theorists later expanded upon the Mismatch Theory by focusing on mechanisms by which error detection influences behavior. The Reinforcement Learning theory of the ERN (Holroyd & Coles, 2002) suggests that the motor system is trained through reward and punishment. According to this model, the ERN is generated when the ACC receives feedback via dopaminergic projections from the basal ganglia when outcomes are worse than expected. Some work has linked dopamine and the ERN: administering a dopamine agonist (D-amphetamine) leads to an increased ERN amplitude (De Bruijn, WouterVerkes, F., & C., 2004), while administration of a dopamine antagonist (haloperidol) leads to a decreased ERN (de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006; Zirnheld et al., 2004). Additionally, individuals with Parkinson's disease, which is characterized by dopamine depletion, display a diminished

ERN (Beste, Willemssen, Saft, & Falkenstein, 2009; Jocham & Ullsperger, 2009; Stemmer, Segalowitz, Witzke, & Schönle, 2004; Willemssen, Müller, Schwarz, Hohnsbein, & Falkenstein, 2008). We have found an additive effect of two dopamine genes on ERN magnitude in a group of 6 year old children (Meyer, Klein, et al., 2012), and other studies that have found associations between the ERN and other dopamine polymorphisms (DRD2, DRD4, DAT, COMT) (Manoach & Agam, 2013).

Another model of the ERN that has been proposed is the Conflict monitoring theory, which focuses on competition between possible responses, suggesting that co-activation of the error and error-correcting response generates the ERN (Carter et al., 1998; Yeung, Botvinick, & Cohen, 2004). On correct trials, conflict prior to the response is thought to generate the stimulus-locked N2 (Yeung et al., 2004). The Conflict Monitoring theory also posits that the ACC monitors conflict and that projections to the prefrontal cortex signal the need for increased cognitive control (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998). Evidence that larger CRNs are associated with incongruent trials types (Bartholow et al., 2005) suggest that conflict can be detected at different points in the information processing stream and led theorists to propose that this activity does not reflect the activation of a dedicated error detection system. While the Mismatch/Reinforcement Learning theories suggests that the ERN reflects activity of a dedicated response checking system, the Conflict monitoring theory suggests the ERN reflects one instance of conflict detection.

Although both the Conflict monitoring and Mismatch/Reinforcement Learning theories explain the generation of the ERN by focusing on cognitive functions, neither accounts for the considerable within and between-subject individual differences observed in the ERN magnitude. Both models predict that variation in the ERN should be predicted by behavioral measures – for

example, post-error slowing should be related to the magnitude of the ERN and infrequent errors should give rise to an increased ERN (Holroyd & Coles, 2002; Yeung et al., 2004). Overall, both the Conflict and Reinforcement Learning theories are rooted in the notion that variation in the magnitude of the ERN is related to current behavior and is used to shape subsequent behavior; however, there are many instances in which variation in the ERN occurs without behavioral differences (for review, see:Weinberg, Riesel, & Hajcak, 2012). Consequently, recent theories have sought to address additional sources of variance related to affect and motivation that may contribute to the ERN magnitude.

In line with this, variation in the magnitude of the ERN has recently been conceptualized as reflecting the threat value of errors (Hajcak, 2012; Proudfit, Inzlicht, & Mennin, 2013; Weinberg, Riesel, et al., 2012). Errors are motivationally-salient events and may threaten an individual's safety, often requiring immediate attention and corrective action (Weinberg, Riesel, et al., 2012). Moreover, errors prompt a cascade of physiological and emotional changes: skin conductance response, heart rate deceleration (Hajcak, McDonald, & Simons, 2003b) potentiated defensive startle reflexes (Hajcak, 2008), pupil dilation (Critchley et al., 2005), increased corrugator (i.e., frowning) contraction (Lindström, Mattsson-Mårn, Golkar, & Olsson, 2013), amygdala activity (Pourtois et al., 2010), increased negative affect as evidenced by priming tasks (Aarts, Houwer, & Pourtois, 2012), and increased distress as reported on a trial by trial basis (Spunt, Lieberman, Cohen, & Eisenberger, 2012), all of which suggest an aversive motivational response to errors. Therefore, some variation in the ERN may reflect the degree to which errors are threatening or aversive.

Indeed, the magnitude of the ERN is modulated by the value or cost of errors: the ERN is larger when errors are more important due to incentives (Chiu & Deldin, 2007; Endrass et al.,

2010; Ganushchak & Schiller, 2008; Hajcak, Moser, Yeung, & Simons, 2005; Hajcak, Nieuwenhuis, Ridderinkhof, & Simons, 2005; Pailing & Segalowitz, 2004) and when accuracy is emphasized over speed (Falkenstein et al., 2000; Gehring et al., 1993). The proposal that an increased ERN may reflect an increased threat-value of errors is consistent with data in which punishing errors potentiates the ERN in the lab (Meyer, Gawlowska, & Hajcak, Under Review; Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012). In these studies, in the first half of the experiment, participants were sometimes punished for making mistakes – for example, a participant may have been punished after half of the errors in blocks wherein stimuli were blue, but never punished when stimuli were yellow. In one experiment the punishment was an aversive sound (Riesel et al., 2012) and in another it was an electric shock (Meyer et al., Under Review). In both of these studies, we found that punishment increased the magnitude of the ERN. Furthermore, results suggested that the punishment modulation of the ERN persisted after punished ended (Riesel et al., 2012). Building on these findings, we recently examined the impact of parenting style on error processing in offspring, finding a link between harsh parenting and a larger ERN in children (Meyer, Proudfit, et al., 2014). In this study, harsh parenting as assessed by both an observational and self-report measure were uniquely related to an increased ERN in children 3 years later, further supporting the notion that these children may have attached more threat-value to their errors (via critical parental behavior).

Consistent with this view, the Adaptive Control Hypothesis has recently been put forth, stating that error-related brain activity reflects the need to exert control processes made in the face of uncertainties about actions and their potentially aversive outcomes (Cavanagh & Shackman, 2014; Shackman et al., 2011). This theory suggests that anxiety and negative affect tend to involve the same underlying neural mechanism (activity generated in the anterior

cingulate cortex) as cognitive control processes, positing that the activity observed on error trials is representative of a domain-general function. Evidence supporting this theory includes a series of meta-analyses showing that emotion, pain, errors, and cognitive control activate an overlapping region in the dorsal anterior cingulate (Shackman et al., 2011). Additionally, one study found that within-subject variability in ACC response to errors tracked subjective reports of distress on a trial by trial basis (Spunt et al., 2012), more specifically linking the experience of negative affect with overactive neural responding to error commission. A recent review utilized NeuroSynth to investigate overlap between regions activated for error monitoring and emotion (Koban & Pourtois, 2014). NeuroSynth is a project which uses text-mining techniques to automatically identify, extract, and synthesize human functional brain imaging results based on a large number of studies (currently 9721 published papers). This approach has been shown to be robust and reliable for broad constructs (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). This review suggested reliable overlap between error monitoring and emotion in the dorsal mediofrontal cortex (dMFC), lateral prefrontal areas, anterior insula, and amygdala (Koban & Pourtois, 2014). Furthermore, the authors posited that activity in the dMFC and amygdala during action monitoring may underlie the "affective tagging" of errors.

Building on these within-subject findings, fMRI studies of error related brain activity have consistently found excessive ACC activation in *trait* anxious individuals (Fitzgerald et al., 2005; Huyser, Veltman, Wolters, de Haan, & Boer, 2011; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Paulus, Feinstein, Simmons, & Stein, 2004; Ursu, Stenger, Shear, Jones, & Cameron, 2003; Yücel et al., 2007). Moreover, the magnitude of the ERN has been found to be larger among trait anxious adults in more than a dozen studies now (Hajcak, 2012; for a review, see: Moser, Moran, Schroder, Donnellan, & Yeung, 2013). For example, the ERN is increased

in individuals with generalized anxiety disorder (Weinberg, Klein, & Hajcak, 2012; Weinberg, Olvet, & Hajcak, 2010) and obsessive-compulsive disorder (Endrass, Klawohn, Schuster, & Kathmann, 2008; Gehring, Himle, & Nisenson, 2000; Hajcak, Franklin, Foa, & Simons, 2008; Xiao et al., 2011). Personality traits that characterize anxiety, such as worry (Hajcak, McDonald, & Simons, 2003a), behavioral inhibition (Amodio, Master, Yee, & Taylor, 2008), high negative affect (Hajcak, McDonald, & Simons, 2004), and punishment sensitivity (Boksem, Tops, Wester, Meijman, & Lorist, 2006) have been linked to a larger ERN in adults. In light of these findings, an increased ERN may reflect the disposition to respond strongly to uncertain threat (Proudfit et al., 2013). Furthermore, it may be that for these individuals, errors are more aversive and are thus associated with an increased neural response.

The ERN as a neurobehavioral trait.

In line with viewing the ERN as potentially trait-like, the ERN has been shown to be both reliable and stable over time and across different tasks. For example, the ERN has high test-retest reliability over the course of 2 weeks (Olvet & Hajcak, 2009a) and up to 2 years (Weinberg & Hajcak, 2011). Additionally, the ERN has high internal reliability after approximately 6 error trials (Olvet & Hajcak, 2009b). We have previously investigated the similarities and differences in the ERN elicited by three different tasks (Flankers, Stroop, and Go/NoGo) among adults. Correlations were generally high between the ERN magnitude across tasks at fronto-central electrode sites (approximately .60), supporting the notion that the ERN reflects common neural and cognitive processes across tasks and can be viewed as trait-like (Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013).

In light of these findings, we have begun to view the ERN as a neurobehavioral trait (Patrick & Bernat, 2010): a stable individual difference measure that links neural activity and a

behavioral phenotype. Consistent with this, the ERN has been shown to be relatively unaffected by symptom changes (Hajcak et al., 2008). Measured in a group of children with OCD before and after successful cognitive-behavioral therapy, the ERN magnitude continued to be increased in patients relative to controls, even after children in the OCD group no longer met criteria for the disorder. This pattern of results has recently been replicated in adults (Riesel, Endrass, Auerbach, & Kathmann, 2015). Similarly, one recent study found that while the ERN was enhanced in 72 OCD patients compared to controls, ERN magnitude was unrelated to global symptom severity (Riesel, Kathmann, & Endrass, 2014). Considering the heritability of the ERN is estimated to range from 45 – 60% (Anokhin, Golosheykin, & Heath, 2008) and multiple genetic correlates to the ERN have been found (Manoach & Agam, 2013; Meyer, Klein, et al., 2012), an increased ERN may be a viable endophenotype (Olvet & Hajcak, 2008) or heritable neurobehavioral trait.

Error processing across development.

We have recently extended our psychometric work in adults to children and adolescents, finding reasonable trait-like stability. Specifically, we have examined the reliability and stability of the ERN in children and adolescents initially aged 8 – 13 years-old, over the course of two years (Meyer, Bress, & Proudfit, 2014). These data suggest impressive test-retest reliability (Cronbach's alpha = .51) across time (see Figure 2) and excellent internal reliability (Cronbach's alpha exceeds .70 after 12 errors). Additionally, the split-half correlations for the ERN at both assessments exceeded .80, suggesting that this component is internally reliable across different stages of development. And further, within adolescents, the ERN elicited by the Flankers and Go/NoGo task were moderately correlated (r = .47, p < .001; see Figure 2). Taken together,

these data suggest that the ERN is a reliable and stable measure of error processing in children and adolescents.

While the ERN has been found to be a psychometrically reliable measure in developmental populations, important changes in error-processing occur across development. For example, test-retest reliability may be high if the entire sample is changing at the same rate. Therefore it is important to consider developmental changes in error processing that may be occurring. Indeed, using a letter flanker task in a large sample between the ages of 7 and 18 years old, Davies et al. (2004) observed an increase in ERN magnitude across development. Additionally, they observed a quadratic relationship between ERN and age, with an initial dip in ERN amplitude around the time of pubertal onset, and subsequent rise until reaching adult-like levels around age 18. Furthermore, Davies et al., (2004) observed an interaction between this trajectory and gender, indicating that the ERN began to increase sooner for girls than for boys and therefore the ERN increase observed across development may be related to pubertal onset. Other work from this same group has suggested that children and adolescents (between the ages of 10 and 16) displayed a reduced ERN compared to adults (Santesso & Segalowitz, 2008). Since then, fourteen studies have found an increasing ERN across development (for a review, see:Tamnes, Walhovd, Torstveit, Sells, & Fjell, 2013). One study found that ERN magnitude related to performance during the task, but only in adults and not children, suggesting that the relationship with behavioral measures and the ERN may also change across development (Ladouceur et al., 2007).

In developmental populations, the source of the ERN has been localized to the dorsal ACC (Ladouceur et al., 2007; Santesso & Segalowitz, 2008). Consistent with findings suggesting the that the ERN increases across development, DTI studies have found that the

cingulum bundle (a white matter tract that underlies the cingulate cortex) matures later than most of the other major tracts (Lebel & Beaulieu, 2011; Lebel et al., 2012). And, one functional connectivity study suggests that in children, the dorsal ACC is relatively disconnected from a cinguloopercular control network that has previously been identified in adults (Fair et al., 2007). An fMRI study including participants between the ages of 8 and 27 years old found that error-related dorsal ACC activity increased across development (Velanova, Wheeler, & Luna, 2008). Taken together, these studies suggest that ERN and ACC error-related activity increases across development, and these increases may be related to pubertal onset, although further work is needed to clarify this.

Error related brain activity as a neural correlate of anxiety in children.

Consistent with work in adults, a previous study found an increased ERN in adolescents with non-clinical anxiety symptoms (Meyer, Weinberg, Klein, & Hajcak, 2012) and other studies have similarly found an increased ERN within a heterogeneous group of clinically anxious children (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006), children with obsessive-compulsive disorder (Carrasco et al., 2013; Hajcak et al., 2008; Hanna et al., 2012), children with non-clinical symptoms of obsessive-compulsive disorder (Santesso, Segalowitz, & Schmidt, 2006), and early behavioral inhibition (McDermott et al., 2009). Additionally, one previous study found a stronger age-related increase in error-related ACC activity in pediatric OCD patients relative to controls (Huyser et al., 2011), supporting the notion that over-active or "adult-like" neural reactivity to error commission may be an indicator of anxious pathology early in development. As part of a larger longitudinal study, we recently found an increased ERN in 48 six-year old children with a clinical anxiety disorder as assessed by diagnostic interview compared to 48 age-matched controls (Meyer, Hajcak, et al., 2013) (see Figure 3). This is the

first study to examine the relationship between the ERN and anxiety in children this young and is important to the current proposal in demonstrating that error processing is a neural correlate of clinical anxiety beginning early in the course of development.

While a wealth of research suggests the ERN may be considered a neurobehavioral trait or correlate to anxiety, there is also evidence to suggest the ERN may index *risk* for anxiety. Unaffected first-degree relatives of both adults and children with OCD have larger ERNs compared to controls (Carrasco et al., 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011). Additionally, ERN amplitude in children has been linked to other risk factors - maternal anxiety and temperamental fear (Torpey et al., 2013). Importantly, two prospective studies have examined the relation of the ERN to subsequent anxiety, both finding that among children high in early temperamental behavioral inhibition, an increased ERN predicted anxiety symptoms later in development (Lahat et al., 2014; McDermott et al., 2009). However, neither of these studies controlled for baseline anxiety symptoms. Recently, we found that increased error-related brain activity in a group of 6 year old children predicted the onset of new anxiety disorders three years later (by 9 years of age), even when controlling for baseline anxiety symptoms and maternal history of anxiety (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, In Press), suggesting that the ERN may be elevated in children on pathological trajectories even before the onset of perceptible symptoms.

