Cognitive Role of Medial PFC in Error Processing:
Lessons Learned from Healthy Children and Pediatric OCD, Anxiety, and ASD

by

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Dedication

To my parents, Arturo Carrasco and Madeline Alamo,

whose **infinite** love, support, and sacrifice has made all of this possible.

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ABSTRACT

Cognitive role of medial PFC in error processing: Lessons Learned from Pediatric
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Although the tendency to err may be considered to be an unavoidable human
quality, the ability to effectively acknowledge and to make up for previous mistakes
during task execution varies from one person to the next. Error-processing is a key
neurocognitive mechanism that conveys the ability to detect errors and also gives rise to a
series of compensatory mechanisms meant to adapt behavior and correct for previous
mistakes. As part of this dissertation, I will present data supporting the use of the error-
related negativity (or ERN) and other error-related ERPs, as endophenotypes for the
study of obsessive-compulsive behavior (OCD), anxiety, and autism.

Chapter I

Introduction

The purpose of this dissertation was to assess the development of error-processing in healthy development and in pediatric samples with autism, obsessive-compulsive disorder, and anxiety. The increased efficiency in the collection of event-related potential (ERP) data over the past decade has opened the doors towards improved exploration of the brain-based mechanisms underlying executive functions in each of these populations, using non-invasive and well-tolerated methods. Among its other uses, ERP methods have allowed for the recording of increased neural activity occurring immediately following error commission (Gehring et al., in press). Error-processing involves the *detection* of mistakes and the subsequent processes that are initiated to *counter* said mistakes, in an effort to improve task performance (Barnes et al., 2011).

Performance on behavioral tasks is constantly overseen by a complex brain system that is reactive to errors (Gehring et al., in press; Mathalon et al., 2003). Evidence using a wide array of converging methodologies has confirmed the role of the anterior cingulate cortex in supporting error-processing. Recent neuropathological, neuroimaging, and metabolic studies in autism, anxiety, and OCD have confirmed the presence of significant abnormalities in brain regions related to error monitoring, hence suggesting that this circuitry mediates atypical error processing in all three disorders (Agam et al., 2010; Bush et al., 2000; Hammer et al., 2009; Milad and Rauch, 2012; Yucel et al., 2003).

Justification: ERP study of error processing in psychiatric populations

ERP methods offer a promising tool for the investigation of the neural markers that underlie psychiatric disease processes. In 2009, a call to action by members of the National Institute of Mental Health (NIMH) and the *Research Domain Criteria (RDoC) Project* highlighted the value of studying overlapping cognitive mechanisms among psychiatric disorders, for the purpose of facilitating greater understanding of the shared etiology and pathogenesis in related disorders (Insel and Cuthbert, 2009). The research findings presented in this dissertation attempt to address the RDoC's call head on, by providing an *in-depth characterization* of error-related ERPs in OCD, anxiety, and autism, and by *addressing the commonalities* across each of these neural signatures in all three disorders (Hanna and Carrasco, personal communication).

Additional reasons to study error-processing in children include the need to investigate and better understand the differences in cognitive development between healthy children and pediatric psychiatric samples, for the purpose of understanding where typical and atypical developmental trajectories begin to diverge (Torpey et al., 2012). Finally, because ERP methodologies may be used in the future for the purpose of assessing neural responses to pharmacological treatment and behavioral interventions (Banaschewski and Brandeis, 2007; Luck et al., 2011), the research presented as part of this dissertation may become useful in order to further describe and validate ERP-based biomarkers that may one day be useful as neural indicators of disease severity.

Introduction to error-related ERP components

The electrophysiological study of the neural system underlying error-processing has centered on the error-related negativity (Stern et al.) or negativity error (Iacono and

Malone), the correct response negativity (CRN), and the error positivity (Pe) (Arbel and Donchin, 2009; Coles et al., 2001; Falkenstein et al., 1991). The ERN is a negative deflection in the response-locked event-related potential that is frontally-maximal. It peaks about 0-100 ms after an erroneous response (Gehring et al., in press); this potential originates from the anterior cingulate cortex (Herrmann et al., 2004; Ladouceur et al., 2007). The CRN peaks approximately at the same time as the ERN, albeit following correct responses; given its similarities in timing and localization to the ERN, it is believed that the CRN reflects a similar performance monitoring mechanism during the processing of correct trials (Moser et al., 2012).

The ERN is followed by the error positivity (Pe), a positive deflection peaking 100 - 500 ms following error-commission (Gehring et al., in press). Recent evidence has shown that the Pe is a *complex* consisting of two distinct waveforms: the early, fronto-central Pe and the late posterior Pe (Arbel and Donchin, 2009). While most research has focused on the role of the ERN in error detection, the field of cognitive neuroscience is just beginning to uncover the functional significance of the early and late Pe. The specific function of the early positivity (early Pe) and late positivity (late Pe) has been debated, though it has been observed that the early Pe may reflect activity of a neural mechanism associated with the initiation of post-error adjustments in behavior, for the purpose of improving task accuracy (Hajcak et al., 2003). The late Pe seems to reflect the conscious recognition and awareness that a mistake was made and the initiation of a mechanism involving the updating of working memory for the purpose of initiating learning mechanisms following error-commission (Shalgi et al., 2009).

The ERN as an endophenotype

The use of endophenotypes for advancing our understanding of the brain mechanisms that give rise to psychiatric illness has been a major focus within the field of psychiatry over the past decade. Endophenotypes are quantitative traits that, in theory, are: a) relatively easy to measure, and b) reflect genetically-influenced qualities associated with brain function, and c) provide a link between genetic predisposition and eventual disease onset. In the past, endophenotypic research strategies have been useful for identifying and characterizing susceptibility genes associated with disease. In addition, it has been suggested that endophenotypes may have a wider impact in determining vulnerability to illness, and may be suitable for guiding the translation of human findings to animal models (Courtet et al., 2012).

The ERN has been proposed as a potential endophenotype for internalizing disorders, and is thought to represent an irregularity in information-processing that links genetic predisposition to subsequent psychopathology (Olvet and Hajcak, 2008). The research highlighted in this dissertation seems to suggest that the ERN may be useful as an endophenotype that is both present and easily characterizable from an early age in children at risk for OCD and anxiety. I will next review the attributes defined by Gottesman & Gould (Gottesman and Gould, 2003) as criteria for designating a given trait as an endophenotype.

Criteria 1: Endophenotypes are characterized by their association to disease, but are not influenced by changes in disease-related state levels in symptom severity. By definition, an endophenotype should be associated with a particular disease; this is particularly true in the case of the ERN, in the sense that elevated ERN amplitude has

been observed in a wide array of psychiatric disorders, including OCD, anxiety, depression, and autism (Olvet and Hajcak, 2008). Curiously, the ERN does not appear to change with fluctuating levels in symptom severity in most clinical studies. Specifically, increasing state levels of OCD (Hammer et al., 2009; Johannes et al., 2001; Riesel et al., 2011; (Endrass et al., 2008)) and anxiety (Ladouceur et al., 2006) do not appear to affect the amplitude of the ERN in many studies. In addition, recent studies have provided evidence for an enhanced ERN that did not decrease in amplitude following effective CBT and pharmacological treatment in OCD (Hajcak et al., 2008; Stern et al., 2010), thus providing additional evidence for the use of the ERN as an endophenotype.

However, not all studies of the ERN in psychiatric populations agree with the notion that ERN amplitude *does not* change as a function of state symptom severity. It is important to point out that these studies were, for the most part, exploratory, underpowered, and either a) did not correct for multiple comparisons (thus severely escalating the possibility of Type I error), and/or b) used parametric methods of analysis based on invalid assumptions about the characteristics of their clinical data (Gehring et al., 2000; Hajcak et al., 2003; Vocat et al., 2008; Xiao et al., 2011). Whether any of these options could have in turn led to invalid conclusions of the relationship between state levels of symptom severity and ERN amplitude in the afore-mentioned studies could potentially be the subject for future research.

Criteria 2: Endophenotypes must also be heritable and present in individuals at genetic risk for a particular disorder (including first degree relatives, such as siblings and offspring). The ERN meets *Criteria 2*, and shows moderate heritability (Anokhin et

al., 2008), Additionally, elevated ERN amplitudes have been observed in both adult patients with OCD and their unaffected siblings (Riesel et al., 2011).

Criteria 3: Endophenotypes are, according to theory, present before disorder onset. They remain static throughout development or, alternatively, change over the years in a way that is well characterized and understood (Iacono and Malone, 2012). To our knowledge, pediatric research in regards to the presence of elevated ERN amplitudes in unaffected siblings of children with OCD has yet to be pursued. This dissertation aims to address this gap in the literature, for the purpose of further validating the use of the ERN as a potential endophenotype in psychiatric research. In addition, this dissertation will aim to describe the ERN and other error-related ERP components in a series of well-characterized pediatric ASD and anxiety populations, for the purpose of beginning to determine whether the ERN may be a useful endophenotype that is potentially present early on in children with both ASD and anxiety.

The ERN and Psychopathology: A review of the pertinent literature

Previously, it was mentioned that the ERN may represent an irregularity in information-processing that may potentially link genetic predisposition to subsequent psychopathology and therefore may be a useful endophenotype. The specific link between ERN and psychopathology has yet to be fully understood. A review of the current understanding on how increased ERN paves the way towards psychopathology has been included below.

In 2010, Aarts and Pourtois proposed a link between increased ERN and deficient processing efficiency in high-anxious individuals (Aarts and Pourtois, 2011). According to *Eysenck's Processing Efficiency Theory* and its application to anxiety disorders

(Eysenck et al., 2007), attention is often allocated to internal threatening stimuli (such as worrying thoughts, ruminations, repetitive behaviors) in highly-anxious participants; this in turn leads to a reduction of the attentional focus on the current task demands. Aarts and Pourtois theorized that, to maintain performance during task completion, an anxious individual could compensate for this reduced efficiency state by increasing cognitive effort (Aarts and Pourtois, 2011). This mechanism could potentially account for increased ERN in patients with OCD and anxiety, who are aversive to making mistakes (Frost and Shows, 1993; Rector et al., 2009; Ye et al., 2008). This same mechanism could also clarify the presence of increased ERN in children with ASD, who often suffer from attentional lapses due to the presence of repetitive or impulsive tendencies that may interfere with overall task performance (Sasson, 2008 #216). Though this theory was not directly addressed in this dissertation, future studies may aim to investigate whether Eysenck's processing efficiency theory may help explain and better synthesize clinical ERP findings across anxiety, OCD, and autism.

As mentioned earlier, while most research has focused on the role of the ERN in error detection, the field of cognitive neuroscience is just beginning to uncover the functional significance of the early and late Pe. An additional aim associated with this dissertation was to perform exploratory analyses for the purpose of characterizing the relationship between Pe measures and clinical features.

The Eriksen Flanker Task and its use for Eliciting the ERN and Pe

The ERN, CRN and the early/late positivities can be recorded following errors during a number of different speeded response tasks, including the Eriksen Flankers task, the Simon task, color Stroop task, and the Go/No-Go task. For the purpose of my

dissertation, subjects were tested using the Eriksen Flanker task. The choice of use of a flanker task as part of our assessment battery was based on the fact that this is a relatively simple task to make, and easy for the children to understand. In addition, this task is able to engage error-processing mechanisms in young children; a previous meta-analysis of several flanker task studies showed increased activation in specific regions of the medial frontal cortex (MFC), including the ACC, which has been implicated in error-processing (Nee et al., 2007).