Developmental issues: the ERN and anxiety.

While an increased ERN has consistently been related to anxiety disorders and symptoms in older children and adolescents (Carrasco et al., 2013; Hajcak et al., 2008; Ladouceur et al., 2006; Meyer, Weinberg, et al., 2012), some findings in younger children have shown the opposite pattern (Meyer, Weinberg, et al., 2012; Torpey et al., 2013). In 6 year old children,

temperamental fear and maternal history of anxiety were both related to a *decreased* ERN amplitude (Torpey et al., 2013). However, in this same sample, children with a clinical anxiety disorder were characterized by an increased ERN, displaying the same relationship between anxiety and ERN that has previously been observed in adults, adolescents, and older children (Meyer, Hajcak, et al., 2013). Although preliminary, it appears that at the Age 9 follow-up in this sample, the same children that were characterized by high fear and small ERNs at Age 6, now display an increased ERN at Age 9. Intriguingly, in a separate developmental sample spanning the ages of 8 - 13, we found that the relationship between the ERN and anxiety symptoms changed across development (Meyer, Weinberg, et al., 2012). As depicted in the Figure 4, among older children, a larger ERN was related to increased anxiety symptoms. Although the relationship was only significant at a trend level, in younger children, increased anxiety symptoms were related to a blunted ERN.

We have begun to conceptualize this pattern in relation to work on normative developmental changes in anxiety. As children grow older, anxiety tends to transition from fear of external threat (e.g., the dark, spiders, monsters) to self-conscious shyness and worry about behavioral competence and social evaluation (i.e., internal threat) (Copeland, Angold, Shanahan, & Costello, 2014; Crozier & Burnham, 1990; Spence, Rapee, McDonald, & Ingram, 2001; Vasey, Crnic, & Carter, 1994). It may be that younger children with increased levels of normative anxiety are characterized by anxious arousal (i.e., fear) and concern with external threat. These children may be more preoccupied by the lab environment (e.g., the dark room, the experimenter, separation from the parent) than their performance on the task, and thereby display a decreased ERN. However, older children who are characterized by increased levels of normative anxiety may have begun to be concerned with social evaluation and behavioral

competence and thereby display an increased response to errors. Moreover, younger children with *clinical* anxiety may have already begun to monitor for behavioral competence and are more sensitive to internal threat, thereby displaying an increased ERN. Although further work is still needed to clarify these trajectories, it is clear that the relationship between the ERN and anxiety may differ across development. In light of the potential utility of using the ERN as a neurobehavioral risk marker to predict the onset and course of anxiety, it is important to further characterize the relationship between normative levels of anxiety and error processing in children and adolescents, while considering the potential moderating role of development.

Multimodal assessment of error processing and anxiety.

Although some studies in adults have utilized both ERP and fMRI measures of error processing (Agam et al., 2011; Debener et al., 2005; Donamayor et al., 2012; Edwards et al., 2012; Huster et al., 2011), to our knowledge, no studies in children have done so. Indeed, most studies on error processing and anxiety have relied on a single neural measurement and task to characterize error-related brain activity, and generally only one or two measures to characterize individual differences in anxiety. Previous psychometric work suggests that a considerable amount of variance in error-related brain activity is task-specific (Riesel et al., 2013) - partial correlations indicated that the ERNs elicited by two tasks shared variance even when controlling for the variance accounted for by the third task, suggesting that each task did not capture the same information—the ERNs were not fully redundant. A similar pattern was found in children across two different tasks (Meyer, Bress, et al., 2014). Taken together, these findings suggest that using multiple tasks and methods (EEG and fMRI) to construct a latent construct of error sensitivity may provide both overlapping and unique variance in relation to anxiety symptoms.

The current proposal.

The current proposal aims to examine two issues that have not yet been fully addressed: 1.) the use of multiple neural measures to model error sensitivity and anxiety, and 2.) the potential moderating role of pubertal development on the relationship between anxiety and error sensitivity. To do so, the current project uses neuroimaging and ERP measures of error sensitivity as well as questionnaires and interviews regarding anxiety and puberty, to model error processing, anxiety, and development as latent traits in 150 females spanning childhood and adolescence (8 – 14 years old).

The current proposal seeks to examine error sensitivity as a latent construct that can be measured with multiple tasks (i.e., flankers and Go/NoGo for ERN) and with multiple approaches (ERP and fMRI). Indeed, while we expect error processing to be related between the two ERP tasks, we also expect each to contribute unique variance to the latent trait. And, while ERPs provide important information about the time-course and magnitude of neural reactivity, fMRI has excellent spatial resolution, enhancing the ability of the proposed research to identify more precise neural substrates that predict anxiety. Although fMRI and ERP measures of error sensitivity may relate to one another, they are measuring different brain processes (i.e., the hemodynamic response following brain activity and immediate electrical activity produced by many neurons firing in synchrony). Additionally, our previous work suggests that child and parent report of anxiety and puberty often differ (Meyer, Weinberg, et al., 2012), as well as interview based measures, and may therefore contribute additive information. As depicted in Figure 5, we plan to model these constructs using SEM, which will increase our ability to remove measurement error, thereby producing a more reliable and powerful index of error sensitivity. In addition to modeling error sensitivity and anxiety as latent variables and examining the relationship between them, we also plan to investigate the potential moderating

role of development on this relationship. Previous work suggests that parent and child-rated puberty scores are not fully redundant with each other, or with age (Bress, Smith, Foti, Klein, & Hajcak, 2012), so we plan to model development as a latent variable as well. Our hypotheses include the following: 1.) ERP and fMRI measures will contribute both overlapping and unique variance to the latent variable of error sensitivity, 2.) self and parent report of anxiety, as well as anxiety symptoms as reported during a clinical interview will contribute overlapping and unique variance to the latent variable of anxiety, 3.) We will examine the power of each manifest marker of error sensitivity and anxiety to explain latent measures, but have no *a prior* hypotheses regarding whether specific manifest measures will be superior to others, 4.) the relationship between error sensitivity and anxiety will be moderated by development, such that the relationship between error sensitivity anxiety will be stronger among girls more advanced in pubertal development.

Given that this project focuses on the stage of development that is a core risk period for the development of anxiety disorders (Beesdo et al., 2009; Reardon, Leen-Feldner, & Hayward, 2009) and on females, who are 2-3 times more likely than males to have an anxiety disorder (Pine et al., 1998; Wittchen, Nelson, & Lachner, 1998), the design of the current proposal is optimal insofar as we will be able to relate neural measures to increases in anxiety during a key developmental period. This work will pave the way for future developmental work regarding risk for anxiety disorders. And, because ERPs can be used across the lifespan and are relatively non-invasive and inexpensive, they may be useful in clinical settings for assessment purposes, making it important to validate the prospective utility of specific neural biomarkers. Additionally, fMRI data can shed light on specific mechanisms that can inform models of etiopathogenesis and identify potentially novel targets.

Method

Recruitment of Participants.

Participants in the proposed research included 150 females between the ages of 8 and 14 who are part of a larger and longitudinal ongoing NIMH-funded R01 study examining reward and depression across adolescence. We recruited children and adolescents who live within a 30 mile radius of Stony Brook's campus; to do this, we used a commercial mailing list of families that have a 8-14 year-old female living at home. We sent letters describing the study prior to an initial call, and screened families based on the following criteria: the child must live with at least one biological parent, the child and caretaker must speak English, and the child must not have a significant developmental or medical disability.

Protocol.

During the lab visit, when families arrived in the laboratory, parents and children were consented by a graduate student. Parents then completed the KSADS-PL with a trained interviewer while the child completed the laboratory assessment. The assessment consisted of a number of behavioral and psychophysiological measures that were part of a larger study, as well as the Flankers and Go/NoGo task described below. The fMRI and EEG recordings were counterbalanced and usually took place on the same day. After this, the child completed the KSADS-PL with the same interviewer. During the laboratory visit, children and parents both completed the SCARED and the PDS.

Anxiety Measures.

The current proposal focuses on dimensional measures of symptoms measured by the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1997) questionnaire. Two versions of the SCARED were administered: one to child and adolescent

participants (C-SCARED) and one to the parent who accompanied the child or adolescent to the laboratory (P-SCARED). Both versions of the SCARED broadly assess symptoms of anxiety as they manifest in children, including symptoms of panic, general anxiety, separation anxiety, social phobia, and school phobia. Each version contains a 38 item scale on which the participant can answer: 0 ("not true or hardly ever true"), 1 ("sometimes true"), or 2 ("true or often true"). The maximum score for each version is 76 and both versions include 5 subscales scores: Panic/Somatic, General Anxiety, Separation Anxiety, Social phobia, and School Phobia.

To further assess child psychopathology, the parent and child were both interviewed using the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Versions (KSADS-PL) (Kaufman, Birmaher, Brent, & Rao, 1997), a semi-structured clinical interview for the assessment of psychopathology in children and adolescents. Dimensional measures of symptoms were calculated from the current KSADS. This interview has been shown to have good validity and is widely used to diagnose psychopathology in children. The same interviewer interviewed the child and parent separately. All interviews were reviewed and final diagnoses derived in a monthly diagnostic case conference with all of the interviewers (a total of 6) and Dr. Greg Hajcak. All interviews were recorded and we completed reliability analyses on a subset of interviews, oversampling for psychopathology. Previous studies suggest 6 – 20% of children will experience the onset of an anxiety disorder during this developmental period (Beesdo et al., 2009), indicating that approximately 9- 30 children in the current sample will have a clinical anxiety disorder.

Development Measures.

Parents and children also completed the Pubertal Development Scale (PDS: Petersen, Crockett, Richards, & Boxer, 1988) to assess the degree to which several indicators of puberty

(e.g. growth spurt, body hair) are present. The PDS consists of 5 items rated on a scale from 1 – 4 indicated "no development" to "completed development", that are averaged together into a summary score.

Flankers Task.

The EEG was recorded while participants engage in a computer task used frequently in our lab to study error related brain activity: an arrowhead version of the flankers task (Eriksen & Eriksen, 1974). During the task, participants were shown five arrowheads, and instructed to press the left or right mouse button as quickly as possible depending on the direction of the central arrowhead. There are two "compatible" conditions ("< < < < <" and "> > > > >") and two "incompatible" conditions ("< < > < <" and "> > < > >"). The stimuli are presented randomly such that 50% are incompatible. Each stimuli is presented for 200 ms, and the interval between the offset of one stimulus and the onset of the subsequent stimulus will vary randomly between 2300 to 2800 ms. Participants completed a practice block containing 30 trials during which they are instructed to be both accurate and as fast as possible. The actual task consists of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. To encourage both fast and accurate responding, participants received feedback based on their performance at the end of each block. If performance is 75% correct or lower, the message "Please try to be more accurate" will be displayed; performance above 90% correct will be followed by "Please try to respond faster"; otherwise the message "You're doing a great job" will be displayed.

Go/NoGo Task.

The Go/NoGo task is also frequently used in our lab during EEG recording. During this task, the Go/NoGo task stimuli are presented for 200 ms, followed by an ITI varying randomly between 600 to 1000 ms. The stimuli are green equilateral triangles in three different

orientations; 80% of the triangles are vertically aligned and pointed up ("Go" stimuli) and 20% of the triangles are slightly tilted ("No/Go" stimuli). Children are instructed to respond to upward-pointing triangles by pressing a button and to withhold responses to slightly tilted triangles. There are a total of 420 trials (7 blocks of 60 trials each). At the end of each trial, children receive feedback based on performance. Similar to the Flankers task, children received feedback related to their performance at the end of each block.

Children also completed an fMRI session wherein they completed a Go/NoGo task to elicit errors. This task is similar to the triangle Go/NoGo task used during EEG recording and consists of three runs, 92 trials each. Overall, 75% of the triangles are vertically aligned and pointed up ("Go" stimuli) and 25% of the triangles are slightly titled ("No/Go" stimuli). Stimuli are presented for 200 ms, the average ISI varies between 2800 – 8800 ms, and each run is 323.4 seconds.

EEG recording and data reduction.

Continuous EEG recordings was collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites were used, as well as two electrodes on the left and right mastoids. Electrooculogram (EOG) generated from eye movements and eyeblinks was recorded using four facial electrodes: horizontal eye movements will be measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements and blinks will be measured via two electrodes approximately 1 cm above and below the right eye. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of one by a BioSemi ActiveTwo system. The data was digitized at a 24 bit resolution with a sampling rate of 1024 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz.

Each active electrode was measured online with respect to a common mode sense (CMS) active electrode producing monopolar (non-differential) channel. Offline, all data was referenced to the average of the left and right mastoids, and band-pass filtered between 0.1 and 30 Hz; eye-blink and ocular corrections were conducted per Gratton, Coles, and Donchin (1983).

A semi-automatic procedure was employed to detect and reject artifacts. The criteria applied was a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than .50 μV within 100 ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data were then conducted to detect and reject any remaining artifacts.

The EEG were segmented for each trial beginning 300 ms before the response and continuing for 1,000 ms after the response. The response-locked ERPs was averaged separately for each trial type (e.g., correct and incorrect responses), and baseline correction will be performed using the interval from -500 to -300 ms. Average activity at three sites (FCz, Cz, and Fz) between 0 – 100 ms after response was exported for each subject. In order to obtain a measure of differentiation between errors and correct responses, the average activity related to correct responses was subtracted from the average activity related to errors (i.e., the ΔERN).

Behavioral measures included both the number of error trials for each subject, as well as accuracy expressed as a percentage of all valid trials. Average reaction times (RTs) on error and correct trials were calculated separately, as well as RTs on correct trials following correct and error trials to evaluate post-error RT slowing.

FMRI recording and data reduction.

A research-dedicated 3T Siemens Trio whole body scanner was used to acquire a total of three functional runs (consisting of a 154 volumes, approximately 5:23), collected using a T2*-

weighted sequence with 37 continuous slices (thickness = 3.5mm), TR = 2100ms, TE = 23ms, FOV = 224 x 224mm, 83° flip angle. Data was processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) software. Preprocessing consisted of slice-time correction, unwarping (motion correction) using pre-collected field maps, normalization to the EPI template, and spatial smoothing (8mm) using SPM8 default parameters. A mixed-effects model was then be created with Error minus Correct Go modeled at the first level, with a subsequent second level one-way t-test examining the effects across participants. Resultant statistical maps were corrected for multiple comparisons using a FDR correction of $p < .05$, and beta-value estimates (principle eigenvariate) were extracted for each participant from the functional ROI spanning the ACC. A review of fMRI and source localization studies suggests the ACC as a likely neural generator of error-related activation (Brodmann area 32; Agam et al., 2011). Beta-value estimates for each participant were extracted from the ACC using SPM's principal eigenvariate. Based on the review from Koban and Pourtois (2014), we also extracted beta-value estimates from the functional ROI for error minus correct spanning the anterior insula.

Results

Participants.

The final sample included 223 girls aged 8 – 15, *M* = 11.87, *SD* = 1.76, who completed at least one error-processing measure (e.g., EEG/fMRI). The sample identified as 9% Hispanic, 8% African American, 83% Caucasian, and 6% as other.

Anxiety Measures.

All participants completed the parent and child SCARED, broadly assessing symptoms of anxiety. The average child-reported SCARED score was 20.69, *SD* = 11.80, and the average

parent-reported SCARED score was 11.17, *SD* = 9.54. As expected based on previous work, these measures were moderately correlated, $r(221) = .43$, $p < .001$.

The SCARED includes 5 subscale scores: Panic/Somatic, General Anxiety, Separation Anxiety, Social Phobia, and School Phobia. The means for the parent-reported SCARED subscales are as follows: Panic/Somatic, *M* = 1.37, *SD* = 2.41, General Anxiety, *M* = 3.6, *SD* = 3.50, Separation Anxiety, *M* = 1.77, *SD* = 2.27, Social Phobia, *M* = 3.57, *SD* = 3.41, and School Avoidance, *M* = .86, *SD* = 1.18. For child-reported SCARED subscales: Panic/Somatic, *M* = 4.55, *SD* = 3.90, General Anxiety, *M* = 5.60, *SD* = 3.96, Separation Anxiety, *M* = 3.90, *SD* = 2.92, Social Phobia, *M* = 5.14, *SD* = 3.50, and School Avoidance, *M* = 1.51, *SD* = 1.54.

To further assess child psychopathology, the parent and child were both interviewed using the KSADS-PL. Dimensional measures of lifetime anxiety symptoms were calculated: *M* = 5.35, *SD* = 6.76. The lifetime dimensional measure of anxiety symptoms were correlated to both parent and child-report SCARED scores, $r(221) = .48$, $p < .001$ and $r(221) = .37$, $p < .001$, respectively.

Development Measures.

Parents and children both completed the PDS to assess pubertal stage. The average stage of puberty reported by children was 2.63, *SD* = .83, and reported by parents was 2.62, *SD* = .83. Parent and child reports were significantly correlated with each other, $r(221) = .88$, $p < .001$. Additionally, child age was related to both parent and child report of puberty, $r(221) = .72$, $p < .001$ and $r(221) = .70$, $p < .001$, respectively.

While age did not relate to increases in anxiety symptoms, parental report of pubertal stage related to an increase in parent and child-reported SCARED symptoms, as well as

increased KSADS anxiety symptoms, $r(221) = .19$, $p < .01$, $r(221) = .22$, $p < .001$, and $r(221) = .18$, $p < .01$. Child report of pubertal stage related to an increase in child-reported SCARED symptoms, $r(221) = .21$, $p < .01$, but not to parent reported SCARED or KSADS anxiety symptoms, all ps > .10.

To explore whether puberty predicted increased anxiety symptoms above the influence of age, we performed a hierarchical multiple regression analysis where in the first step parent-reported child puberty was entered, and the second step both parent report of child puberty and child age were entered predicting parent-reported SCARED symptoms. Results suggested that puberty uniquely predicted increases in child anxiety, $B = .25$, $t = 2.59$, $p < .01$, while age did not, $p = .45$. The same pattern of results was found when predicting child-reported SCARED symptoms as well as KSADS anxiety symptoms. Additionally, child-reported SCARED symptoms were uniquely predicted by child-reported pubertal stage, $B = .29$, $t = 3.13$, $p < .01$, but not age, $p = .23$. *Overall, increases in anxiety across development were better accounted for by pubertal development than age.*

We were also interested in exploring whether specific subscales of the SCARED increased with puberty. Correlations between the parent-reported PDS and the parent-reported SCARED subscales suggested that while Panic, $r = .21$, $p < .01$, Generalized Anxiety, $r = .17$, $p < .01$, Social Anxiety, $r = .16$, $p < .01$, and School Avoidance, $r = .28$, $p < .001$, increase across development, Separation Anxiety does not, $r = -.05$, $p = .42$. The same pattern of results was found when examining child-reported pubertal stage and child-reported SCARED symptoms. *As can be seen in Figure 6, the pattern is remarkably similar across child and parent SCARED reports wherein as children advance in puberty - panic, worry, social anxiety, and school avoidance symptoms increase, while separation anxiety does not.*

Flankers Behavioral Data.

Overall, RTs during error trials, M = 371.44, SD = 77.06, were faster than RTs during correct trials, M = 483.09, SD = 109.63, $F(1, 236) = 608.65$, $p < .001$. Additionally, RTs on trials following errors, M = 475.04, SD = 103.89, were slower than trials following correct responses, M = 460.28, SD = 101.19, resulting in post-error slowing, $F(1, 236) = 27.87$, $p < .001$. On average, children made 54 errors, SD = 30.41 (average accuracy = 82.36%).

Flankers ERP Data.

All of the children in the sample completed the flankers ERP task. As can be seen in Figure 7, the ERP response was more negative following errors than correct responses, $F(1, 442) = 282.72$, $p < .001$. Additionally, there was a response by electrode interaction, $F(2, 442) = 284.14$, such that the ΔERN was larger at Fz, M = -3.36, SD = 4.94, and FCz, M = -3.41, SD = 5.22, relative to Cz, M = -2.11, SD = 5.32, but Fz and FCz did not differ from each other.

Flankers ERN and child anxiety.

While the ΔERN did not relate to anxiety symptoms (at any electrode), an increased ERN at Cz related to increased child and parent reported anxiety symptoms on the SCARED, $r(221) = -.17$, $p < .01$, and $r(221) = -.21$, $p < .01$, respectively, as well as increased KSADS anxiety symptoms, $r(221) = -.14$, $p < .05$ (Table 1). The ERN at Fz and FCz both related to increased parent reported anxiety symptoms on the SCARED, $r(221) = -.13$, $p < .05$, and $r(221) = -.16$, $p < .05$, respectively. Additionally, the CRN at both FCz and Cz related to increased parent reported anxiety symptoms on the SCARED, $r(221) = -.15$, $p < .05$, and $r(221) = -.19$, $p < .01$, respectively. *Taken together, increased child anxiety symptoms were related to increases in the ERN and CRN.*

We were also interested in whether specific subscales of anxiety on the SCARED would relate to error-related brain activity. In regards to the child-reported SCARED anxiety symptoms: Panic and Separation Anxiety symptoms were unrelated to the ERN or ΔERN; however, Social Anxiety, School Avoidance, and Generalized Anxiety symptoms were related to an increase in the ERN at Cz, $r(221) = -.19$, $p < .01$, $r(221) = -.15$, $p < .01$, and $r(221) = -.12$, $p = .07$, respectively. Additionally, the ΔERN at FCz was increased amongst children with increased Social Anxiety, $r(221) = -.14$, $p < .05$. In regards to the parent-reported SCARED anxiety symptoms: Separation Anxiety symptoms were unrelated to the ERN or ΔERN; however, Panic, Social Anxiety, School Avoidance, and Generalized Anxiety symptoms were related to an increase in the ERN at Cz, $r(221) = -.17$, $p < .05$, $r(221) = -.17$, $p < .05$, $r(221) = -.16$, $p < .05$, and $r(221) = -.16$, $p < .01$, respectively. The ERN at FCz was also related to parent-reported Panic and Social Anxiety symptoms, $r(221) = -.13$, $p < .05$, and $r(221) = -.15$, $p < .05$. The ΔERN was unrelated to any of the parent-reported SCARED subscales.

To further examine what subscales of the SCARED uniquely predicted error-related brain activity, we completed two stepwise regression analyses. In the first, we entered all the parent-reported SCARED subscales predicting the ERN at Cz. Results suggested that only the Social Anxiety subscale uniquely predicted the ERN, $F(1, 220) = 6.77$, $p < .01$, while all of the other subscales were excluded from the final model. For the second stepwise regression analysis, we entered all the child-reported SCARED subscales predicting the ERN at Cz. Again, the results suggested that only the Social Anxiety subscale uniquely predicted the ERN, $F(1, 220) = 7.79$, $p < .01$, while all the other subscales were excluded from the final model. In Figure 8, a scatter plot depicts the relationship between the ERN at Cz and SCARED Social Anxiety symptoms

(combined parent and child report). *Overall, the ERN elicited by the flankers task seems to have the strongest relationship with social anxiety symptoms.*

Flankers ERN and development.

The ΔERN at Fz, FCz, and Cz increased with age, $r(221) = -.18$, $p < .01$, $r(221) = -.19$, $p < .01$, and $r(221) = -.20$, $p < .01$ (Table 2). Increases in the ΔERN at Fz, FCz, and Cz were also related to increased child-reported pubertal stage, $r(221) = -.16$, $p < .05$, $r(221) = -.19$, $p < .01$, and $r(221) = -.20$, $p < .01$. Additionally, an increased ΔERN at FCz and Cz was related to parent-reported pubertal stage, $r(221) = -.17$, $p < .01$, and $r(221) = -.19$, $p < .01$. We performed a hierarchical multiple regression to explore whether puberty and age had unique influences on the ΔERN. Results suggested that these are not unique predictors, R^2 change = .009, $p = .16$. Additionally, neither the ERN nor the CRN (at any electrode) related to child age or pubertal stage, all *p*s > .07. *In contrast to the relationship between child anxiety symptoms and the ERN and CRN separately, these results suggest that developmental changes are occurring in the ΔERN.*

Previous work has found a quadratic relationship between ERN and age (Davies et al., 2004), finding an initial dip in ERN amplitude around the onset of puberty and subsequent rise until adulthood. Consistent with this work, in the current study we found a significant quadratic relationship between child age and the ΔERN at FCz, $F(2, 215) = 7.25$, $p < .001$. *As can be seen in Figure 9, an initial dip appears to occur around the age of 11 years old and then a subsequent rise in ERN magnitude.*

Given the findings regarding the changes in error-related brain activity and anxiety across development, we wanted to explore whether the ERN/CRN associations with anxiety could be

accounted for by development. To do this, we completed partial correlations between the ΔERN, ERN, CRN and anxiety symptoms, while first controlling for age and then pubertal stage. When we did this, the pattern of results remained consistent - child anxiety symptoms were related to increases in the ERN and CRN, but not the ΔERN. We also examined partial correlations between the ΔERN, ERN, CRN and anxiety symptoms while controlling for behavior during the task (error and correct RTs, post-error slowing, and accuracy rates). When we did this, again, the pattern of results remained the same, wherein child anxiety symptoms were related to increases in the ERN and CRN. And, finally, even after controlling for child depression symptoms (as reported by the parent and child on the Child Depression Inventory, CDI), increases in child anxiety symptoms related to increases in both the ERN and CRN in children.

Go/NoGo Behavioral Data.

Overall, RTs during error trials (a go response on a NoGo trial), $M = 333.12$, $SD = 67.82$, were faster than RTs during correct trials (a go response on a Go trial), $M = 396.04$, $SD = 77.71$, $F(1, 147) = 416.75$, $p < .001$. Additionally, RTs on trials following errors, $M = 323.78$, $SD = 70.90$, were slower than trials following correct responses, $M = 313.22$, $SD = 54.96$, $F(1, 147) = 7.71$, $p < .01$. On average, children made 40.57 errors, $SD = 12.94$ (average accuracy = 85.13%).

Go/NoGo ERP Data.

Of the current sample, 141 girls completed the Go/NoGo ERP task. As can be seen in Figure 10, the ERP response was more negative following errors than correct responses, $F(1, 280) = 217.89$, $p < .001$. Additionally, there was a response by electrode interaction, $F(2, 280) = 110.06$, such that the ΔERN differed at all three electrodes and was largest at Cz, $M = -5.46$, $SD = 6.24$, and then at FCz, $M = -4.93$, $SD = 6.40$, and was smallest at Fz, $M = -3.13$, $SD = 5.82$.

Go/NoGo ERN and child anxiety.

While neither the ΔERN, ERN, or CRN related to any of the anxiety measures, an increased ΔERN and ERN at Fz was related to increased anxiety symptoms on the KSADS at a trend level, $r(139) = -.17$, $p = .06$, and $r(139) = -.15$, $p = .08$, respectively (Table 3). Additionally, neither the ΔERN nor ERN related to any of the parent or child-reported anxiety subscales on the SCARED. *These results suggest that, similar to the flankers task, error-related brain activity during the Go/NoGo task is related to increased anxiety symptoms; however, overall, the ERN elicited by the flankers task seems to have a more robust relationship with child anxiety symptoms.*

Go/NoGo ERN and development.

Similar to the results for the flankers task, the ΔERN increased with age at Cz, FCz, and Fz, $r(139) = -.24$, $p < .05$, $r(139) = -.24$, $p < .01$, and $r(139) = -.25$, $p < .01$ (Table 4). Additionally, the ΔERN at FCz and Fz increased with pubertal stage as reported by the parent, $r(139) = -.16$, $p = .05$, and $r(139) = -.17$, $p = .05$. The ERN at Fz and FCz increased with age, $r(139) = -.28$, $p < 001$, and $r(139) = -.19$, $p < .05$, and the ERN at Fz increased with parent-reported PDS, $r(139) = -.19$, $p < .05$. We performed a hierarchical multiple regression to explore whether puberty and age had unique influences on the ΔERN at FCz. Similar to the flankers task, results suggested that these are not unique predictors, R^2 change = .000, $p = .91$. Additionally, as depicted in Figure 11, we found a significant quadratic relationship between child age and the ΔERN at Cz, $F(2, 138) = 4.17$, $p < .05$. *The pattern was similar to that of the ERN, with a dip around age 11 and then subsequent rise in magnitude.*

We also performed follow-up analyses wherein we examined the associations between the ΔERN, ERN, and CRN and child anxiety symptoms while controlling for both age and puberty. When we did this, the trend associations between the ERN and ΔERN at Fz with KSADS anxiety symptoms persisted. And, when we controlled for behavior during the task (RT on correct and error trials, post-error slowing, and accuracy), the association between the ERN and ΔERN at Fz with KSADS anxiety symptoms remained. Similarly, when we controlled for child depression symptoms (as measured by the CDI), the pattern of results remained the same.

We were also interested in examining the relationships between error-related brain activity across the tasks. Pearson correlations for the ERN across the Go/NoGo and flankers task were moderate: at Fz, $r(139) = .42$, $p < .001$, at FCz, $r(139) = .51$, $p < .001$, and at Cz, $r(139) = .48$, $p < .001$. For the CRN, the correlations were: at Fz, $r(139) = .56$, $p < .001$, at FCz, $r(139) = .64$, $p < .001$, and at Cz, $r(139) = .69$, $p < .001$. And, for the ΔERN, the correlations were: at Fz, $r(139) = .23$, $p < .001$, at FCz, $r(139) = .31$, $p < .001$, and at Cz, $r(139) = .23$, $p < .001$. Consistent with previous work (Meyer et al., 2014), relationships of error-related brain activity across the tasks was moderate to large for the CRN and ERN, and small to moderate for the ΔERN.

Go/NoGo fMRI behavioral data.