As evidenced in **Figure 1**, during the Eriksen flanker task, participants were asked to respond to a target stimulus that is surrounded by flanker stimuli on each side. In this particular task, a right- or left-pointing central arrow is surrounded by right- or left-pointing distractor arrows (Eriksen & Eriksen, 1974). In the incompatible/*incongruent* condition (e.g. < < > < <), the flanker stimuli point in a direction opposite to the target stimulus; thus, the participant must resolve the conflict between the two potential responses. Reaction times and error rates tend to be inflated in the incompatible/*incongruent* condition, relative to a compatible/*congruent* condition (e.g. < < < < <) in which only one response is elicited. The stimuli remain on the screen for 250 msec, with the interval between consecutive stimuli lasting 1500 msec. Following a practice block of 32 trials, subjects completed 8 blocks of 64 trials (total: 512 trials).

Dissertation Goals

As a whole, this dissertation proceeds to examine the concept of "error processing" in both healthy and psychiatric pediatric populations. Better characterizing error-related ERPs across these populations will allow for the increased understanding of error processing across child psychopathology.

Figure 1.1. Dissertation Task. The Eriksen flanker task (presented here) consisted of 50% congruent and 50% incongruent trials. Children were instructed to identify the direction in which the middle arrow was pointing.
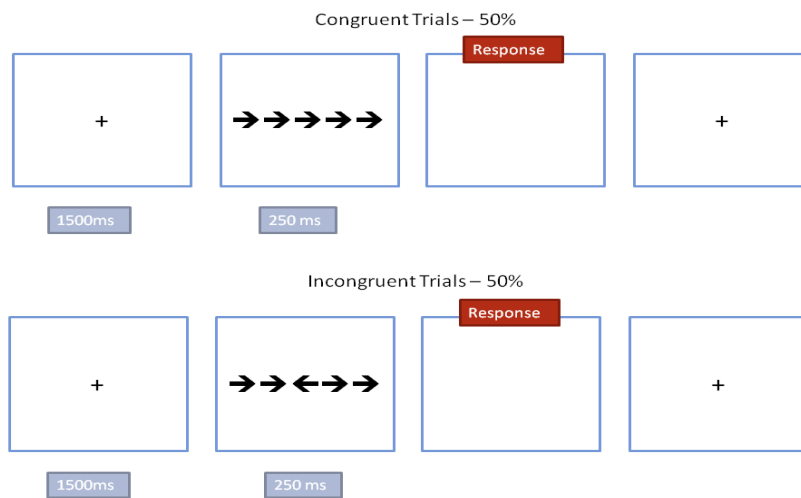
Congruent Trials – 50%

Response

+

➔➔➔➔➔

+

1500ms

250 ms

Incongruent Trials – 50%

Response

+

➔➔⬅➔➔

+

1500ms

250 ms

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Chapter II

Error-processing Mechanisms in Healthy Children: Changes in ERN and Early Pe Across
Development

Introduction

Across a broad spectrum of disciplines, spanning cognitive neuroscience and
electrophysiological perspectives, interest has mounted in a circuitry of higher-order
networks that support efficient goal-directed behavior, self-regulation, and the capacity to
flexibly adapt thoughts and behaviors. Efficient execution of goal-directed behavior relies
on the ability to learn and correct previous mistakes in task execution, a function that is
primarily referred to as *error-processing* (Barnes et al., 2011; Simons, 2010). Although
there have been significant advances in the recognition of the brain-based mechanisms
supporting error-processing (Mathalon et al., 2003), the development of this executive
function across childhood has yet to be fully understood.

The electrophysiological study of the neural system underlying error-processing
has centered on the error-related negativity (Stern et al.) or negativity error (Iacono and
Malone), the correct response negativity (CRN), and the error positivity (Pe) (Arbel and
Donchin, 2009; Coles et al., 2001; Falkenstein et al., 1991). The ERN is a negative
deflection in the response-locked event-related potential that is both frontally-maximal
and peaks about 0-100 ms after an erroneous response (Gehring et al., in press); this
potential originates from the anterior cingulate cortex (Herrmann et al., 2004; Ladouceur
et al., 2007). The CRN peaks approximately at the same time as the ERN, albeit

following correct responses; given its similarities in timing and localization to the ERN, it is believed that the CRN reflects a similar performance monitoring mechanism during the processing of correct trials (Moser et al., 2012).

The ERN is followed by the error positivity (Pe), a positive deflection peaking 100 - 500 ms following error-commission (Gehring et al., in press). Recent evidence has shown that the Pe is a *complex* consisting of two distinct waveforms: the early, fronto-central Pe and the late posterior Pe (Arbel and Donchin, 2009). While most research has focused on the role of the ERN in error detection, the field of cognitive neuroscience is just beginning to uncover the functional significance of the early and late Pe. The specific function of the early positivity (early Pe) and late positivity (late Pe) has been debated, though it has been observed that the early Pe may reflect activity of a neural mechanism associated with the initiation of post-error adjustments in behavior, for the purpose of improving task accuracy (Hajcak et al., 2003a). The late Pe seems to reflect the conscious recognition and awareness that a mistake was made and the initiation of a mechanism involving the updating of working memory for the purpose of initiating learning mechanisms following error-commission (Shalgi et al., 2009).

Efforts to characterize the development of the ERN commenced early in the twenty-first century (Davies et al., 2004a; Ladouceur et al., 2007; Wiersema et al., 2007). A series of papers have since suggested that ERN amplitude increases as a function of age, a process likely driven by the increased maturation of the anterior cingulate over time (Adleman et al., 2002; Cunningham et al., 2002; Rubia et al., 2007).

Though it was originally presumed that the ERN could not be observed prior to age 10, investigators have recently reported observing a small ERN early in life, using far

simpler tasks (Torpey et al., 2012). An unreplicated report by Berger in 2006 showed a broad negative deflection similar in structure and localization to the ERN in children 6-9 months of age, after observing an incorrect solution to a simple arithmetic problem (such as "1 doll + 1 doll = no dolls") (Berger et al., 2006). Meanwhile, in a study seeking to link ERN amplitude to age and academic success, there was evidence to suggest that an ERN may be observed in children as young as 5 years of age (Brooker et al., 2011; Grammer et al., in preparation). The ERN then continues to grow in size through late childhood and adolescence (Davies et al., 2004a; Davies et al., 2004b; Hogan et al., 2005; Santesso and Segalowitz, 2008; Santesso et al., 2006; Segalowitz and Davies, 2004), though ERN amplitude may not become adult-like until the late teens (Coch and Gullick, in press). We predicted that, in our sample of healthy children, ERN amplitude would increase as a function of age as well.

Some studies have suggested that the undifferentiated Pe complex (i.e. the entire positive deflection consisting of the early and late Pe) does not change with age (Davies et al., 2004a). To our knowledge, a study of the developmental time course of the early and late error positivities drawing from a large sample of children and adolescents has yet to be performed.

The primary purpose of this study was to study error-related brain activity – including the ERN, CRN and the early and late Pe – in 60 healthy children performing a flanker task. We also aimed to assess the relationship between age and the error-related ERP amplitude among the children in this sample. Given that there remains a paucity of studies examining the collective simultaneous effects of psychological symptoms and personality traits on error monitoring in children, a final goal was to characterize the

relationship between emotional, behavioral, and personality traits vs. error monitoring, as measured by the ERN, CRN, the early Pe, and the late Pe.

Methods

Participants

An original sample of 61 healthy participants were recruited from the surrounding community; one child dropped out after refusing to complete the EEG. All participants lived with at least one English-speaking biological parent who was willing to participate in research and all were currently enrolled at school, did not have a history of learning disability or grade retention. All were paid for their interviews and psychophysiological recordings. As shown in **Table 1**, the average age of the participants was 14.4 years (std. dev. 3.1, age range: 8 – 19 yo). The group consisted of 27 males and 33 females.

In order to evaluate error-related ERP changes across early development, the final sample of 60 participants was divided into three groups based on age: Group 1 included the 33% oldest children in the sample (average age (years): 17.6; std. dev. (years): 0.9; age range (years): 16.3 – 19.7; n = 20). Group 2 included the middle 33% oldest children in the sample (average age (years): 14.6; std. dev. (years): 1.2; age range (years): 12.7 – 16.2; n = 20). Group 3 included the youngest 33% children in the sample (average age (years): 10.8; std. dev. (years): 1.3; age range (years): 8.3 – 12.6; n = 20).

Parent- and Child-Report Clinical Interviews and Questionnaires

All 60 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version (Kaufman et

al., 1997) and the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (Hanna, 2007).

The Child Behavior Checklist (CBCL) is broad assessment of emotional and behavioral problems that was completed by parents of all study participants (Achenbach, 1991). The measure is appropriate for use in children ages 6–18, and consists of a number of empirically-supported rating scales (based on DSM-IV criteria), and additional syndrome subscales, developed using principal component analysis. The CBCL provided raw scores for total behavioral problems, internalizing problems (a combination of withdrawn, anxiety, and depressive symptoms), and externalizing problems. Additional raw syndrome scores measured negative affectivity (anxious/depressed symptoms), withdrawn behaviors (withdrawn/depressed symptoms), and anxiety problems. Other self-report scales completed by all child participants included the Children's Depression Inventory (CDI) (Kovacs, 1992).

Task

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions. They were instructed to respond as quickly and accurately as possible to the central arrow target, while ignoring the adjacent arrows, by pressing one of two buttons indicating the direction of the middle arrow (i.e., right versus left). The stimuli remained on the screen for 250 msec, with the interval between consecutive stimuli lasting 1500 msec.

Procedure

Each participant was seated 0.65 meters directly in front of the computer monitor and told to place equal emphasis on speed and accuracy in responding. Following a practice block of 32 trials, each subject completed 8 blocks of 64 trials for a total of 512 trials. The subjects were told to place equal emphasis on speed and accuracy in their responses. Performance feedback was provided after every block to yield error rates of approximately 10%, ensuring an adequate number of trials for stable error-related waveforms.

Electrophysiological Recording, Data Reduction, and Analysis

The EEG was recorded from DC-512 Hz using scalp electrodes, two mastoid electrodes, and four EOG electrodes using the BioSemi ActiveTwo system, an EEG active-electrode sensor system that is well-tolerated by children because it does not require scalp abrasion. Data were recorded referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode. A nylon mesh cap was used with sensors embedded in it. EEG data were screened for artifacts using visual inspection as well as automated artifact rejection algorithms in the Matlab-based analysis software EEGLAB. Eye movement artifacts were corrected using the Gratton regression procedure (Gratton et al., 1989). Behavioral measures included accuracy expressed as a percentage of all trials. Average reaction times on error and correct trials were calculated separately.

The error-related negativity and both error positivity components were quantified using mean amplitude measures relative to a pre-response baseline from -200 to -50 msec. The mean amplitude of the error-related negativity was computed at FCz in a window from 0 to 100 msec following incorrect response trials; measurements were

made at FCz given that the difference between ERN and CRN was largest at this electrode. The correct response negativity consisted of the same measure computed on correct response trials. The mean amplitude of the early error positivity was computed at Cz in a window from 100 msec to 200 msec following the incorrect response on error trials and the mean amplitude of the late error positivity in a window from 250 msec to 350 msec following the incorrect response on error trials; measurements were made at Cz given that the difference between error and correct waveforms at their respective time windows was largest at this electrode.