Overall, RTs during error trials (a go response on a NoGo trial), $M = 397.41$ $SD = 83.96$, were faster than RTs during correct trials (a go response on a Go trial), $M = 460.02$, $SD = 84.12$, $F(1, 67) = 189.44$, $p < .001$. On average, children made 23.18 errors, $SD = 10.91$ (average accuracy = 90.95%).

Go/NoGo fMRI data.

Sixty-eight children had usable fMRI data from the Go/NoGo task in the current study. Reasons for exclusion include the following: scheduling issue with the family or scan center (28 children), scan technician error (18 children), child ended scan (7 children), movement during the scan (9 children), child fell asleep during the scan (3 children), children made 6 errors or less (13 children), child had accuracy less than 50% (2 children), behavioral data between fMRI and ERP discrepant – more than 3 SD above or below mean (2 children). Having missing fMRI data did not relate to any other study variables (anxiety, EEG, development, all *p*s > .10). A mixed-effects model was created with error (a go response on a no-go trial) minus correct (a go response on a go trial) modeled at the first level, with a subsequent second level one-way t-test examining the effects across participants. An examination of within-group *t*-maps, thresholded at $p < .05$, *FWE* corrected, revealed a large cluster of activation (voxel extent =1256) that spanned the anterior cingulate cortex, maximal activation at MNI: 2, 23, 35; as well as the insula, (voxel extent = 1856), maximal activation at MNI: 35, 19, 7 (see Figure 12).

None of the fMRI measures of error-related brain activity related to child anxiety symptoms on the SCARED or KSADS, all *p*s > .10. Additionally, there were no bivariate correlations between error-related brain activity measured during fMRI and age or puberty, all *p*s > .10. However, there was a significant quadratic relationship between child age and error-related ACC (anatomically defined) activation, $F(2, 65) = 3.04$, $p = .05$. *As can be seen in the Figure 13, the pattern is similar to that seen in the flankers and Go/NoGo ERN, wherein a dip occurs around age 11*.

We also wished to examine the relationships between fMRI and ERP measures of error-related brain activity. While neither the ERN, CRN, nor ΔERN elicited during the flankers task related to fMRI measures of error activation, the ΔERN at Cz during the Go/No-Go task was

related to error-related ACC activation in the scanner (anatomically defined), $r(66) = -.25$, $p < .05$. *As can be seen in Figure 14, increases in the magnitude of the ΔERN at Cz are related to increases in error-related ACC activation.* This relationship remains significant when controlling for age, $r(64) = -.26$, $p < .05$, and accuracy during the ERP and fMRI task, $r(64) = -.21$, $p < .05$. Error-related activity in the insula did not relate to any of the ERP measures, all *p*s > .10.

Latent Variable Modeling.

In order to increase our ability to remove measurement error, we modeled error sensitivity and anxiety as latent constructs using SEM. Given the significant amount of missing fMRI data, we examined these models both: 1.) in the sample of children only with complete fMRI data and 2.) in the full sample, estimating missing data. All ERP data were reverse coded to increase clarity of interpretation (i.e., more negative ERNs are larger).

In the first model, we examined the relationship between error sensitivity and child anxiety in the children who had complete fMRI data, using the Go/NoGo ERN at Cz, the flankers ERN at FCz, (where error-related activity was maximal)and the error-related ACC activity (anatomically defined), as well as the total parent and child-reported SCARED and KSADS anxiety symptoms. This model achieved overall good fit, RMSEA = .000, 90% CI .000 - .120. As can be seen in Figure 15, the Go/NoGo ERN at Cz had the largest loading on the error sensitivity factor, then the flankers ERN at FCz, and then error-related ACC activity. The KSADS and parent-reported SCARED anxiety symptoms had the largest loading on the anxiety factor, followed by child-reported SCARED symptoms. *Additionally, the two latent variables*

were related to each other in the expected way: increased error sensitivity was related to increased anxiety in children (Figure 16).

We examined this same model in the full sample, while estimating the means and intercepts for missing data. The overall model achieved good fit, RMSEA = .000, 90% CI .000 - .050. As can be seen in Figure 17, the pattern of results is similar to that observed in the subsample. As depicted in the scatter plot (Figure 18), increased anxiety in children was related to increased error sensitivity, $r(221) = .23$, $p < .001$.

We also examined the role of development using latent variable modeling. To do this, in the full sample, we modeled development using the manifest variables of parent and child-reported pubertal scores (PDS) and age. In the first model, we examined a model wherein development related to both child anxiety and error sensitivity. This model achieved moderately good fit, RMSEA = .059, 90% CI .029 - .088. As depicted in Figure 19, both the child and parent report of puberty loaded strongly onto the development factor, with age showing a moderate loading. *Increased development was related to increased child anxiety, as well as increased error-sensitivity (although the magnitude of this relationship was small).*

To investigate the potential moderating role of development on the relationship between child anxiety and error sensitivity, we exported the latent variables: development, child anxiety, and error sensitivity and used a nonparametric bootstrapping method (SPSS Macro from Preacher & Hayes) to examine the interaction. Results suggested that while anxiety was significantly related to error sensitivity, $t = 5.05$, $p < .001$, CI [.03 - .06], *the interaction between development and anxiety did not significantly predict error sensitivity, t = -1.06, p = .29, CI [-.04 - .01]*.

Overlapping and unique variance of error processing measurements.

One aim of the current investigation was to examine the power of each manifest marker of error processing to predict anxiety. As can be seen in all of the latent variable models, the fMRI measure of error-related ACC activity did not account for a large amount of variance in the latent variable of error sensitivity (around 3%). However, both the Go/NoGo and flankers ERN had large loadings on the latent variable of error sensitivity (accounting for approximately 69% and 44% of variance, respectively). To investigate to what extent the shared versus the unique variance of these measures related to child anxiety, we modeled error sensitivity and child anxiety in separate models and imputed the latent variables for each. We then completed a simultaneous regression analysis wherein the latent variable of error sensitivity (reflecting the common variance between the manifest error processing variables) was entered as a predictor, along with the Go/NoGo ERN, flankers ERN, and error-related ACC activity (reflecting the unique variance of each error processing variable) all predicting child anxiety. Results suggested that while the latent variable of error sensitivity significantly predicted child anxiety, $B = 1.03$, $t = 2.66$, $p < .001$, neither the Go/NoGo ERN, flankers ERN, nor error-related ACC predicted child anxiety, all ps $> .10$.

Discussion

In the current study, we sought to characterize the development of anxiety and error sensitivity across childhood and adolescence. The results from the current study suggest that anxiety symptoms generally increased during adolescence – and that these increases were better accounted for by pubertal development than age. Additionally, increased pubertal development was associated specifically with increases in worry, social anxiety, school avoidance, and panic, but not separation anxiety. Error-related brain activity elicited by the flankers task was

associated with increases in child anxiety, and seemed to have a unique relationship with increases in social anxiety. While error-related brain activity elicited by the Go/NoGo task related to increases in child anxiety, these associations were not as consistent as those observed using the flankers task. Consistent with previous work, we observed error-related ACC activity using the Go/NoGo task, which correlated with the Go/NoGo ERN, but was itself unrelated to child anxiety. Error-related neural activity as measured during both ERP tasks and in the scanner increased across development in a quadratic fashion, with a dip occurring around age 11. A model wherein error sensitivity, child anxiety, and development were modeled as latent traits showed excellent fit - suggesting that increased child anxiety related to increased error sensitivity, even when accounting for the impact of development.

Relationships between ERP and fMRI error-processing measures.

Consistent with previous findings (Meyer, Bress, et al., 2014; Riesel et al., 2013), although error-related brain activity was correlated between the flankers and Go/NoGo tasks, associations were larger for the ERN relative to the ΔERN. This may be due to the fact that difference scores are generally less reliable (Chiou & Spreng, 1996; Edwards, 2001; Johns, 1981). Furthermore, we observed a divergent topographical distribution of the ΔERN across tasks – with a more frontal distribution during the flankers task (maximal at Fz and FCz) compared to the Go/NoGo task (maximal at Cz). We previously observed this pattern in a separate developmental sample (Meyer et al., 2014). In the current study, error-related ACC activity measured using fMRI was related to the magnitude of the ΔERN during the Go/NoGo task. While no previous work had yet examined the association of the ERN and error-related ACC activity in children, work in adults suggests that these two measures have relationships that are significant, but small in magnitude (Agam et al., 2011; Kiehl et al., 2000; Mathalon et al.,

2003). Taken together, the associations we observed across tasks (Go/NoGo vs. flankers) and across methods (ERP vs. fMRI), suggest that we are measuring a common neural process reflecting error commission – and that there is both shared and unique variance associated with both task and method.

Anxiety across development.

Anxiety generally increased across development – although this increase was related to increases in pubertal development more than age. This is consistent with other work that has found links between puberty and increased anxiety (Carrion, Weems, Ray, & Reiss, 2002; Huerta & Brizuela-Gamiño, 2002; Reardon et al., 2009; Susman, Dorn, & Chrousos, 1991). For example, amongst girls of the same age, there is a two-fold increase in the likelihood of having a panic attack for every one-point increase in Tanner stage (Hayward, Killen, Kraemer, & Taylor, 2000). Additionally, the pattern observed using both parent and child report of anxiety symptoms was remarkably consistent: worry, social anxiety, school avoidance, and panic increase with pubertal development, whereas separation anxiety did not. This is consistent with some previous work specifically linking increases in worry and social anxiety to pubertal development (Ge, Brody, Conger, & Simons, 2006), and to work suggesting that anxiety tends to transition from fear of external threat (e.g., the dark) to self-consciousness and worry about competence and evaluation (Copeland et al., 2014; Crozier & Burnham, 1990; Spence et al., 2001; Vasey et al., 1994).

Error sensitivity and child anxiety.

Consistent with previous work finding an association between the ERN and anxiety in children and adolescents (Carrasco et al., 2013; Ladouceur et al., 2006; Meyer, Weinberg, et al.,

2012; Santesso et al., 2006), we found that an increased ERN elicited by the flankers task related to increases in child and parent-reported anxiety symptoms on the SCARED, as well as dimensional symptoms scores as measured by a diagnostic interview (the KSADS). To our knowledge, this is the first study to use both self- and parent-report as well as a diagnostic interview-based assessment of anxiety to examine the association between the ERN and anxiety in children and adolescents.

We were also able to examine what specific subscales of anxiety may relate to an increased ERN in children and adolescents. Two stepwise regression analyses (using parent and then child report of anxiety symptoms) suggested that social anxiety symptoms uniquely related to increases in ERN magnitude in children and adolescents. This is in line with our conceptualization of the ERN as a neural marker that, in part, measures the threat value of errors. Socially anxious individuals are characterized by increased fear regarding their own behavior and performance (Clark & Wells, 1995), and thus may experience errors as more distressing. Indeed, previous work has found an increased ERN in adults with Social Anxiety Disorder (Endrass, Riesel, Kathmann, & Buhlmann, 2014). Additionally, within-subject studies have found that the ERN is enhanced when performance is critically evaluated (Hajcak, Moser, et al., 2005) and when errors are observed by a peer (Kim, Iwaki, Uno, & Fujita, 2005). Furthermore, a recent investigation found that the ERN magnitude is increased during a social evaluation context, but only among socially anxious individuals (Barker, Troller-Renfree, Pine, & Fox, In Press). And, the degree of modulation in the ERN due to social evaluation correlated with individual differences in social anxiety symptoms, further suggesting that trait and state modulations in ERN magnitude are related to the threat value of error commission.

Similar to the flankers task, error-related brain activity during the Go/NoGo task related to increased anxiety symptoms; however, this relationship was only observed in relation to the KSADS dimensional anxiety symptoms, and at a trend level. We did not observe associations between the Go/NoGo ERN and child anxiety symptoms reported on the SCARED. Although no previous study has examined how error-related neural activity elicited by multiple tasks may differentially relate to anxiety symptoms, previous psychometric work suggests that the Go/NoGo ERN may be less internally reliable than the flankers ERN in adults (Meyer, Riesel, & Proudfit, 2013) and children (Meyer, Bress, et al., 2014). Considering that internal reliability places an upper limit on the predictability of any variable (Cronbach & Meehl, 1955), it is possible that we failed to see anxiety/ERN associations due to the relatively lower internal reliability of the Go/NoGo ERN. Alternatively, it is also possible that there are different neural and/or cognitive processes associated with each task that may impact the relationship between the ERN and anxiety.

Similarly, we did not observe a significant relationship between error-related ACC activity during the Go/NoGo task and child anxiety. This could be due, in part, to the relatively smaller sample size of children and adolescents with adequate fMRI data in the current study (although this is a large sample by imaging standards). As discussed above, it is also possible that error-related activity elicited by the Go/NoGo task has relatively low internal reliability and that this restricted our ability to detect associations with anxiety. To our knowledge, no previous study has investigated the psychometric properties of error-related ACC activity in the scanner. It is also possible, as previously stated, that the Go/NoGo task recruits different error-related neural networks that are not associated with increased anxiety. In fact, many studies that have found an association between error-related ACC activity and anxiety have used a modified

version of the flankers task (Fitzgerald et al., 2005; Huyser et al., 2011; Paulus et al., 2004), and to our knowledge, only one has used a Go/NoGo task – finding that ACC activity during high conflict *correct* trials better differentiated anxious and non-anxious individuals (Maltby et al., 2005) . Additionally, during the Go/NoGo task in the scanner, children's reaction times were slower and they made fewer errors – thus, children performed the task much better in the scanner, and this may have potentially impacted our ability to detect relationships with anxiety. Future work should investigate issues related to tasks and psychometric properties of error-related ACC activity in the scanner to determine how best to investigate relationships with anxiety.

Using latent variable modeling, we found a significant relationship between increased error sensitivity and increased child anxiety. We modeled error sensitivity using the ERN elicited during the Go/NoGo and flankers task as well as error-related ACC activity during a Go/NoGo task, and child anxiety using the parent and child report of symptoms on the SCARED as well as a dimensional symptoms score from the KSADS clinical interview. Results suggested that the shared variance (and not the unique variance) amongst the error-processing variables related to increases in child anxiety. While a significant portion of variance was accounted for by the Go/NoGo and Flankers ERN (69% and 44%, respectively), only 3% of variance was accounted for by error-related ACC activity, suggesting that the ERP measures were superior in their predictive ability. Taken together, results from the current study suggest that an increased neural response to errors is related to increased anxiety symptoms in children and adolescents – and that these relationships are observed amongst the flankers and Go/NoGo ERN separately; and, furthermore, that the shared variance across different tasks and methods for measuring error processing relate to increased anxiety.

Development of error sensitivity.

Consistent with an extensive amount of previous work, the current findings suggest that the magnitude of the ERN increases across development (for a review, see: Tamnes, Walhovd, Torstveit, Sells, & Fjell, 2013). One previous study in a large sample of children and adolescents between the ages of 7 and 18 years old (Davies, Segalowitz, & Gavin, 2004) found a quadratic relationship between the ERN and age, with an initial dip in ERN amplitude around the time of pubertal onset, with a subsequent rise through adulthood. In this same study, they observed an interaction between this trajectory and gender, suggesting that the ERN began to increase sooner for girls than boys –implicating puberty in this developmental change. In the current study, we found a quadratic relationship between age and all three of the error-processing measures (i.e., flankers and Go/NoGo ΔERN, as well as error-related ACC activity). For all three of these measures, we observed a "dip" in error-related brain activity around age 11, which is consistent with Davies et al. (2004). Indeed, pubertal hormones have important activating and organizational influences on brain structure and function (Peper et al., 2009; Sisk & Zehr, 2005), and several recent studies have implicated pubertal hormones in the development of the ACC (Brouwer et al., 2015; Koolschijn, Peper, & Crone, 2014; Nguyen et al., 2013). For example, Koolschijn et al., (2014) found that testosterone and estradiol levels related to changes in grey matter volume in the ACC, even after controlling for age. Future work should investigate the extent to which pubertal hormones may relate to the transient decrease and then subsequent increase in ERN magnitude observed across development.

Anxiety and error sensitivity across development.

Previous work has indicated that the relationship between anxiety and error sensitivity may change across development. For example, we have found that temperamental fear relates to an increased ERN in 9 year old children, but related to a *decreased* ERN when those same children were 6 years old (Torpey et al., 2013). Additionally, in a sample of children spanning the ages of 8 – 13, we previously found that the relationship between anxiety and the ERN was moderated by development, such that it was only among older children that increased anxiety was associated with increased error sensitivity (Meyer, Weinberg, et al., 2012). We conceptualized this pattern as a reflection of the developmental trajectory of anxiety wherein children transition from being fearful of external threat (e.g., the dark) to more self-consciousness and worry about behavioral performance. However, in the current study, we did not find that the relationship between error sensitivity and anxiety changed as a function of development. Instead, we found that anxiety and error sensitivity both increased with puberty, and the relationship between these constructs remained consistent across development. One reason for this may be that the highly anxious young children in the current sample (8 and 9 years old) may be less characterized by fears related to external threat than in previous samples. In fact, the 8 and 9 years olds in the current sample are characterized by relatively less separation anxiety (SCARED subscale: $M = 2.5$) compared to the younger children from the Meyer et al., (2012) sample, ($M = 3.6$), although this was only in a small sample (approximately 15 children per study) and this difference did not reach significance, $p = .10$. One possibility is that children in the current study were lower on separation anxiety due to the fact that the parents and children were told about the fMRI scan on the phone during recruitment. Separation-anxious kids may have declined to participate. Future work might investigate the extent to which different types of

anxiety may relate to the ERN magnitude in larger samples of children between the ages of 8 and 9—perhaps in studies that do not include fMRI.

Task and method considerations.

In addition to characterizing the development of anxiety and error sensitivity across childhood and adolescence, we also examined whether specific tasks (Go/NoGo vs. flankers) or methods (fMRI vs. EEG) for measuring error processing would be more powerful in detecting relationships with anxiety. Results from the correlation and regression analyses suggested that the flankers task had more consistent relationships with anxiety symptoms compared to the Go/NoGo task. And, results suggested that error-related ACC activity did not relate robustly to anxiety symptoms. However, using the latent variable approach, we did find that anxiety related to error sensitivity - and the Go/NoGo ERN had a large loading on this factor. That is, variance that the Go/NoGo ERN shared with the flankers ERN and error-related ACC activity did relate to the latent trait of anxiety in children. Furthermore, the relationship between error-related ACC activity and the latent factor of error sensitivity was small in magnitude, suggesting that EEG may be preferable to fMRI in detecting relationships with anxiety. It is possible that the substantial amount of missing fMRI data may have contributed to these findings. However, previous work has suggested that the original factor structure and factor weights are largely retained with substantial amounts of missing data in latent variable models (Kamakura & Wedel, 2000). Additionally, we completed the latent variable models in both the whole sample and only in those children with fMRI data – finding the same pattern of results. It is also important to consider that a different task in the scanner may have been more effective in measuring relationships between error-related neural activity and anxiety. Future work should explore the

use of various tasks in the scanner to elicit error-related activity in children and adolescents in relationship to anxiety symptoms.

Strengths/Limitations and Conclusions

While findings from the current study are largely consistent with our hypotheses and previous work, it is important to note some limitations. As mentioned previously, there was a substantial amount of missing fMRI data in the current study. A large portion of this data (approximately 60%) was lost due to factors that we would not expect to relate to individual differences in the child (e.g., scan technician error). However, some of the data (approximately 40%) was lost due to factors that may have impacted results: the child ending the scan, the child moving or falling asleep during the scan, the child making too few or too many errors. Although having missing fMRI data did not relate to any other study variables (anxiety, EEG, development, all *p*s > .10), we cannot be certain that this did not influence the pattern of results.

Other limitations to the current investigation include the fact that we only used one error-processing task in the scanner. Given that the flankers ERN had more consistent relationships with child anxiety symptoms, we may have found relationships between error-related ACC activity and anxiety had we also used that task in the scanner. Additionally, the current study was limited to females. Future work should investigate to what extent the pattern of findings is the same across development in males. Furthermore, the current study used cross-sectional data to investigate developmental trajectories—and it will be important for future studies to examine measurements at multiple time points in the same individuals to better study the development of anxiety and error sensitivity.

Despite these limitations, the current study has a number of strengths. Foremost, the current study provides substantial evidence confirming the relationship of anxiety and error sensitivity across development. Although previous studies have found similar effects, this is the first investigation to use multiple markers and tasks of these constructs to create latent variables, thereby increasing our ability to remove measurement error and confirm the validity and relationships of these constructs. We have also extended the developmental literature examining error processing – replicating the finding of a quadratic relationship between age and error processing across all measures of error-related brain activity.. Furthermore, we have built on and extended previous work by examining what specific facets of anxiety symptoms may be most related to an increased ERN in child and adolescent females – finding that social anxiety as reported by both the parent and the child relates to an increased flankers ERN. Future work in this area should focus on further characterizing the timing of the association between ERN and anxiety. That is, when should an increased ERN be considered a correlate versus a marker of risk? Is the ERN modifiable, and does its malleability vary across developmental stages? These question will shed light on critical issues related to the differentiation of anxious versus healthy trajectories.

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Table 1. Flankers ERPs and child anxiety symptoms.

	C-SCARED	P-SCARED	KSADS dimensional symptoms
ERN Fz	.01	**-.13***	-.04
ERN FCz	-.11	**-.16***	-.09
ERN Cz	**-.17***	**-.21***	**-.15***
CRN FZ	.04	-.11	-.07
CRN FCz	-.03	**-.15***	-.08
CRN Cz	-.11	**-.19****	**-.13***
ΔERN Fz	-.04	-.02	.03
ΔERN FCz	-.09	-.02	-.01
ΔERN Cz	-.08	-.04	-.03

* $p < .05$, ** $p < .01$

Table 2. Flankers ERPs and development variables.

	Age	P-PDS	C-PDS
ERN Fz	-.13	-.09	-.10
ERN FCz	-.07	-.08	-.08
ERN Cz	-.03	-.12	-.12
CRN FZ	.04	.03	.04
CRN FCz	.09	.07	.07
CRN Cz	.12	.02	.03
ΔERN Fz	**-.18****	-.12	**-.15***
ΔERN FCz	**-.19****	**-.17****	**-.18****
ΔERN Cz	**-.20****	**-.19****	**-.19****

* $p < .05$, ** $p < .01$

Table 3. Go/NoGo ERPs and child anxiety symptoms.

	C-SCARED	P-SCARED	KSADS dimensional symptoms
ERN Fz	.03	.03	-.14
ERN FCz	-.02	-.01	-.12
ERN Cz	-.09	-.07	-.10
CRN FZ	.03	-.01	.00
CRN FCz	-.00	-.10	.00
CRN Cz	-.06	**-.18***	-.05
ΔERN Fz	.00	.04	**-.17**[t]
ΔERN FCz	-.02	.07	-.13
ΔERN Cz	-.04	.09	-.06

[t] $p < .10$, * $p < .05$, ** $p < .01$

Table 4. Go/NoGo ERPs and development variable.

	Age	P-PDS	C-PDS
ERN Fz	**-.28****	**-.19***	-.12
ERN FCz	**-.19***	-.14	-.05
ERN Cz	-.13	-.14	-.04
CRN FZ	-.08	-.06	.00
CRN FCz	.05	.02	.08
CRN Cz	.11	-.00	.04
ΔERN Fz	**-.25****	-.17	-.15
ΔERN FCz	**-.24****	-.16	-.12
ΔERN Cz	**-.24****	-.14	-.08

* $p < .05$, ** $p < .01$

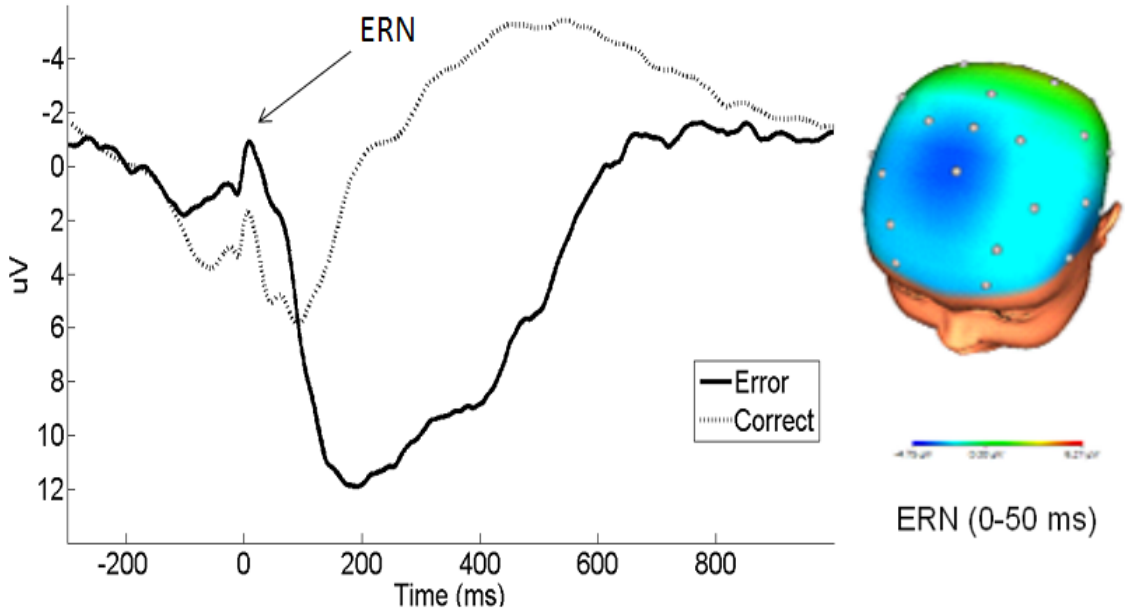
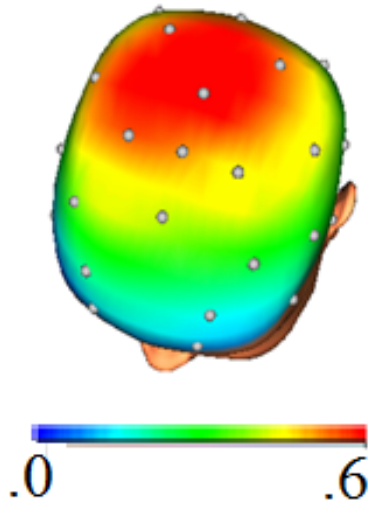


Figure 1. The ERN in a group of 55 children aged 8 - 13 during a flankers task.

Correlations: Time 1 and 2 Flankers



Correlations: Go/No-Go and Flankers

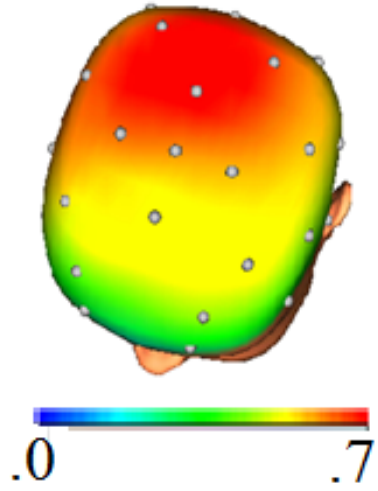


Figure 2.

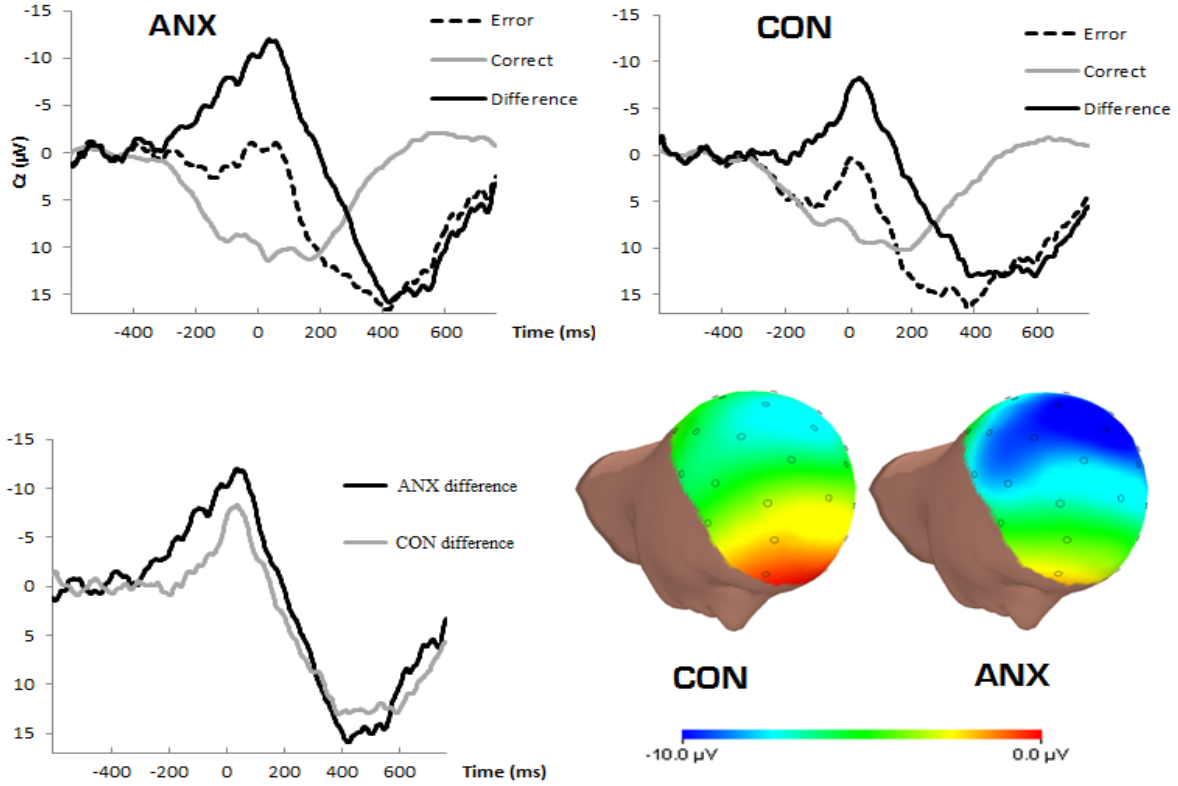


Figure 3. On the top, ERP waveforms for 6 year-old children with anxiety disorders (ANX:left) and age-matched controls (HC:right). On the bottom left, ERP difference wavesforms for both groups and on the right, topographic maps (error minus correct) for both groups.