Separate analyses of the correct-related negativity (in correct trials) error-related negativity and both error positivity components (in error trials) were conducted with a repeated-measure analysis of variance and Student's t-tests in order to assess for changes in the CRN, ERN and Pe components across development. Additional post-hoc tests across the developmental groups were pursued using the Tukey adjustment for multiple comparisons. Correlation analyses involving Pearson correlation coefficients and Spearman's rank correlation coefficients were performed in order to determine the relationship between the behavioral and CBCL clinical measures (respectively) vs. the ERP component amplitudes.

All behavioral and clinical measures were statistically evaluated using SPSS 19, whereas event-related potential measures were analyzed using custom software written in C and in Matlab, as well as the Matlab-based EEGLAB software package (http://www.sccn.ucsd.edu/eeglab/). All statistical tests were two-tailed with the alpha level set at 0.05.

Results

Preliminary Analyses

Clinical, behavioral and ERP measures were examined for skewness and outliers. Both ERP and task-related behavioral measures satisfied assumptions of parametric statistics, although one outlier (ERN over +/- 3 std. devs.) was identified; subsequent ERP analyses included this outlier, though all analyses were repeated without this outlier in order to confirm whether this changed our results. Meanwhile, group differences across the CBCL measures were analyzed with methods other than standard parametric tests, given that this data was heavily skewed, and characterized by an over-abundance of zero values.

Behavioral and Clinical Data Overview

Behavioral data for all 60 participants are presented in **Table 1**. In general, children responded faster on error as opposed to correct trials ($t(59)$=43.145, p<.001). In addition, significant correlations were observed between age and accuracy (r = .3458, p<0.05), age and correct RT (r = -.6374, p<0.001), age and error RT (r = -.4041, p<0.001), and age and post-error slowing (r = -.3788, p<0.05), indicating that older children responded faster and more accurately than younger children.

Error-related Potential Data

ERP components for all 60 participants are highlighted in **Figure 1** and summarized in **Table 1**. Greater error-related negativity amplitude at electrode FCz was significantly correlated with greater accuracy (r = -.3208, p<0.05, n = 60). Meanwhile, CRN amplitude at FCz had significant negative correlations with correct RT (-.2990, p p<0.05), error RT (-.2679, p<0.05), and post-error slowing (-.4203, p<0.001). Removal of an outlier subject did little to change these results (p still < 0.05).

Developmental time course of the ERN, early Pe, and late Pe

Error-related negativity amplitude was significantly correlated with age (r = -.3909, p<0.05, n = 60). As evidenced by the scatterplot in **Figure 2** and the waveforms in **Figure 3**, ERN amplitude increased (i.e. became more negative) as a function of increasing age. Early Pe amplitude correlated with age at trend-level (r = -.2530, p = p=.051, n = 60), i.e. early Pe amplitude became smaller with increasing age (also evidenced by the plot in **Figure 2**). Removal of an outlier did not change these results. No additional ERP components significantly correlated with age.

The sample of 60 participants was next divided into three groups based on age: Group 1 included the 33% oldest children in the sample (average age (years): 17.6; std. dev. (years): 0.9; age range (years): 16.3 – 19.7; n = 20). Group 2 included the middle 33% oldest children in the sample (average age (years): 14.6; std. dev. (years): 1.2; age range (years): 12.7 – 16.2; n = 20). Group 3 included the youngest 33% children in the sample (average age (years): 10.8; std. dev. (years): 1.3; age range (years): 8.3 – 12.6; n = 20). A significant ERN amplitude x Age group effect was observed ($F_{(2, 57)}$ = 4.160, p<0.05 (i.e., ERN became more negative with increasing age). Following correction for multiple comparisons, a significant difference was observed in ERN amplitude between the oldest 33% and youngest 33% of children in the distribution ($t(39)$=2.882, p<0.05).

Meanwhile, an early Pe amplitude x Age group effect was also observed ($F_{(2, 57)}$ = 3.899, p = 0.026, i.e. early Pe became less positive with age). Following correction for multiple comparisons, a significant difference was observed in early Pe amplitude between the oldest and youngest 33% of the children in the distribution $t(39)$=2.788,

p<0.05). Removal of an outlier outlier across each of these analyses did little to change these results (p still < 0.05).

Finally, the relationship between the ERN, CRN, early Pe, and late Pe amplitude and wide array of CBCL symptom measures was evaluated. When considering all 60 participants, ERN, CRN, early Pe, and late Pe amplitude did not significantly correlate with any of the CBCL symptom scales.

Discussion

Consistent with work in healthy youth, we here provided evidence that ERN amplitude increased as a function of age in a sample of 60 healthy children, ages 8 – 19 years old. This process is likely driven by the increased maturation of the anterior cingulate across the lifespan (Adleman et al., 2002; Cunningham et al., 2002; Rubia et al., 2007). However, it is quite possible that the emergence of increased ERN amplitude during adolescence may also be attributable to age-related increases in children's concern about committing errors (leading to the augmented engagement of the response monitoring system, and hence an increased ERN). Future research elucidating the functional basis of increased ERN amplitude in later childhood will provide invaluable insight into our understanding of the development of error-processing.

While the developmental time course of the Pe complex (including both the early *and* late Pe) have been examined in several studies, efforts to map the changes in the individual early and late Pe components across childhood and adolescence had yet to be performed until now. The present study extends previous research by being the first to

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present evidence of decreased early Pe amplitude in older adolescents, in comparison to younger children. No change was found in the late Pe, with increasing age.

Post-error slowing refers to the fact that, when subjects commit errors in speeded reaction-time tasks, post-error trials are characterized by unusually long reaction times for the purpose of initiating efforts to improve accuracy in future trials. A relationship has been observed between Pe amplitude and post-error slowing, where decreased amplitude of the combined Pe complex (including the early *and* late Pe) correlates with less post-error slowing (Hajcak et al., 2003b; Ladouceur et al., 2007). Our findings are in line with previous research, where post-error slowing has been observed to decrease with age in some (Fairweather, 1978), but not all studies (Hogan et al., 2005).

The decrease in Pe amplitude presumably reflects the decreased neural exertion required to efficiently address changing strategies following errors in order to avoid future slip-ups (Gupta et al., 2009); however, this relationship was not directly tested as part of this study. We approach these findings with extreme caution, specially given that the presence of broad slow negative wave following the ERN may have influenced our measurements of the early Pe. Future studies with more precise methodologies for measuring the early Pe (including PCA and time frequency analyses) may help better sort the relationship between this component and age.

One key limitation associated with this study was the divergence in the numbers of males (n = 25) and females (n = 35) that were recruited to participate in our analyses. Our study did not find any gender differences in the ERN, CRN, early Pe or late Pe; however, because males and females were not carefully matched to each other (based on

age and gender) for this analysis, it is possible that our study lacks the overall statistical power in order to gage for gender differences across error-related components.

A second limitation worth reporting involves the nature of our experimental design. For the purpose of this study, a cross-sectional approach was taken in order to assess differences in ERN and other error-related ERPs across development. This approach has its own shortcomings, including its inability to definitively prove a direct causal effect between age and ERN/early Pe changes across development. The understanding of changes in ERN and early Pe across development will be best served by the use of longitudinal methods that would avoid some of the shortcomings associated with the study of the ERN using cross-sectional methods. Future studies may aim to address this gap in the literature.

In sum, this study highlights changes in ERN and early Pe amplitudes in healthy children and adolescents. The study also confirms changes in the structure of the ERN across childhood and adolescence. Finally, the study presented evidence for decreased early Pe amplitude in older children, an effect possibly brought forth by a more efficient neural mechanism that is in charge of initiating post-error processes for the purpose of improving accuracy in subsequent trials. In the next chapter, we will turn our attention to the study of error-related ERP components, in children with anxiety disorders and obsessive-compulsive disorder.