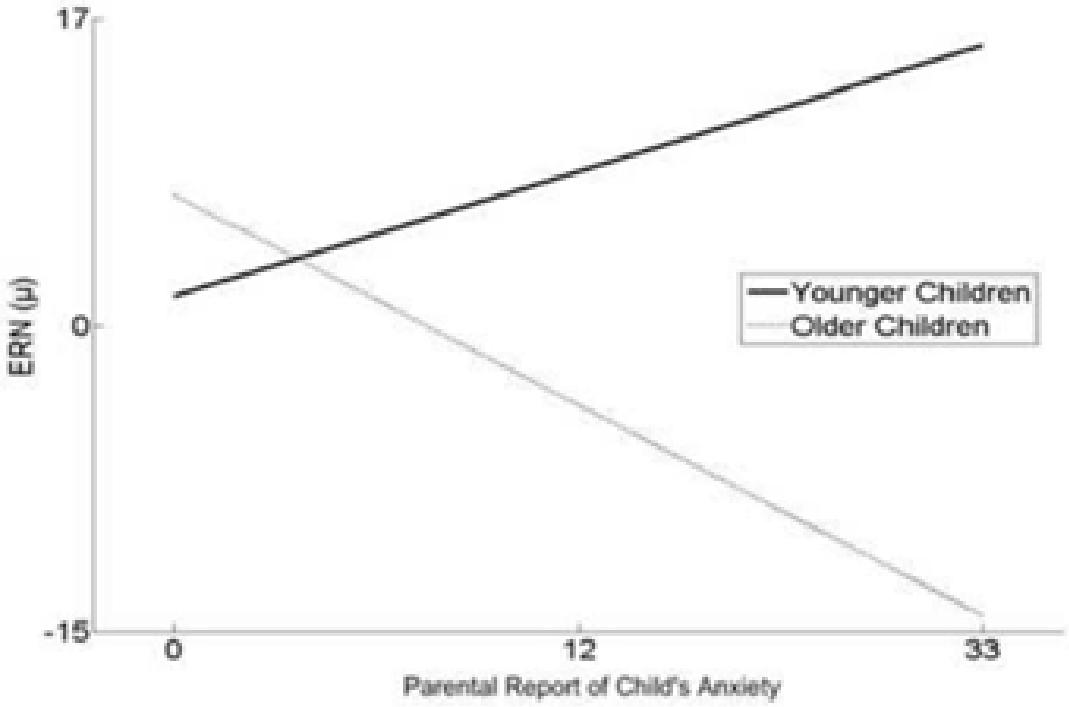


Figure 4. Interaction of age and child anxiety in predicting ERN.

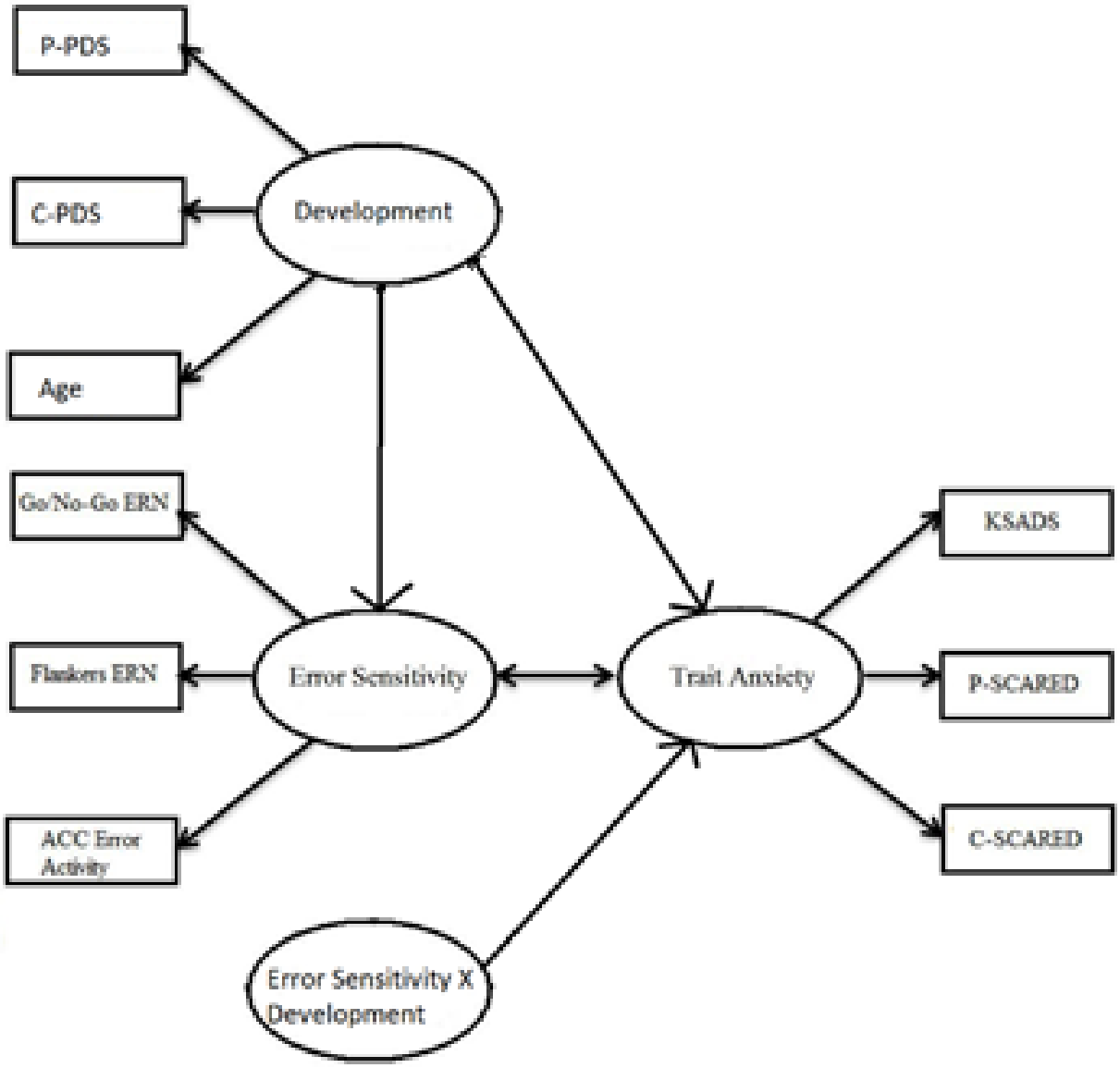

P-PDS
C-PDS
Development
Age
Go/No-Go ERN
Flankers ERN
Error Sensitivity
ACC Error Activity
Trait Anxiety
KSADS
P-SCARED
C-SCARED
Error Sensitivity X Development

Figure 5.

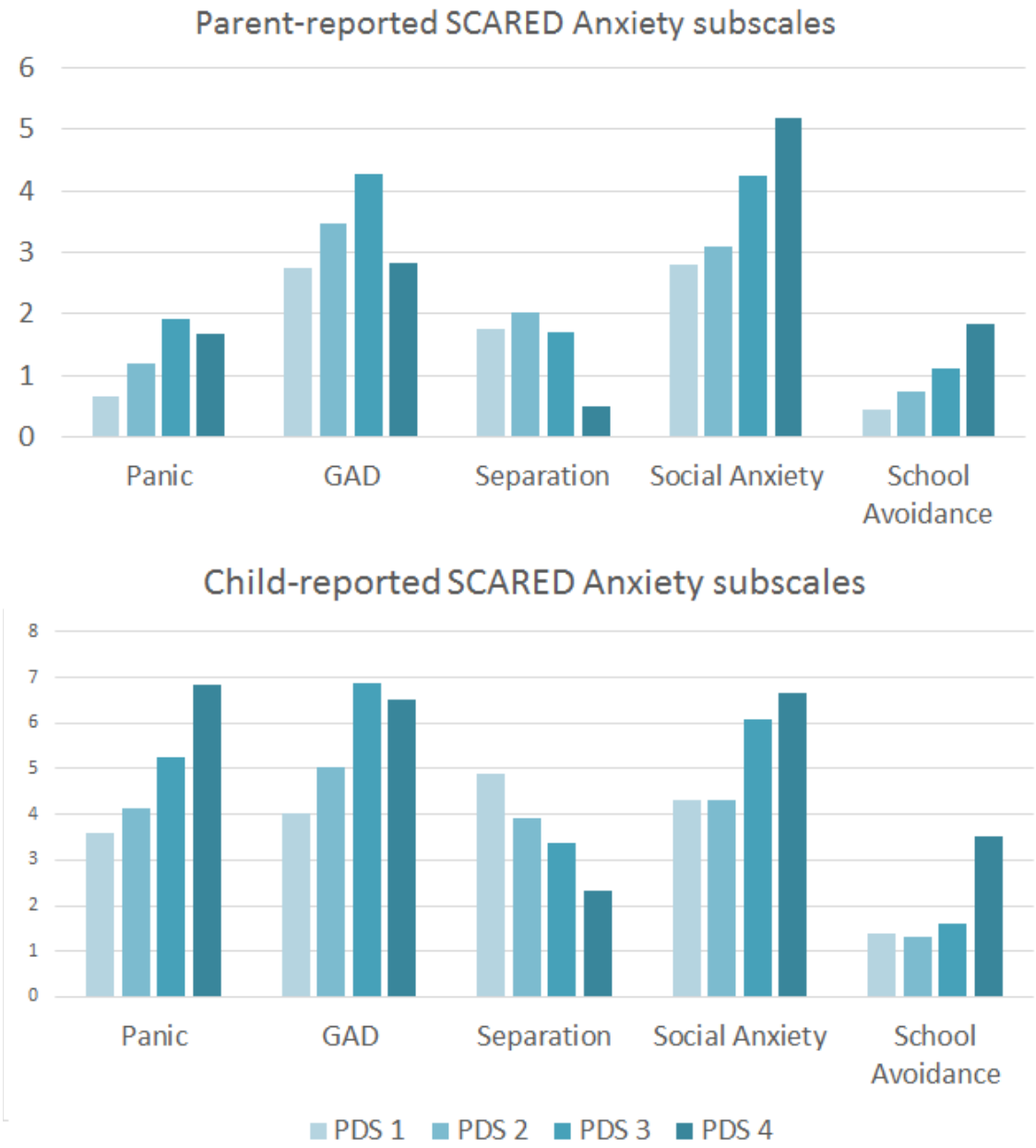


Figure 6. Parenet and Child-reported Anxiety subscales depicted by pubertal stage (PDS) as reported by the parent.

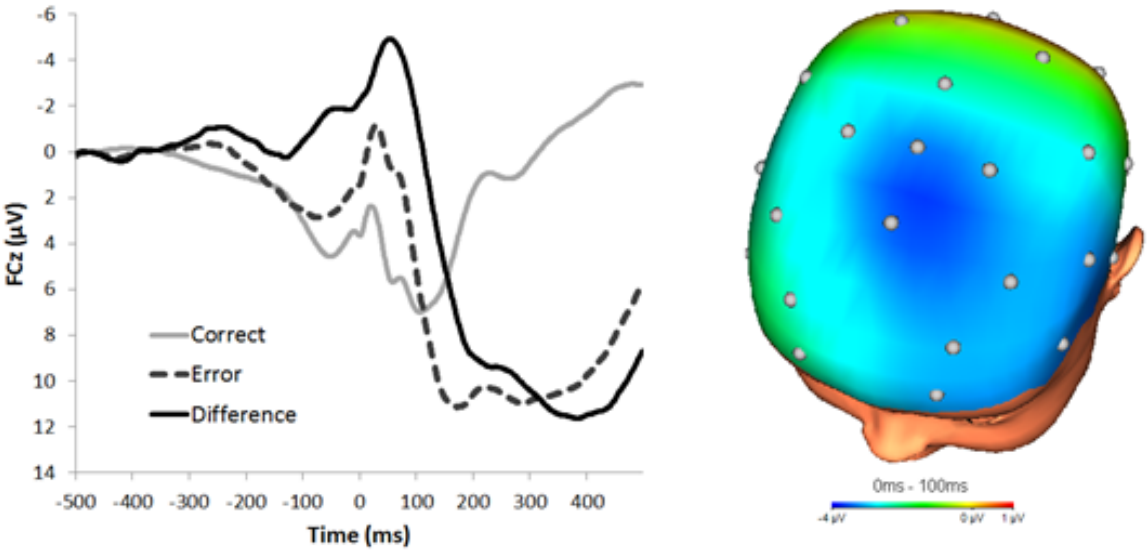


Figure 7. Response-locked ERP waveforms at FCz during the flankers task. On the right, a topographical map depicting the difference between error and correct responses in the time range of the ERN (0-100ms) during the flankers task.

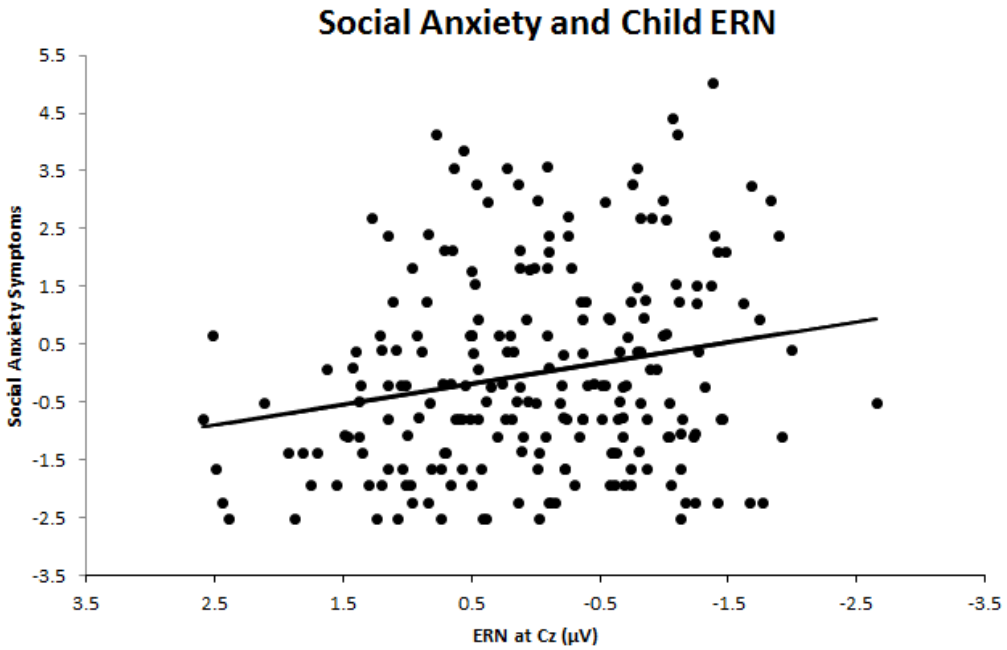


Figure 8. Scatterplot of the association between the flankers ERN at Cz and child social anxiety symptoms.