Figure 2.1. Response locked ERP waveforms at FCz and Cz comparing correct and error trial waveforms in a sample of 60 healthy children. The ERN and CRN were measured at FCz, while the early and late Pe were measured at Cz. Response onset occurred at 0ms and negative is plotted up.
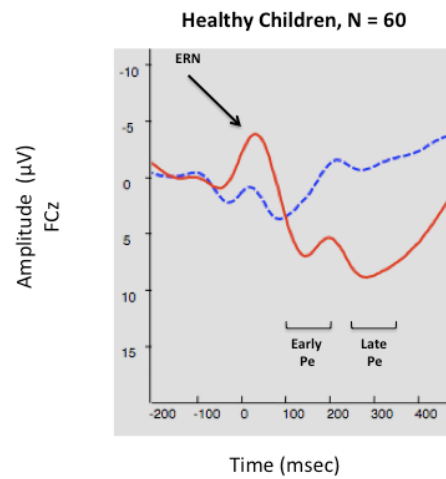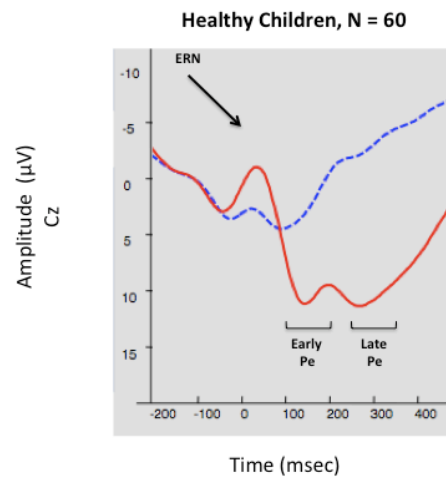
Figure 2.2. Developmental time course of the ERN and Early Pe. Error-related negativity amplitude was significantly correlated with age ($r = -.3909$, $p<0.05$, $n = 60$). Meanwhile, the Early Pe amplitude correlated with age at trend-level ($r = -.2530$, p = p=.051, n = 60). No additional ERP components significantly correlated with age.
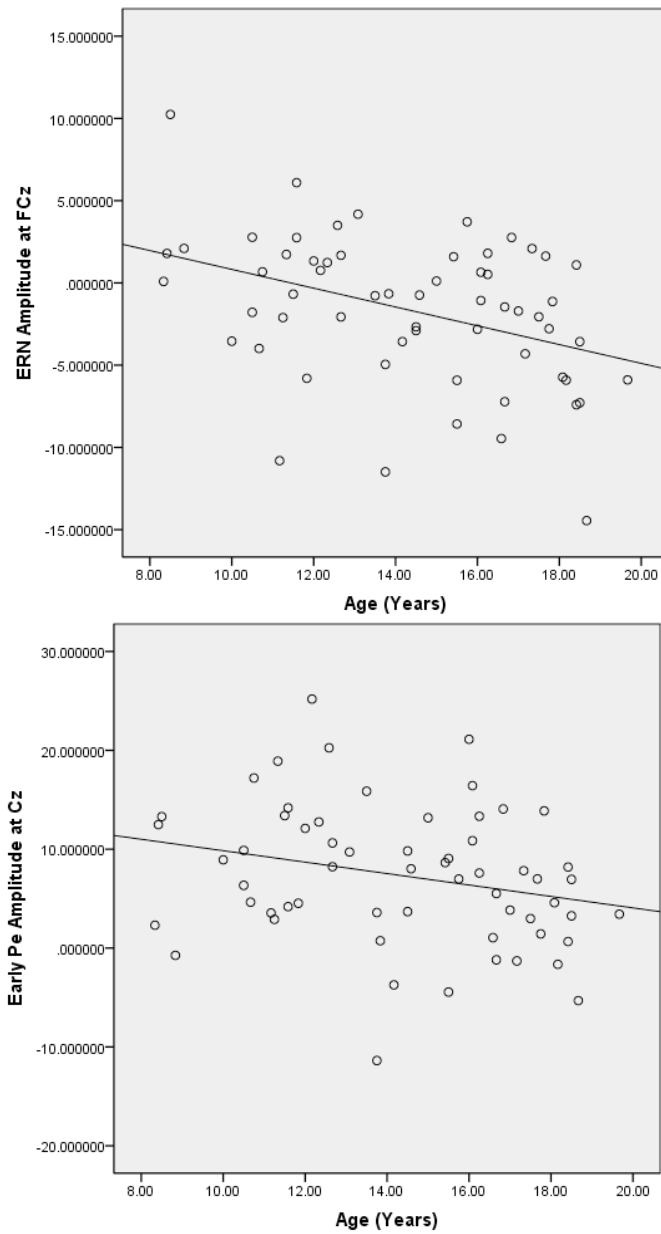
Figure 2.3. Response-locked ERPs at FCz and Cz across different developmental stages. The ERN and CRN were measured at FCz, while the early and late Pe were measured at Cz. For each panel, response onset occurred at 0ms and negative is plotted up.
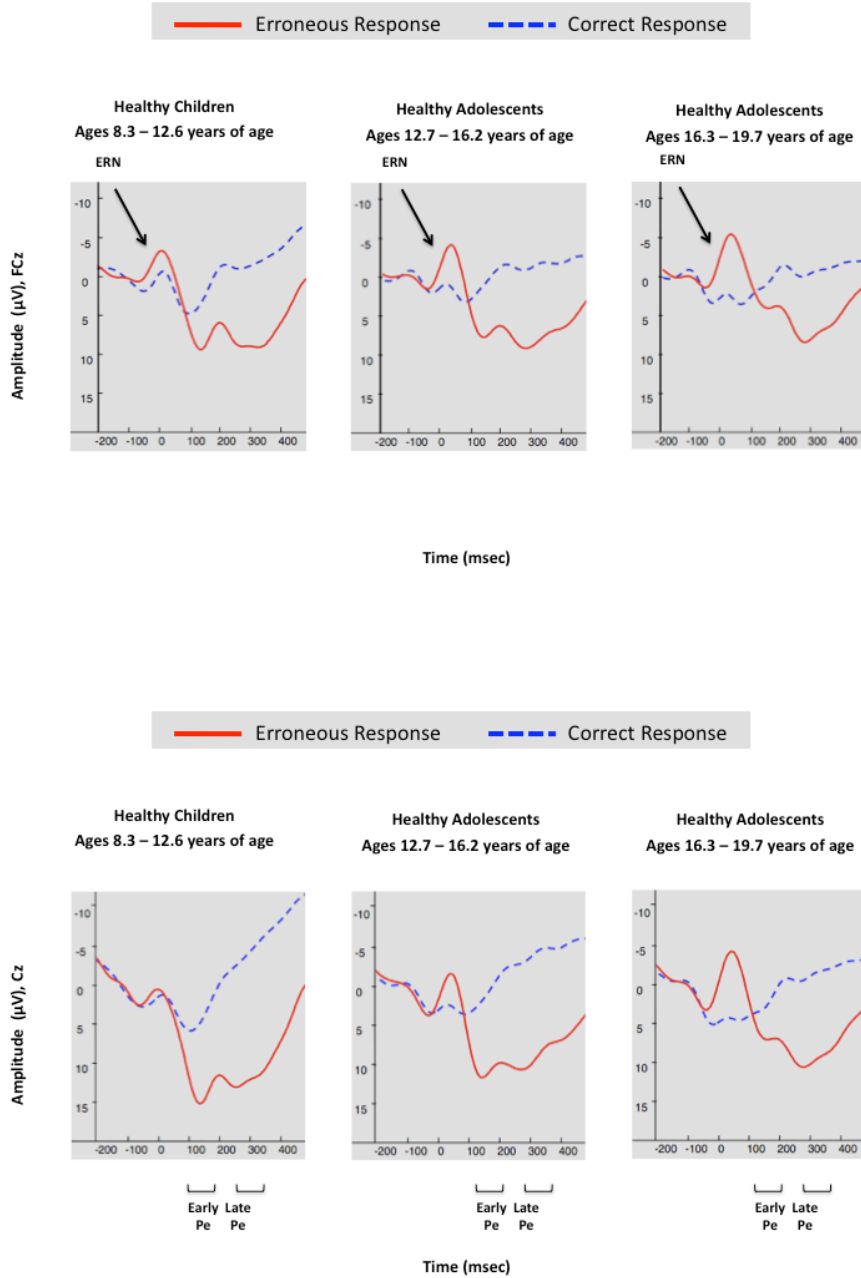
Table 2.1. Demographic and Clinical Data: All Healthy Children, Ages 8-19.

		Mean (Standard Deviation)
Age (years)		14.368 (3.033)
Child Behavior Checklist		
	Total score	7.050 (5.264)
	Internalizing score	2.400 (2.076)
	Externalizing Score	1.917 (2.044)
	Negative Affectivity	1.217 (1.367)
	Withdrawn/Depressed Scale score	0.700 (0.962)
	Anxiety	0.333 (0.655)
Child Depression Inventory (CDI)		
	Total score	2.400 (2.618)
Task Performance Data		
Accuracy		0.894 (0.052)
Error reaction time (msec)		420.061 (126.035)
Correct reaction time (msec)		485.705 (110.249)
Post-error reaction (msec)		480.097 (183.428)
ERP Mean Amplitude Measures		
CRN	*FCz (uV)*	2.243 (3.927)
ERN	*FCz (uV)*	-1.673 (4.470)
Early Pe	*Cz (uV)*	7.324 (6.991)
Late Pe	*Cz (uV)*	6.673 (9.963)

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Chapter III

Error-processing mechanisms in anxious children:
A direct comparison of Generalized Anxiety Disorder/Separation Anxiety and OCD

Introduction

In general, anxiety disorders are associated with fears that are atypical (e.g. developmentally inappropriate) and maladaptive (e.g. involve persistent crying, and excessive fears) (Beesdo et al., 2009; Borkovec and Roemer, 1995; Costello et al., 2003; Shin and Liberzon, 2010). Among children, anxiety disorders have an overall prevalence rate of 8–21% (Albano et al., 2003; Costello et al., 2003) and a median age of onset of 11 years of age (Kessler et al., 2005). A child with generalized anxiety disorder (GAD) may feel significantly distressed over a number of issues, including his or her performance at school, inclement weather, his/her own safety and that of close friends and family members (Weisberg, 2009); the disorder is prevalent in approximately 3% of children (Chavira et al., 2004). Meanwhile, children with separation anxiety, or SEP (prevalence ranging from 3.5% to 5.4%) present with developmentally unseemly fears associated with the separation from major attachment figures or from the home environment (Masi et al., 2001); approximately 36.1% of children with separation anxiety have the illness persist into adulthood (Shear et al., 2006).

Obsessive-compulsive disorder (OCD) is a severe anxiety disorder with a prevalence of 1-3% in adults and a prevalence of 1-2% in children and adolescents

(Gilbert and Maalouf, 2008; Leonard et al., 2005). OCD is characterized by recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions); such acts are often aimed at averting or reducing distress (Calvocoressi et al., 1998). Several studies indicate that an early age at onset in OCD is associated with increased levels of commorbidity, greater OCD global severity, worse outcome, and decreased quality of life (Bloch et al., 2009; Lack et al., 2009; Stewart et al., 2004; Taylor, 2011).

The neural mechanisms underlying anxiety in OCD and GAD/SEP are just beginning to be fully understood. The anterior cingulate (ACC), a brain structure that readily integrates both cognitive and affective information (Bush et al., 2000), has been suggested to be involved across both disorders (Damsa et al., 2009). The role of the ACC in promoting anxiety in children remains unclear, though it has been suggested that the ACC's regulatory effects on amygdala activity are relatively weak in anxious individuals, thus allowing an increase in the processing of goal-irrelevant threatening information and a lack of extinction of fear and negative affect that paves the way towards disease (Monk et al., 2008; Phan et al., 2005; Phelps and LeDoux, 2005).

Meanwhile, in OCD, the anterior cingulate displays increased, and presumably compensatory activity at rest (Swedo et al., 1989), following symptom provocation (Rauch et al., 1994), during task planning (van den Heuvel et al., 2005), and following errors (Fitzgerald et al., 2005; Gehring et al., 2000; Ursu et al., 2003). Specific to OCD, the anterior cingulate has been implicated as part of a corticostriatal–corticothalamic network that also includes the orbitofrontal cortex, the caudate nucleus, and the thalamus (Del Casale et al., 2011; Fineberg et al., 2010; Menzies et al., 2008).

The anterior cingulate is involved in the processing of errors (Holroyd et al., 1998), a link that has been supported by a wide myriad of functional imaging studies (Carter et al., 1998; Kiehl et al., 2000; Mathalon et al., 2003). The error-related negativity (Stern et al.) is a psychophysiological potential involved in error processing that arises from the ACC. It is also a negative deflection in the response-locked event-related potential that is both frontally-maximal and peaks about 0-100 ms after an erroneous response (Gehring et al., in press).

Given that error-commission is particularly threatening to OCD and anxious individuals, it has been speculated that increased ERN, a phenomenon that has been readily observed in individuals with anxiety and OCD, is primarily driven by an overly pathological worry about making mistakes (Frost and Hartl, 1996; Frost and Shows, 1993; Ollendick and March, 2004; Weinberg et al., 2011). Sensitivity to making mistakes in generalized anxiety can lead to the avoidance of school-work (Ollendick and March, 2004). In pediatric OCD, fears of making mistakes have been associated with the increased co-morbid expression of depressive symptoms, decreased self-esteem, and the inability to sustain long-lasting friendships with peers (Ye et al., 2008). Given the nature of associated maladaptive behavior and distress experienced by patients following error-commission, the study of error-processing in OCD and anxiety should be considered a top priority within the field of cognitive neuroscience.

The study of the ERN and error-processing in GAD/SEP populations has been limited, and has been mostly restricted to adult populations with anxiety disorder or healthy undergraduates displaying elevated (yet not necessarily clinical) levels of worry (Aarts and Pourtois, 2011; Hajcak et al., 2003; Weinberg et al., 2011). Two exceptions

include a study in anxious children (Ladouceur et al., 2006) and a study in adolescents that expressed higher levels of behavioral inhibition as children (McDermott et al., 2009). Specifically, research by Ladouceur and colleagues in 8- to 14-year-olds diagnosed with anxiety showed a larger ERN, in comparison to healthy controls. Meanwhile, more negative ERN during adolescence is associated with having had a history of behavioral inhibition in infancy (McDermott et al., 2009). This research closely follows findings in adult anxiety research, where greater ERN amplitude has been associated with increased self-report of depression and anxiety symptoms in adults with generalized anxiety (Wienberger, 2010).

The study of the ERN in OCD pediatric populations has been limited as well, though two individual studies have shown evidence of increased ERN in children with OCD (Hanna et al., under revision; Santesso et al., 2006a). These findings closely mirrored those observed in the adult literature, which has reported increased ERN in adults with OCD as well (Endrass et al., 2008; Gehring et al., 2000; Stern et al., 2010). Increased ERN has also been observed in healthy undergraduate students displaying elevated levels of obsessive and compulsive behaviors (though not high enough to merit a diagnosis of OCD) (Hajcak and Simons, 2002). Though a direct comparison of the ERN in children with OCD and GAD/SEP is not currently available, a study by Xiao and colleagues did report increased ERN when performing a direct comparison of this event-related potential between adult samples of OCD and anxiety (Endrass et al., 2008).

A second psychophysiological potential involved in the conscious processing of errors includes the error-positivity (Pe), an index of error awareness, possibly involving updating of working memory for the purpose of initiating learning mechanisms following

error-commission (Shalgi et al., 2009). The Pe is a broad positive wave appearing about 100-500 ms following an incorrect response (Gehring et al., in press). Recent findings have suggested that the Pe is a complex, and that it actually consists of two waveforms: an early and a late Pe (Arbel and Donchin, 2009). Research on the developmental trajectories of the early and late Pe in anxiety have yet to be tested directly; though there is evidence to suggest that, in children and adults with anxiety, the combined early and late Pe complex is not significantly different from healthy comparison subjects (Ladouceur et al., 2006; Weisberg, 2009). The literature in OCD has been mixed, with some studies reporting greater Pe (Santesso et al., 2006b) or no differences in the Pe (Ruchsow et al., 2007) between OCD and healthy controls.

The primary goal of the following study was to compare error-related brain activity – including the ERN, and the early and late Pe– in children with OCD, GAD/SEP, and healthy controls performing a flanker task. Efforts were made to find a link between OCD and GAD/SEP symptomatology and error-related brain activity. Group differences were identified in the ERN and the early Pe, amongst children with OCD, GAD/SEP, and healthy controls, thus providing ample evidence for a shared error-processing mechanism that may underlie severe symptomatology in both OCD and GAD/SEP.

Methods

Participants

Patients with generalized anxiety disorder or separation anxiety (GAD/SEP, n = 10) and obsessive-compulsive disorder (OCD, n = 19) were recruited through the University of Michigan Section of Child and Adolescent Psychiatry within the

Department of Psychiatry at the University of Michigan. Children were initially referred to this clinic for possible OCD diagnosis. Comparison subjects (n = 29) were recruited from the surrounding community and all had previously been included in an analysis of error-related ERP components across development (please refer to Chapter 2 in this dissertation). All participants lived with at least one English-speaking biological parent who was willing to participate in research and all were currently enrolled at school, did not have a history of learning disability or grade retention. Participants were paid for their interviews and psychophysiological recordings. There were no drop-outs to report.

All 58 study participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version (Kaufman et al., 1997) and the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (Hanna, 2007). All participants were subject to exclusion if they had a history of mental retardation, head injury with a sustained loss of consciousness, or a chronic neurological disorder such as a seizure disorder. Patients were excluded if they had a lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar I disorder, autism, conduct disorder, or substance-related disorder or a current diagnosis of attention-deficit hyperactivity disorder, major depressive disorder, or anorexia nervosa. Healthy comparison subjects were excluded if they had a raw score greater than 15 in the Social Communication Questionnaire (Constantino et al., 2004).

Only one anxious subject (out of ten) and four OCD patients (out of nineteen) were medicated at the time of assessment; patients were included in the study only if they were taking a stable dose of a selective serotonin reuptake inhibitor (4 were taking fluoxetine, 1 sertraline). Previous studies have suggested that serotonergic

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antidepressants have no effect on error-related negativity amplitude (de Bruijn et al., 2006); however, all analyses were repeated (and children on medication removed) in order to confirm that specific effects were not driven by differences in medication status.

The GAD/SEP group consisted of 10 pediatric patients who were age- and gender-matched to 19 OCD and 29 healthy comparison subjects. As part of our analyses, subjects were entered into blocks (consisting of an anxious child, his/her OCD match, and their respective control matches). Specifically, blocking allowed for us to minimize variation between subjects that was not attributable to the factors being evaluated in the study (i.e. clinical and ERP differences); in other words, such stratification reduced overall experimental error variance.

As shown in **Table 1**, the average age of the HC group was 12.58 (stand. dev. 2.16), the average age of the GAD/SEP group was 11.72 (stand. dev. 2.48), and the average age of the OCD group was 11.99 (stand. dev. 2.02). There were no group differences in age ($F(2, 55)=.775$, $p=.466$) amongst the three groups. The GAD/SEP group had 3 males, the OCD group had 6 males, whereas the HC group had 14 males.

Parent- and Child-Report Clinical Questionnaires

The Child Behavior Checklist (CBCL) is a parent-report questionnaire that was completed for all participants in order to assess severity of a wide array of emotional and behavioral problems (Achenbach, 1991). The CBCL provided raw scores for total behavioral problems, internalizing problems, and externalizing problems, as well as raw scores for syndrome subscales measuring negative affectivity (anxious/depressed symptoms), withdrawn behaviors (withdrawn/depressed symptoms), obsessions/compulsions, and anxiety.

Task

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions. They were instructed to respond as quickly and accurately as possible to the central arrow target, while ignoring the adjacent arrows, by pressing one of two buttons indicating the direction of the middle arrow (i.e., right versus left). The stimuli remained on the screen for 250 msec, with the interval between consecutive stimuli lasting 1500 msec.

Procedure

Each participant was seated 0.65 meters directly in front of the computer monitor and was told to place equal emphasis on speed and accuracy in responding. Following a practice block of 32 trials, each subject completed 8 blocks of 64 trials for a total of 512 trials. The subjects were told to place equal emphasis on speed and accuracy in their responses. Performance feedback was provided after every block to yield error rates of approximately 10%, ensuring an adequate number of trials for stable error-related waveforms.

Electrophysiological Recording, Data Reduction, and Analysis

The EEG was recorded from DC-512 Hz using scalp electrodes, two mastoid electrodes, and four EOG electrodes using the BioSemi ActiveTwo system, an EEG active-electrode sensor system that is well-tolerated by children because it does not require scalp abrasion. Data were recorded referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode. A nylon mesh cap was used with sensors embedded in it. EEG data were screened for artifacts

using visual inspection as well as automated artifact rejection algorithms in the Matlab-based analysis software EEGLAB. Eye movement artifacts were corrected using the Gratton regression procedure (Gratton et al., 1989).

Behavioral measures included accuracy expressed as a percentage of all trials. Average reaction times on error and correct trials were calculated separately. Reaction times were analyzed with group as a between-subject factor and response type as a within-subject factor. Reaction time after errors were evaluated to determine if there were group differences in post-error behavioral adjustments.

The error-related negativity and both error positivity components were quantified using mean amplitude measures relative to a pre-response baseline -200 to -50 msec. The mean amplitude of the error-related negativity was computed at FCz in a window from 0 to 80 msec following incorrect response trials, measurements were made at FCz given that the difference between ERN and CRN was largest at this electrode. The correct response negativity consisted of the same measure computed on correct response trials. The mean amplitude of the early error positivity was computed in a window at Cz from 80 msec to 200 msec following incorrect response trials and the mean amplitude of the late error positivity in a window from 200 msec to 300 msec following incorrect response trials; measurements were made at Cz given that the difference between error and correct waveforms at their respective time windows was largest at this electrode.

Separate analyses of the correct-related negativity (in correct trials), the error-related negativity and both error positivity components (in error trials) were conducted with a repeated-measure analysis of variance and Student's t-tests; furthermore, these analyses were corrected for multiple comparisons using Tukey's test statistic.

In accordance to standard statistical convention, group differences across the CBCL measures were analyzed with methods other than standard parametric tests, given that this data: a) did not follow a normal distribution, and b) was characterized by an over-abundance of zero values (Delucchi and Bostrom, 2004). This phenomenon (the over-abundance of zero values associated with clinical measures) is common across the field of clinical research, especially when evaluating questionnaire data where subjects are given the option to evaluate symptom severity on a scale ranging from "0" (or "no symptoms are present") and on. Our control sample consisted of healthy individuals who displayed minimal or no clinical symptoms; therefore, the clinical data for these individuals tended to cluster around the "0" (or "no symptoms are present") value. In order to deal with this peculiarity in our sample, comparisons of the clinical symptom distributions across the control, OCD, and GAD/SEP groups were statistically evaluated by a chi-square test using a Monte Carlo simulation (Corder and Foreman, 2009).

Correlation analyses involving Pearson correlation coefficients and Spearman's rank correlation coefficient were performed in order to determine the relationship between the behavioral and CBCL clinical measures (respectively) vs. the ERP component amplitudes. CBCL measures that significantly correlated with ERP component amplitudes were next included as part of an univariate analysis of variance (General Linear Model), for the purpose of addressing whether these measures could effectively predict error-related negativity and error positivity amplitudes. The univariate analysis of variance was pursued while controlling for age, gender, drug status, block assignment, and diagnosis.

All behavioral and clinical measures were statistically evaluated using SPSS 19, whereas event-related potential measures were analyzed using custom software written in C and in Matlab, as well as the Matlab-based EEGLAB software package (http://www.sccn.ucsd.edu/eeglab/). All statistical tests were two-tailed with the alpha level set at 0.05.

Results

Preliminary Analyses

Clinical, behavioral and ERP measures were examined for skewness and outliers. Both ERP and task-related behavioral measures satisfied assumptions of parametric statistics, although one outlier was identified while evaluating ERN values across the 58 children in the sample (1 HC, with ERN values greater than +/- 3 std. devs. from each group's mean). For all ERP analyses pursued in this chapter, results were first evaluated by including the entire n = 58 sample, followed by analyses excluding the one outlier.

Behavioral Data

Behavioral data for participants are presented in **Table 1**. There were no group differences in accuracy (F(2, 55)=.277, p = .759), reaction time during error (F(2, 55)=.308, p = .736) or correct trials (F(2, 55)=.103, p = .902), or post-error slowing (F(2, 55)=.537, p = .588) between OCD, GAD/SEP children and the HC subjects. Overall, participants were faster following incorrect, as opposed to correct responses (*t*(56)= 32.314, p<0.05). No main effect of group and no interaction between group and response type for reaction time reached significance (p = .844 and 0.470, respectively).

Clinical Data

Means and standard deviations for the CBCL subscales are presented in **Table 1**. As highlighted in **Table 1**, there were several differences across the three groups in CBCL score, including the total CBCL score ($F(2, 55)=30.563$, $p<0.001$), total internalizing score ($F(2, 55)=32.432$, $p<0.001$), total externalizing score ($(2, 55)=7.983$, $p<0.001$), total OCB score ($F(2, 55)=30.933$, $p<0.001$), total withdrawn score ($F(2, 55)=6.84$, $p<0.05$), total negative affectivity score ($F(2, 55)=46.775$, $p<0.001$), and total anxiety problems score ($F(2, 55)=49.497$, $p<0.001$).

When correcting for multiple comparisons, pos-hoc tests revealed no differences in symptom presentation between GAD/SEP and OCD patients across most CBCL scales, including: total CBCL score ($\chi^2=3.032$, $p = .082$), total internalizing score ($\chi^2=2.480$, $p = .115$), externalizing scale ($\chi^2=2.956$, $p = .086$), and total withdrawn score ($\chi^2=.952$, $p = .329$). There was a trend for a difference in total negative affectivity score between the OCD and GAD/SEP groups ($\chi^2=3.860$ $p = .052$); specifically, the GAD/SEP group scored higher in the negative affectivity scale. This trend was explained by the slight overlap in anxiety-related items between this and the total anxiety problems scale (in which the GAD/SEP group also scored higher in comparison to the OCD group, $\chi^2=6.453$, $p<0.05$). The OCD group scored higher in the total OC scale ($\chi^2=6.739$, $p<0.05$).