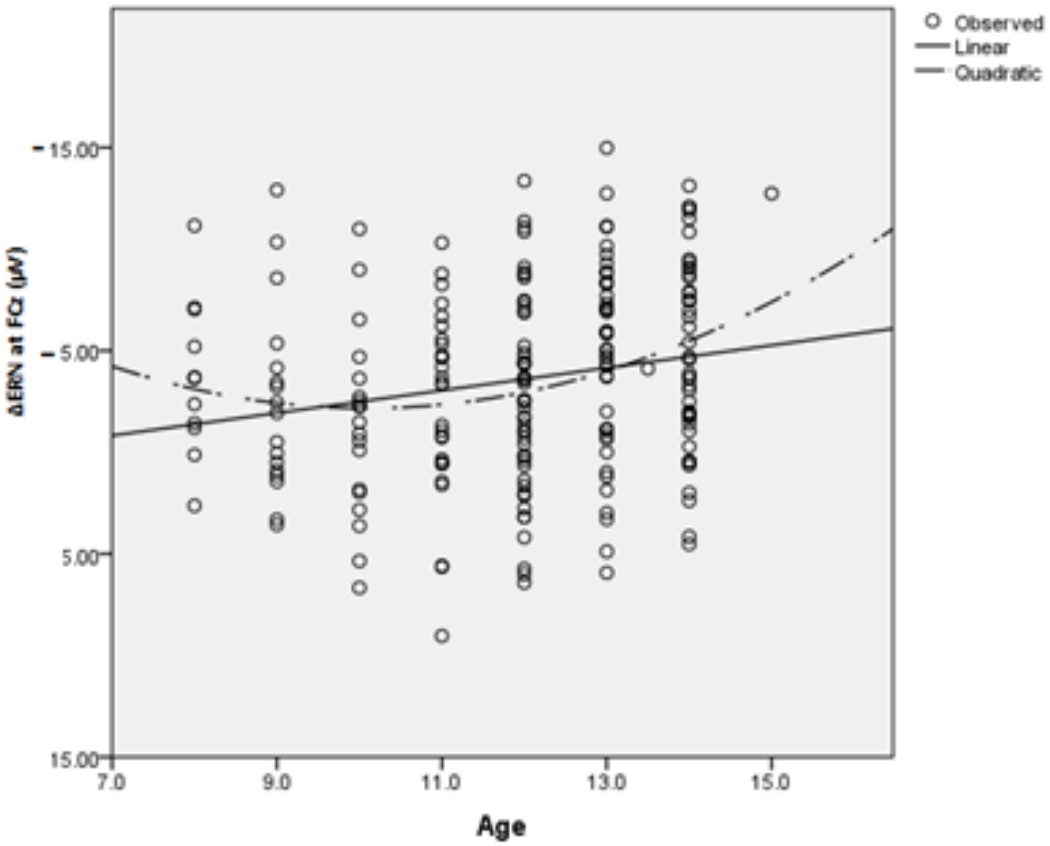


Figure 9. Scatter plot depicting the linear and quadratic relationship between age and the flankers ΔERN at FCz.

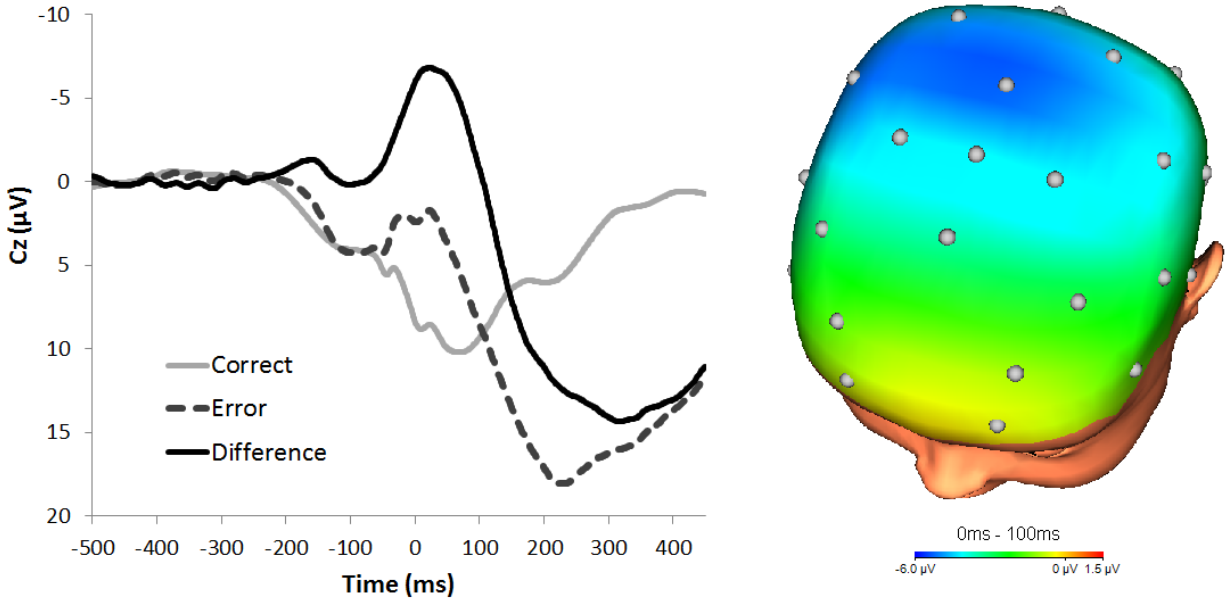


Figure 10. Response-locked ERP waveforms at Cz during the Go/NoGo task. On the right, a topographic map depicting the difference between error and correct respones in the time range of the ERN (0 - 100 ms) during the Go/NoGo task.

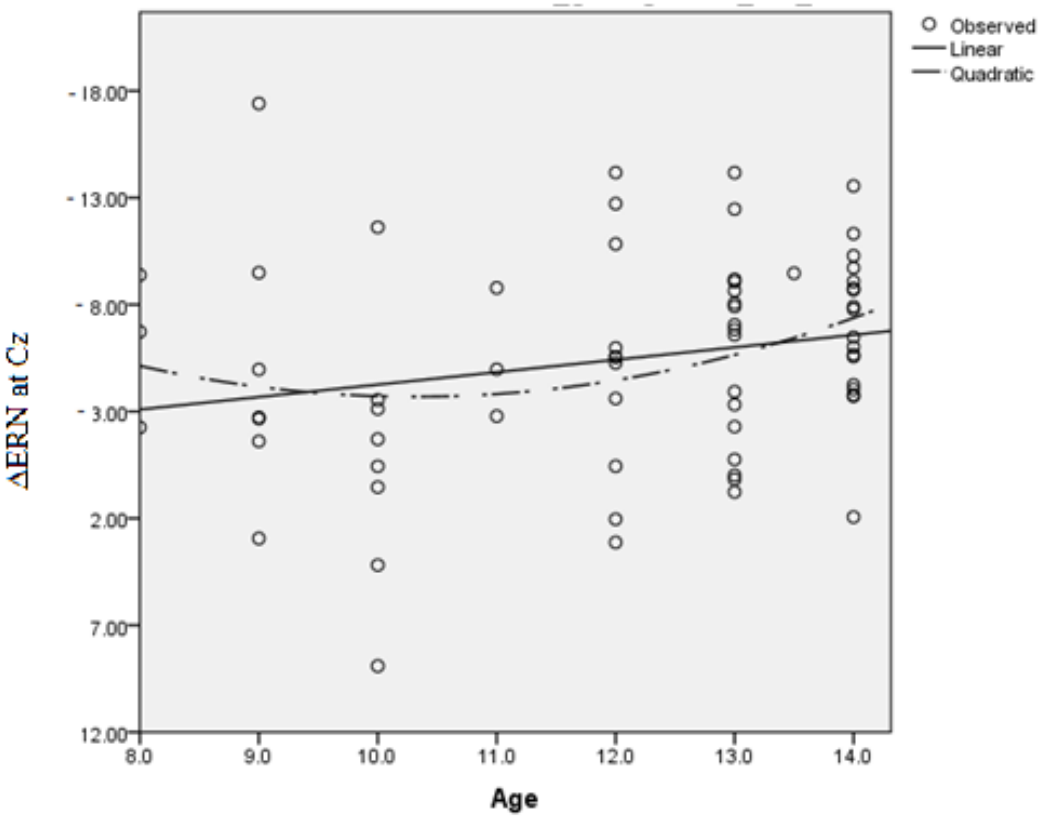


Figure 11. Scatter plot depicting the linear and quadratic relationship between age and the Go/NoGo ΔERN at Cz.

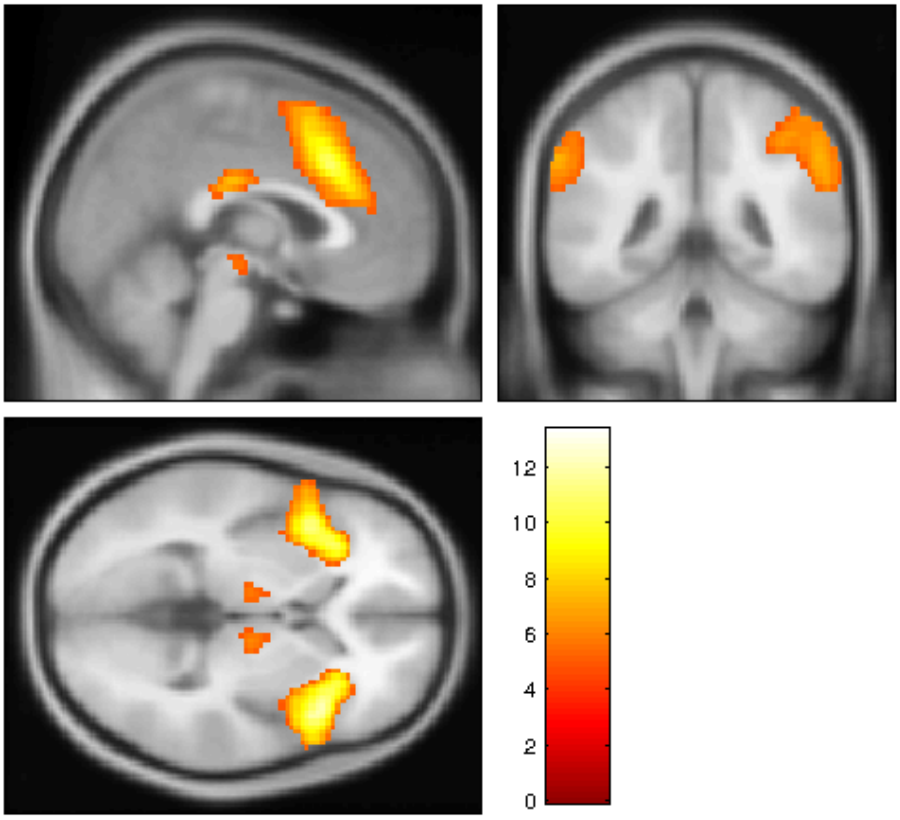


Figure 12. Go/NoGo fMRI activation for error minus correct trials.

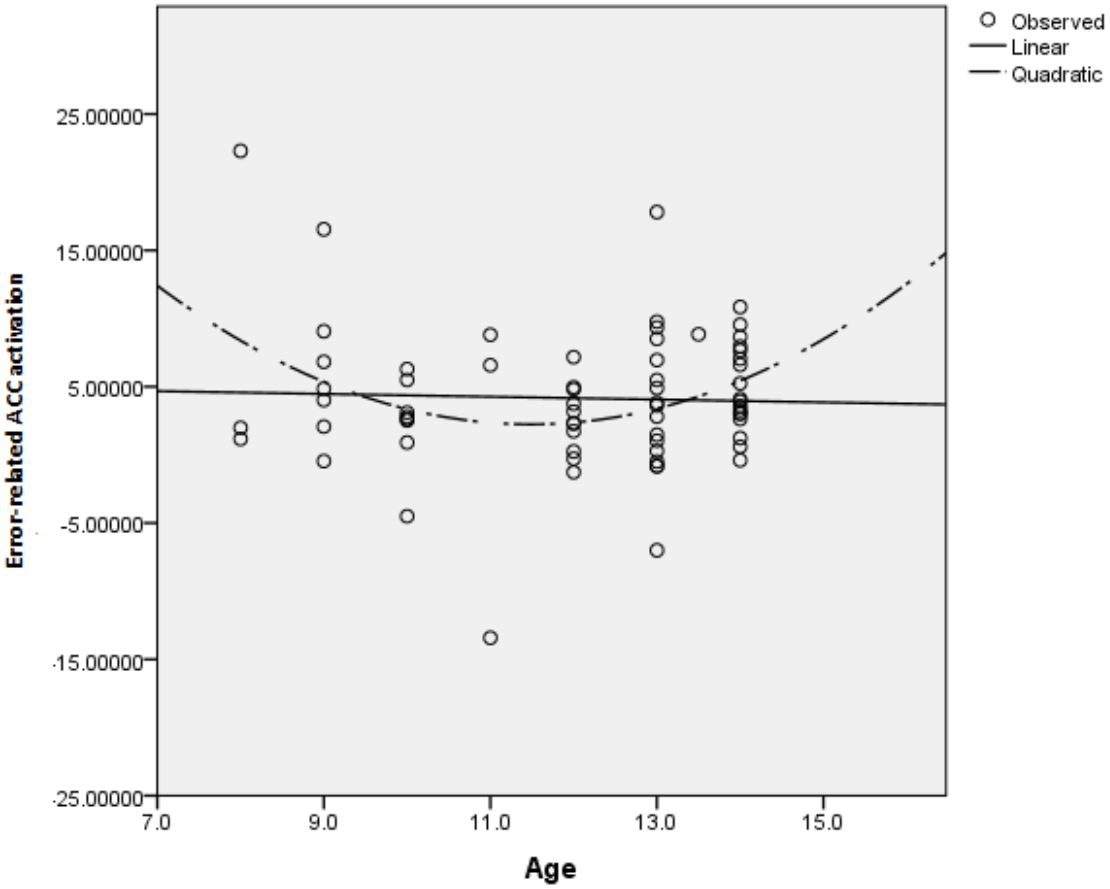


Figure 13. Scatter plot depicting the linear and quadratic relationship between age and error-related ACC activation.

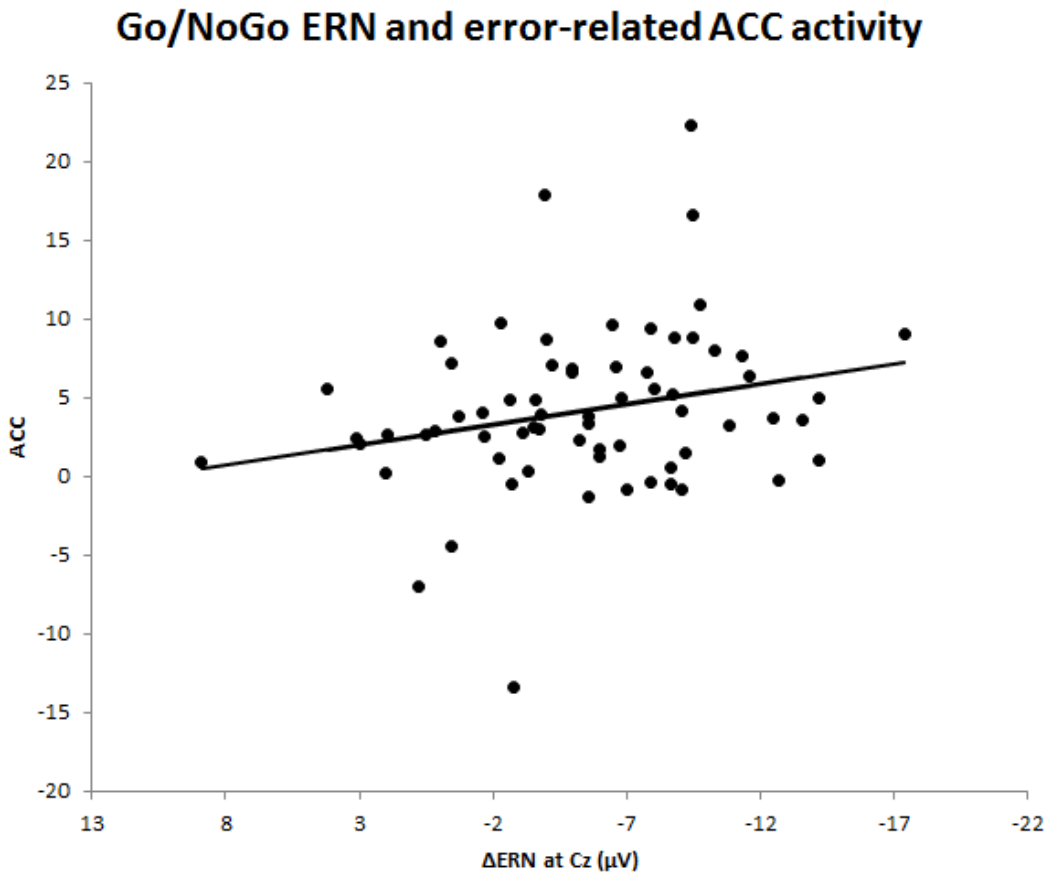


Figure 14. Scatter plot depicting the relationship between the Go/NoGo ΔERN at Cz and error-related ACC activation.

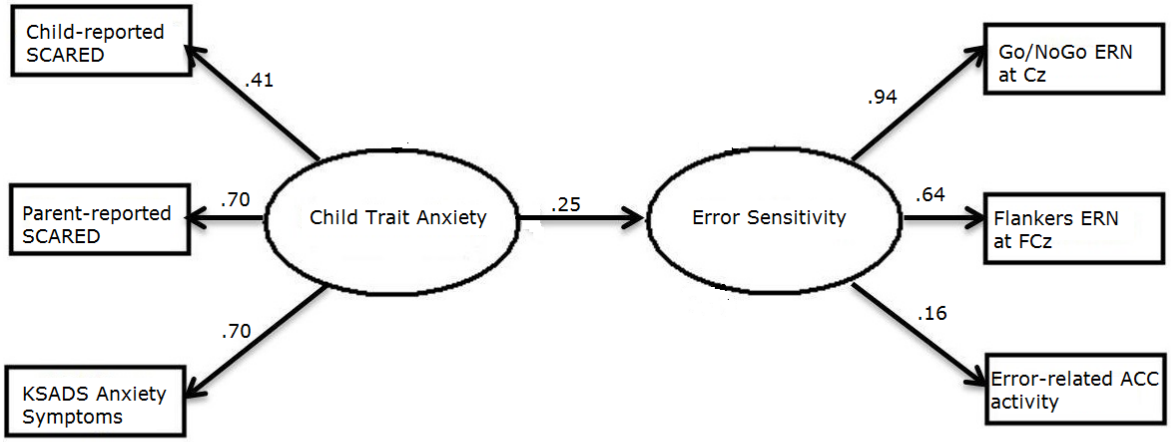


Figure 15. Latent variable model depicting the relationship between child trait anxiety and error sensitvity in the subsample of children with fMRI data.

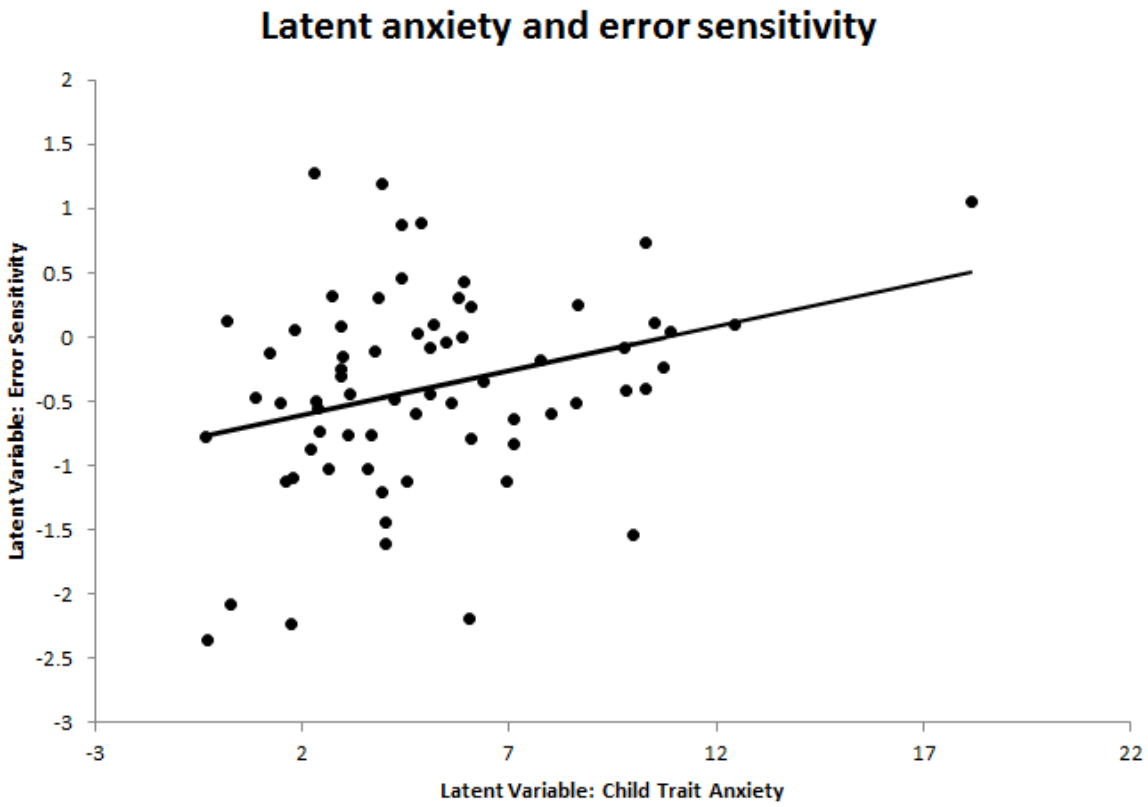


Figure 16. Scatter plot depicting the relationship between the latent variables: child trait anxiety and error sensitivity.

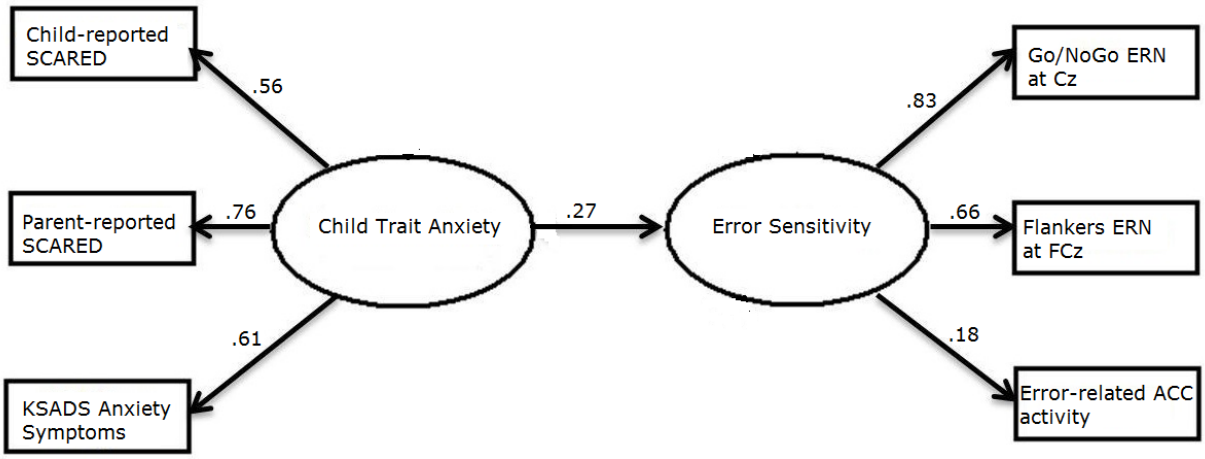


Figure 17. Latent variable model depicting the relationship between child trait anxiety and error sensitivity in the full sample

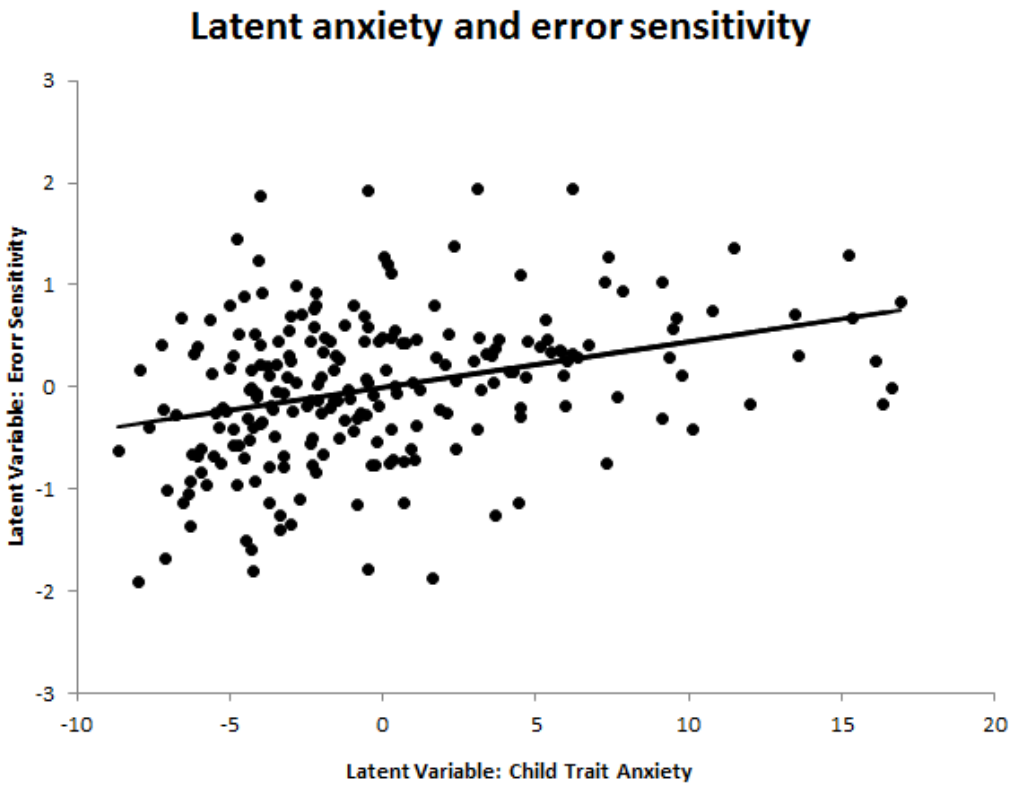


Figure 18. Scatter plot depicting the relationship between the latent variables: child trait anxiety and error sensitivity in the full sample

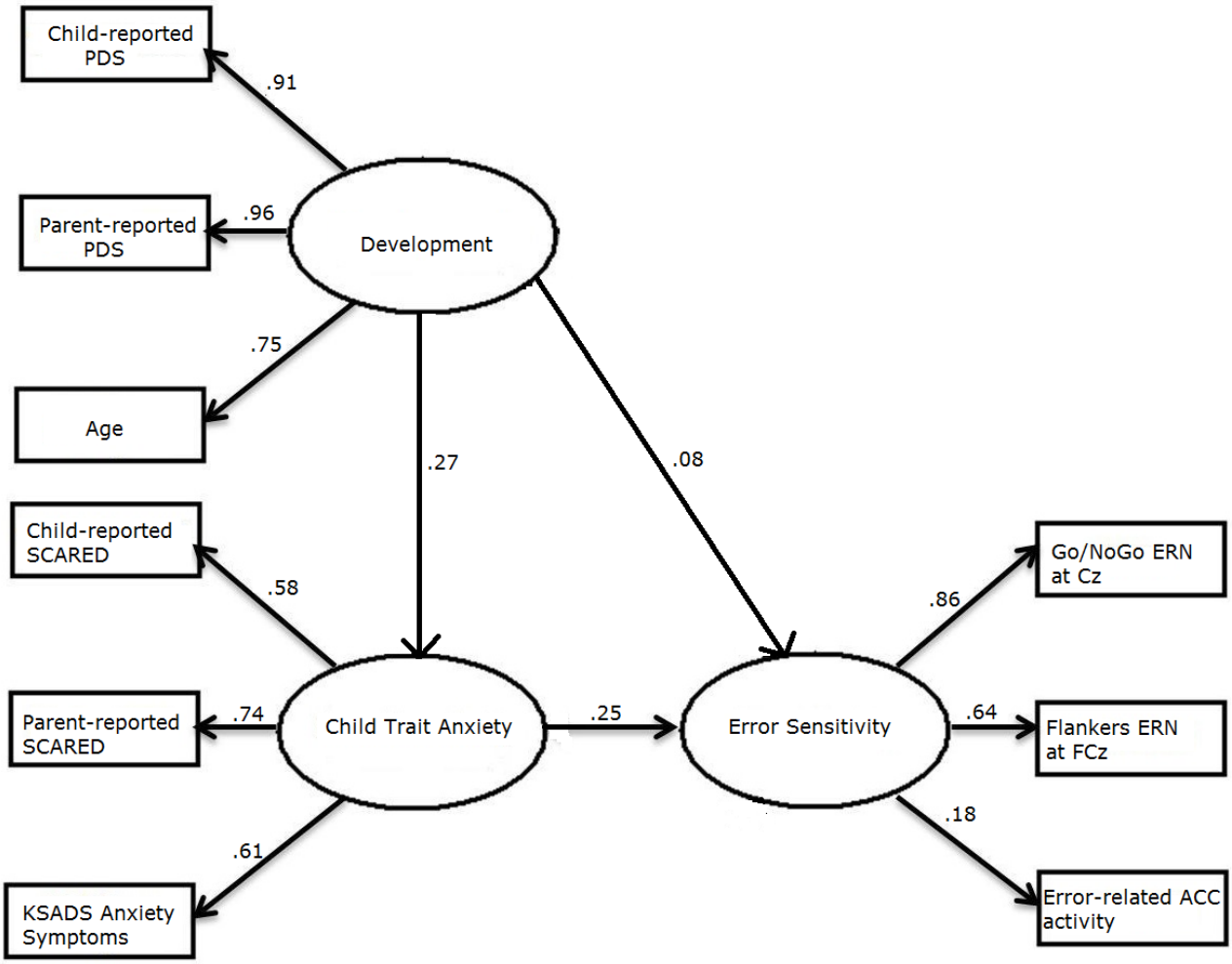


Figure 19. Latent variable model depciting the relationship between child trait anxiety, error sensitivity, and development in the full sample.