Meanwhile, post-hoc t-tests revealed significant differences in symptom presentation between OCD children and HC subjects across all CBCL scales (OCD children presented with greater symptom severity), including: total CBCL score ($\chi^2=21.552$, $p<.001$), total internalizing score ($\chi^2=20.697$, $p<.001$), total externalizing score ($\chi^2=4.734$, $p<.05$), total negative affectivity score ($\chi^2=23.909$, $p<.001$), total

withdrawn score (χ^2=7.087, p<.05), total anxiety problems score (χ^2=25.899, p<.001), and total OC behaviors score (χ^2=25.775, p<.001).

In addition, post-hoc t-tests revealed significant differences in symptom presentation between GAD/SEP children and HC subjects across all CBCL scales (GAD/SEP children presented with greater symptom severity), including: total CBCL score (χ^2=25.623, p<.001), total internalizing score (χ^2=29.295, p<.001), total externalizing score (χ^2=12.109, p<.05), total withdrawn score (χ^2=10.171, p<.05), total negative affectivity score (χ^2=32.456, p<.001), total anxiety problems score (χ^2=29.783, p<.001), and total OC behaviors score (χ^2=23.992, p<.001).

Error-related Potential Data

As summarized in **Table 1**, group differences were identified in the ERN ($F_{(2, 55)}$=4.411, p<0.05). A trend for a group difference was identified in the early Pe ($F_{(2, 55)}$=2.9151, p=.063) across the three groups. Post-hoc t-tests (with a Tukey adjustment for multiple comparisons) confirmed that there were no differences between the OCD and GAD/SEP patients in the ERN, (t (27) = 1.352, p >0.05), early Pe (t (27) = 4.985, p >0.05, or late Pe amplitude (t (27) = 4.943, p>0.05). Meanwhile, a significant difference in ERN between the HC and OCD children (t (46) = 4.841, p<0.05) and between the HC and GAD/SEP children (t (30) = 4.193, p < 0.05) was observed. In addition, a significant difference in the early Pe was observed between the HC and GAD/SEP children (t (37) = 2.980, p < 0.050), but not the HC and OCD children (p>0.05). No group differences were observed in the correct-related negativity ($F_{(2, 55)}$=.813, p>0.05) or late Pe ($F_{(2, 55)}$=1.329, p>0.05) across the three groups. Error-related negativity amplitude at

electrode FCz correlated with accuracy (r = -.334, p<0.05). Removal of an outlier HC or of the medicated patients across each of these analyses did not change the reported results.

Correlations with Symptom Severity (CBCL)

When considering all 58 subjects, ERN correlated with greater CBCL Internalizing symptom severity (r = -.423, p<0.05) and with CBCL Withdrawn severity (r = -.420, p<0.05). Removal of an outlier HC across each of these analyses did not change the reported results. Additional error-related ERP components, including the CRN, early Pe, and late Pe, did not correlate with symptom severity as assessed by any of the CBCL scales.

An univariate analysis of variance was carried out in order to evaluate whether the CBCL withdrawn symptom severity scale could significantly predict ERN amplitude. Given that this scale is embedded within the CBCL Internalizing scale, the latter was not included as an independent variable in this analysis. Because additional CBCL scores did not significantly correlate with ERN, CRN, or early and late Pe amplitude, they were not included in subsequent analyses.

Univariate Analysis of Variance (CBCL Scales)

As summarized in **Table 2**, the withdrawn scale did not significantly predict ERN amplitude, when correcting for age, diagnosis, block, age, drug status, and gender. Findings did not change when an HC outlier was excluded from this analysis (model p>0.05).

Discussion

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Research on the error-related negativity (Stern et al.) in pediatric samples of OCD and anxiety has been limited, and a cross-comparison of the four error-related potentials (the ERN, the correct-related negativity, and the early and late error positivities) across pediatric OCD, anxiety (GAD/SEP), and healthy comparison subjects had yet to be performed till now. We observed group differences in ERN and early Pe amplitude across the three groups of interest. Post-hoc t-tests confirmed a significant difference in ERN between the OCD and HC subjects and also between the GAD/SEP and HC subjects; meanwhile, no difference in ERN amplitude was observed between the OCD and GAD/SEP patients, suggesting that both patient groups likely share mechanisms underlying enhanced error-related brain activity specific to the ERN. Though previous research had revealed enhanced CRN (the ERN's counterpart during the processing of correct trials) in adult patients with anxiety (Endrass et al., 2008; Hajcak et al., 2003; Hajcak and Simons, 2002) we did not observe increased CRN in our GAD/SEP sample. Nor were group differences observed with regard to the late Pe amplitude.

Whereas our ERN amplitude findings are in line with existent child and adult ERP data, to our knowledge we are the first group to report differences in the early Pe between a sample of GAD/SEP and HC subjects (the GAD/SEP sample had smaller early Pe amplitude). This difference was not observed when comparing early Pe amplitude between OCD children and HC subjects. A recent report by Carrasco et al. showed that, in healthy children ages 8 – 19, early Pe amplitude decreased as a function of age between childhood and late adolescence (Carrasco et al., in preparation). It is possible that decreased early Pe in the current study's GAD/SEP sample is indicative of precocious maturation of the neural structures underlying this fronto-centrally localized

component. Replication of these findings in a larger GAD/SEP population will be the next logical step in determining the relationship between decreased early Pe amplitude and GAD/SEP status.

Our study has two key limitations worth revisiting. First: although the OCD and GAD/SEP children included in this study were not at present taking medication for additional co-morbid disorders (examples: ADHD, specific phobias, depression, etc), each child presented with a heterogeneous symptom profile that may be worth looking into in greater depth in the future. The interpretation of the present results might also be limited by the fact that some patients may present with differing, non-clinical levels of impulsivity and depression; because both traits have been associated with changes in the error-related event potentials (Hajcak et al., 2003), future analyses may benefit from further addressing these patients' co-morbidity status and their effect on ERN expression.

In addition, we are aware that our design is likely under-powered (i.e. lacked the requisite patient numbers) in order to detect relationships among the different variables (including clinical and ERP measures). Recruitment for the GAD/SEP sample is still ongoing; present analyses will be revisited in the future once we've collected an n = 25 GAD/SEP patients).

An informative direction for future research would be to collect an independent measure of psychological worry and perfectionism, as the young patients and healthy comparison subjects perform the flanker task. The ability to measure distress and helplessness in OCD and anxious subjects (while participating in the flanker task) would help cement the relationship between increased ERN and performance worries. Distress could also be measured using measures of cortisol levels (known to correlate with

increasing ERN) during task performance, as recently evidenced in a study by Tops and colleagues (Tops and Boksem, 2011).

In sum, an increase in ERN amplitude was observed in children and adolescents with OCD and GAD/SEP, further evidencing the role of the ACC in the pathology of these disorders. The idea that both OCD and GAD/SEP share similar brain substrates that are involved in bringing about psychopathology will be of benefit for the purpose of creating new therapies aimed at addressing atypical function within the ACC across both disorders. Taken together, our research suggests that error-processing in OCD and anxiety plays a critical role in bringing about symptomatology.

Figure 3.1. Response locked ERP waveforms at FCz and Cz comparing correct and error trial waveforms for OCD, Anxious (GAD/SEP), and Healthy Comparison subjects. The ERN and CRN were observed at electrode FCz, while the early and late Pe were observed at electrode Cz. For each panel, response onset occurred at 0ms and negative is plotted up.
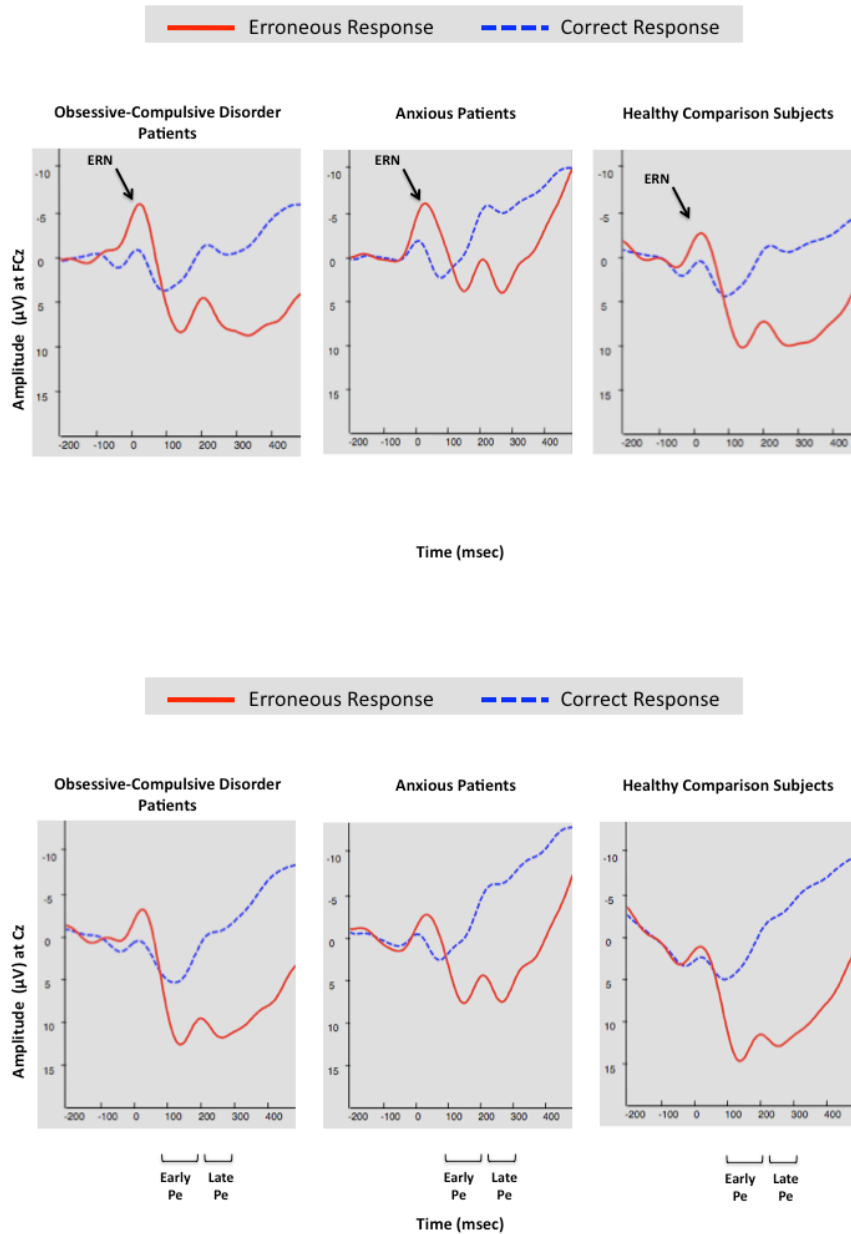
Table 3.1. Summary of ERP, Behavioral, and Clinical Data for OCD, Controls and Anxious patients.

	OCD, n = 19 Mean (Std.Dev.)	Controls, n=29 Mean (Std.Dev.)	Anxiety, n=10 Mean (Std.Dev.)
CRN at FCz	0.871 (4.141)	1.915 (4.054)	0.098 (4.769)
ERN at FCz	-3.610 (5.132)	-0.769 (3.266)	-4.962 (5.686)
Early Pe at Cz	10.425 (5.279)	12.622 (8.485)	5.440 (11.137)
Late Pe at Cz	11.083 (8.494)	12.421 (10.431)	6.140 (13.927)
Age	11.994 (2.016)	12.583 (2.158)	11.718 (2.478)
Correct RT	536.857 (140.82)	523.596 (115.39)	539.605 (83.06)
Error RT	480.209 (212.670)	448.314 (138.985)	437.079 (109.42)
Post-Error Slowing	589.925 (322.717)	508.900 (216.024)	534.600 (278.26)
Accuracy	0.873 (0.079)	0.885 (0.058)	0.8883 (0.039)

Child Behavioral Checklist:

CBC Total Score	25.842 (15.910)	6.310 (4.684)	37.600 (17.958)
Internalizing Score	11.579 (8.071)	2.207 (1.971)	16.3000 (6.056)
Externalizing Score	3.842 (4.970)	1.552(1.824)	8.2000 (8.230)
OC Scale	5.158 (3.202)	0.586 (0.682)	3.6000 (1.713)
Withdrawn Scale	1.842 (1.834)	0.655 (1.045)	2.6000 (2.271)
Anxiety Problems Scale	3.737 (2.557)	0.138 (0.351)	6.8000 (3.120)
Negative Affectivity	6.211 (3.966)	0.931 (0.961)	9.1000 (2.558)

Table 3.2. Univariate Analysis of Variance for evaluating the effects of withdrawn behaviors on ERN amplitude. The CBCL withdrawn scale was observed to not significantly predict ERN amplitude.

Tests of Between-Subjects Effects

Dependent Variable: FCz_Err_0_80_ERN

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	504.924[a]	15	33.662	1.938	.047
Intercept	39.311	1	39.311	2.264	.140
Covariate: Main Diagnosis	6.471	2	3.236	.186	.831
Covariate: Block	274.173	9	30.464	1.754	.107
Covariate: Drug Status	2.754	1	2.754	.159	.692
Covariate: Gender	.357	1	.357	.021	.887
Covariate: Age (Years)	34.259	1	34.259	1.973	.168
Withdrawn CBCL Score	36.567	1	36.567	2.106	.154
Error	729.406	42	17.367		
Total	1574.743	58			
Corrected Total	1234.330	57			

a. R Squared = .409 (Adjusted R Squared = .198)

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Chapter IV

Error-related Brain Activity in Unaffected Siblings of Children with OCD:
Evidence of shared psychophysiological indicators of atypical error-processing

Introduction

While it is known that healthy children with OCD relatives share in some of the

cognitive deficits affecting their OCD family members, there is more uncertainty as to

which brain-based mechanisms give rise to the shared deficits in cognition in both groups.

In addition, whether such deficits in cognition predict eventual OCD diagnosis in

unaffected siblings has yet to be determined. As part of this study, efforts were made to

characterize group differences between error-related ERPs in children with OCD, their

unaffected siblings, and healthy comparison controls. Similarities were identified in ERN

amplitude, thus providing evidence for an atypical error-processing mechanism shared

between both OCD children and their unaffected siblings.

Obsessive-compulsive disorder (OCD) is a severe anxiety disorder with a

prevalence of 1-3% in the general population and 1-2% in children (Gilbert and Maalouf,

2008; Leonard et al., 2005). OCD is characterized by recurrent, unwanted thoughts

(obsessions) and/or repetitive behaviors (compulsions); such acts are often aimed at

averting or reducing distress (Calvocoressi et al., 1998). Several studies indicate that an

early age at onset in OCD is associated with increased levels of comorbidity, greater

OCD global severity, worse outcome, and decreased quality of life (Bloch et al., 2009; Lack et al., 2009; Stewart et al., 2004; Taylor, 2011).

Heritability in OCD ranges from 45-65% in children and 27-47% in adults (van Grootheest et al., 2005). Multiple studies have shown that first-degree relatives are likelier to develop OCD symptoms, in comparison to individuals in the larger population with no affected relatives (Nestadt et al., 2000). Specifically, a number of family studies have reported increased prevalence rates of OCD (7% to 15%) in first-degree relatives of child and adolescent OCD patients (Lenane et al., 1990; Riddle et al., 1990; Swedo et al., 1989a).

In OCD, the anterior cingulate has been implicated as part of a corticostriatal–corticothalamic network that also includes the orbitofrontal cortex, the caudate nucleus, and the thalamus (Del Casale et al., 2011; Fineberg et al., 2010; Menzies et al., 2008). Abnormalities in the white matter tracts connecting these structures, including the cingulum bundle, have been observed in OCD using diffusion tensor imaging (Cannistraro et al., 2007). In OCD, the anterior cingulate displays increased, and presumably compensatory activity at rest (Swedo et al., 1989b), following symptom provocation (Rauch et al., 1994), during task planning (van den Heuvel et al., 2005), and following errors (Fitzgerald et al., 2005; Gehring et al., 2000; Ursu et al., 2003).

It has been previously evidenced that unaffected siblings of individuals with OCD may share some of the same ACC-dependent cognitive deficits that are salient in OCD, including deficits in response inhibition (Maltby et al., 2005; Menzies et al., 2007), cognitive flexibility (Chamberlain et al., 2007), planning (Cavedini et al., 2010; Delorme et al., 2007), behavioral reversal and decision making (Viswanath et al., 2009), and error

processing (Riesel et al., 2011). Structural similarities have been observed between adult unaffected siblings and OCD patients, who both show evidence of decreased ACC volume (Gilbert et al., 2008); developmental studies of the ACC in children have demonstrated correlations between its size and ability to regulate inhibitory processes (Casey et al., 1997).

To our knowledge, only two studies have combined imaging and behavioral methods to assess the brain-behavioral relationships responsible for the cognitive deficits shared between OCD and their unaffected siblings. For example, Menzies et al. (2007) observed delayed response inhibition on the Stop-Signal task in both OCD adults and their unaffected siblings. During the stop-signal task, subjects performed a "go-task" first, such as reporting the identity of a stimulus. Occasionally, the go stimulus was followed by a stop signal, which instructed subjects to withhold the response. Stopping a response requires a fast control mechanism that prevents the execution of the motor response. Results showed that increased ACC grey matter corresponded with slower SSRT (stop-signal reaction time, or the time required to inhibit a response) in both OCD adults and their unaffected siblings, in comparison to healthy controls (Menzies et al., 2007). SSRT is considered to be a standard measurement of an individual's ability to stop an ongoing response by effectively inhibiting behavior, and is considered to be a faculty supported by the ACC (Barkley, 1997). These findings were the first to support a brain-based mechanisms underlying shared cognitive deficits in OCD and their unaffected siblings.

In addition, atypical error processing and increased error-related negativity (Stern et al.) amplitude was observed by Riesel and colleagues in both OCD adults and their unaffected siblings, in comparison to healthy controls (Riesel et al., 2011). The goal of

the present study was to extend the findings by Riesel and colleagues, by identifying whether the psychophysiological indicators of error-processing originating from the ACC in children who are unaffected first-degree relatives of OCD patients were also atypical; these were compared with OCD patients and healthy comparison subjects without a family history of OCD.

Several error-related potentials were compared across the groups, including the ERN, the correct-related negativity, and the early and late error positivities. The ERN is a event-related potential and a negative deflection in the response-locked EEG that is both frontally-maximal and peaks about 0-100 ms after an erroneous response (Gehring et al., in press); this potential originates from the ACC (Herrmann et al., 2004; Ladouceur et al., 2007), and has been observed to be exaggerated in adults and children with an OCD diagnosis (Gehring et al., 2000; Mathews et al., 2012; Nieuwenhuis et al., 2005) and obsessive-compulsive behaviors (Hajcak and Simons, 2002; Santesso et al., 2006). Increased ERN amplitude has been interpreted as a signal that triggers behavioral adjustments to improve performance (Maier et al., 2011). Because OCD children are aversive to making mistakes (Simons, 2010), increased ERN may reflect a hyperactive mechanism involving quick error detection and correction, for the purpose of preventing further errors. We predicted that these same mechanisms would also be hyperactive in unaffected siblings of children with OCD, given the previous research by Riesel and colleagues. Results would provide evidence for a hyperactive error-processing system in children at high (genetic) risk of developing OCD, thus suggesting that sensitivity towards disesase is established years prior to the national median age of disease onset, as

established by the National Comorbidity Survey Replication (NCS-R) (19 years of age) (Kessler et al., 2005).

The error-related negativity is followed by the error positivity, a second ERP component involved in the conscious processing of errors. The Pe has also been suggested to be involved in the updating of working memory for the purpose of initiating learning mechanisms following error-commission (Shalgi et al., 2009). The Pe is a broad positive wave appearing about 100-300 ms following an incorrect response (Gehring et al., in press). Recent findings have suggested that the Pe is a complex actually consisting of two waveforms: an early and a late Pe (Arbel and Donchin, 2009). The function of the early and late Pe in OCD has yet to be tested directly, though there is evidence to suggest that, in children and adults with OCD, Pe may be increased (Santesso et al., 2006) or no different in structure and timing as the Pe in healthy controls.

Methods

Participants

Pediatric OCD patients (n = 19) and their unaffected siblings (US, n = 19) were recruited in the Department of Psychiatry at the University of Michigan. Patients were initially referred to this clinic for possible OCD diagnosis. Comparison subjects were recruited from the surrounding community (n = 38) and all had previously been included in an analysis of error-related ERP components across development (please refer to Chapter 2 in this dissertation). All participants lived with at least one English-speaking biological parent who was willing to participate in research and all were currently enrolled at school, did not have a history of learning disability or grade retention. After

complete description of the study, written informed consent was obtained from at least one parent of the participant and written informed assent from the participant. Participants were paid for their interviews and psychophysiological recordings. There were no drop-outs to report.

As shown in **Table 1**, the average age of the OCD patients was 13.82 years of age (std. dev. 2.36) and the average age of the US and the HC was 13.68 years of age (std. dev. 2.24) and 13.99 years (std. dev. 2.31), respectively. The OCD group had 21 males, whereas the US group and the HC group had 11 males and 6 males respectively. As part of our analyses, subjects were entered into blocks (consisting of an OCD patient, an age-/gender-matched unaffected sibling, and their respective control matches). Specifically, blocking allowed for us to minimize variation between subjects that was not attributable to the factors being evaluated in the study (i.e. clinical and ERP differences); in other words, such stratification reduced overall experimental error variance.

All 19 patients had a lifetime diagnosis of OCD. Patients were excluded if they had a lifetime diagnosis of autistic disorder, Asperger's disorder, schizophrenia, other psychotic disorder, bipolar I disorder, conduct disorder, or substance-related disorder, or a current diagnosis of attention-deficit hyperactivity disorder, major depressive disorder, or anorexia nervosa. Attention-deficit hyperactivity disorder was excluded because it has been associated with smaller error-related negativity amplitude (28). All 19 US and 38 HC subjects had no history of an axis I disorder. All lifetime and current axis I diagnoses were made independently by two clinicians using all sources of information according to DSM-IV criteria. Patients, US, and HC subjects were also excluded if they had a history of mental retardation, head injury with a sustained loss of consciousness, chronic

neurological disorder such as a seizure disorder, or a score greater than 15 on the lifetime version of the Social Communication Questionnaire (Constantino et al., 2004).

Consistent with previous studies of the error-related negativity in OCD, patients were included in the study if they were taking a stable dose of a selective serotonin reuptake inhibitor, but no other psychotropic medications. Medications being taken (and number of OCD patients taking the medication) were the following: fluoxetine (4), escitalopram (1), sertraline (1). Though previous studies have found that serotonergic antidepressants have no effect on error-related negativity amplitude (de Bruijn et al., 2006), we still provide data here of an analysis excluding OCD children on medications. Unaffected siblings and HC subjects were not included in the study if medicated.

All 76 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and the Lifetime Version (Kaufman et al., 1997) and Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (Hanna, 2007). An additional parent report scale was completed for all participants: the Child Behavior Checklist (Achenbach, 1991). The Child Behavior Checklist (CBCL) provided raw scores for total behavioral problems, internalizing problems, and externalizing problems, as well as raw scores for syndrome subscales measuring negative affectivity (anxious/depressed symptoms), withdrawn behaviors (withdrawn/depressed symptoms), and anxiety.

Task

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions. They were instructed to respond as quickly and accurately as

possible to the central arrow target, while ignoring the adjacent arrows, by pressing one of two buttons indicating the direction of the middle arrow (i.e., right versus left). The stimuli remained on the screen for 250 msec, with the interval between consecutive stimuli lasting 1500 msec.

Procedure

Each participant was seated 0.65 meters directly in front of the computer monitor and told to place equal emphasis on speed and accuracy in responding. Following a practice block of 32 trials, each subject completed 8 blocks of 64 trials for a total of 512 trials. The subjects were told to place equal emphasis on speed and accuracy in their responses. Performance feedback was provided after every block to yield error rates of approximately 10%, ensuring an adequate number of trials for stable error-related waveforms.

Electrophysiological Recording, Data Reduction, and Analysis

The EEG was recorded from DC-512 Hz using scalp electrodes, two mastoid electrodes, and four EOG electrodes using the BioSemi ActiveTwo system, an EEG active-electrode sensor system that is well-tolerated by children because it does not require scalp abrasion. Data were recorded referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode. A nylon mesh cap was used with sensors embedded in it. EEG data were screened for artifacts using visual inspection as well as automated artifact rejection algorithms in the Matlab-based analysis software EEGLAB. Eye movement artifacts were corrected using the Gratton regression procedure (Gratton et al., 1989).

Behavioral measures included accuracy expressed as a percentage of all trials. Average reaction times on error and correct trials were calculated separately. Reaction times were analyzed with group as a between-subject factor and response type as a within-subject factor. Reaction time after errors were evaluated to determine if there were group differences in post-error behavioral adjustments.

The error-related negativity and both error positivity components were quantified using mean amplitude measures relative to a pre-response baseline -200 to -50 msec. The mean amplitude of the error-related negativity was computed in a window at FCz from 0 to 80 msec following incorrect response trials; measurements were made at FCz given that the difference between ERN and CRN was largest at this electrode. The correct response negativity consisted of the same measure computed on correct response trials. The mean amplitude of the early error positivity was computed in a window at Cz from 80 msec to 200 msec following incorrect response trials and the mean amplitude of the late error positivity in a window from 200 msec to 300 msec following incorrect response trials; measurements were made at Cz given that the difference between error and correct waveforms at their respective time windows was largest at this electrode; measurements were made at Cz given that the difference between error and correct waveforms at their respective time windows was largest at this electrode.

Separate analyses of the error-related negativity and both error positivity components were conducted with a repeated-measure analysis of variance and Student's t-tests; furthermore, these analyses were corrected for multiple comparisons using Tukey's test statistic. Group differences across the CBCL measures were analyzed with methods other than standard parametric tests, given that this data did not follow a normal

distribution and was characterized by an over-abundance of zero values. Statistical significance for all clinical comparisons were therefore evaluated using chi-square tests, followed by two-sided Monte Carlo simulations for the purpose of confirming significance.

Correlation analyses involving Pearson correlation coefficients and Spearman's rank correlation coefficient were performed in order to determine the relationship between the behavioral and CBCL clinical measures (respectively) vs. the ERP component amplitudes. CBCL measures that significantly correlated with ERP component amplitudes were next included as part of an univariate analysis of variance (General Linear Model), for the purpose of addressing whether these measures could effectively predict error-related negativity and error positivity amplitudes. The univariate analysis of variance was pursued while controlling for age, gender, drug status, block assignment, and diagnosis.

All behavioral and clinical measures were statistically evaluated using SPSS 19, whereas event-related potential measures were analyzed using custom software written in C and in Matlab, as well as the Matlab-based EEGLAB software package (http://www.sccn.ucsd.edu/eeglab/). All statistical tests were two-tailed with the alpha level set at 0.05.

Results

Preliminary Analyses

Clinical, behavioral and ERP measures were examined for skewness and outliers. Both ERP and task-related behavioral measures (including accuracy and reaction time)

satisfied assumptions of parametric statistics. Three outliers were identified while evaluating ERN values across the 76 children in the sample (1 HC and 2 unaffected siblings with ERN values greater than +/- 3 std. dev.). For all ERP analyses pursued in this chapter, results were first evaluated by including the entire n = 76 sample; analyses were next repeated without outliers. Group differences across the CBCL measures were analyzed with methods other than standard parametric tests, given that this data was heavily skewed and characterized by an over-abundance of zero values.

Behavioral Data

Behavioral data for participants are presented in **Table 1**. There were no group differences in accuracy ($F(2, 73)=1.272$, $p>0.05$), reaction time during error trials or correct trials ($F(2, 73)=1.982$, $p>0.05$ and $F(2, 73)=1.241$, $p>0.05$, respectively), or in post-error slowing ($F(2, 73)=.0231$, $p>0.05$) among the OCD, US, and healthy comparison subjects. Overall, participants were faster on error than correct trials ($F = 86.424$, $df = 1, 75$, $p<0.001$). No main effect of group and no interaction between group and response type for reaction time reached significance ($p = 0.166$ and 0.740, respectively).

Clinical Data

Means and standard deviations for the CBCL subscales are presented in **Table 1**. Group differences were observed across all CBCL scales amongst the OCD, US, and controls. This included the CBCL total score ($F(2, 73)=20.150$, $p<0.001$), total internalizing score ($F(2, 73)=23.091$, $p<0.001$), total externalizing score ($F(2, 73)=6.488$, $p<0.05$), total withdrawn score ($F(2, 73)=9.728$, $p<0.001$), total negative affectivity score

(F(2, 73)=20.144, p<0.001), total anxiety problems score (F(2, 73)=35.566, p<0.001), and total OC behaviors score (F(2, 73)=33.345, p<0.001).

Post-hoc t-tests (using chi-squares and Monte Carlo simulations) revealed no differences in symptom presentation between unaffected siblings and healthy controls across most CBCL scales, including: total CBCL score (χ^2=1.283, p = .257), total internalizing score (χ^2=.731, p = .392), total externalizing score (χ^2=1.644, p = .200), total withdrawn score (χ^2=.157, p = .692), total negative affectivity score (χ^2=1.355, .244), and total OC behaviors (χ^2=1.350, p = .245). There was a trend for a difference in total anxiety problems score (χ^2=3.612, p = .057) between unaffected siblings and healthy controls across (unaffected siblings scored higher in this scale, in comparison to healthy controls), though this difference was not robust enough to reach significance.

Meanwhile, post-hoc t-test revealed significant differences in symptom presentation between OCD children and healthy controls across all CBCL scales (OCD children presented with greater symptom severity), including: total CBCL score (χ^2=19.488, p<.001), total internalizing score (χ^2=21.323, p<.001), total externalizing score (χ^2=8.926, p<.05), total withdrawn score (χ^2=10.885, p<.001), total negative affectivity score (χ^2=20.412, p<.001), total anxiety problems score (χ^2=27.876, p<.001), and total OC behaviors (χ^2=27.070, p<.001).

In addition, post-hoc t-tests revealed significant differences in symptom presentation between OCD children and unaffected siblings across most CBCL scales (OCD children presented with greater symptom severity), including: total CBCL score (χ^2=9.851, p<.05), total internalizing score (χ^2=10.989, p<.05), total withdrawn score

(χ^2=7.283, p<.05), total negative affectivity score (χ^2=9.530, p<.05), total anxiety problems score (χ^2=13.743, p<.001), and total OC behaviors (χ^2=13.687, p<.001). No differences were observed between groups with regards to the total CBCL externalizing score (χ^2=3.270, p>0.05).

Error-related Potential Data

Group differences were observed in the ERN across the three groups ($F_{(2, 73)}$=5.797, p<0.05). Post-hoc t-tests (with a Tukey adjustment for multiple comparisons) confirmed that there was no difference in ERN amplitude between the OCD and unaffected siblings (t (37) = 0.490, p>0.05). Meanwhile, a significant difference in ERN between the HC and OCD children (t (56) = 3.034, p<0.05) and between the HC and US children (t (56) = 2.469, p<0.05) was observed. No group differences were observed in the CRN, early Pe, or late Pe across the three groups. In addition, error-related negativity amplitude at electrode FCz significantly correlated with age (r = -.2433, p=.029, n = 76) and greater reaction time during error trials (r = .2321, p=.037, n = 76). More negative CRN correlated with greater reaction time in correct trials (r = -.2767, p=.012, n = 76). Results remained consistent when 4 outliers were removed from all analyses.

Correlations with Symptom Severity (CBCL)

When considering all 76 subjects, total CBCL and CBCL withdrawn severity both significantly correlated with ERN amplitude (r = -.264, p<0.05, n = 76 and r = -.347, p<0.05, n = 76 respectively). No CBCL scales correlated significantly with the CRN, early Pe, or late Pe amplitudes.

An univariate analysis of variance was carried out in order to evaluate whether the CBCL withdrawn severity scale could significantly predict ERN amplitude. Given that

this scale is embedded within the CBCL total scale, the latter was not included as an independent variable in this analysis. Because additional CBCL scores did not significantly correlate with ERN, CRN, or early and late Pe amplitude, they were not included in subsequent analyses.

Univariate Analysis of Variance (CBCL Scales)

As summarized in **Table 2**, the withdrawn scale did not significantly predict ERN amplitude, when correcting for age, diagnosis, block, age, drug status, and gender. Findings did not change when an HC outlier was excluded from this analysis (model p>0.05).

Discussion:

The present study examined a series of neural indicators of error-processing in children with OCD, their unaffected siblings, and healthy controls. Unaffected siblings of children with OCD showed increased error-related negativity amplitudes, in comparison to healthy comparison subjects. This goes in line with a recent publication (Riesel et al, 2011), which found increased ERN in adult siblings of patients with OCD, in spite of the fact that relatives did not have OCD nor were they taking OC-medications. No group differences were observed in the CRN, early Pe, or late Pe, across the three groups.

In OCD, increased and presumably compensatory activity has been observed in the anterior cingulate (ACC) at rest, following symptom provocation (Rauch et. al, 1994), during task planning, and following errors (Fitzgerald et al., 2005; Gehring et al., 2000; Hanna et al., under revision). In a manuscript by Heuvel et al., imaging results showed increased bilateral anterior cingulate activity in OCD adults, but not control subjects, that

increased as a function of task-load while performing the Tower of London task (van den Heuvel et al., 2005) and thus led to the suggestion that the ACC in OCD acts in a compensatory fashion. It is possible that ACC hyperactivity in unaffected siblings of children with OCD serves a similar, compensatory purpose, though this prediction was not directly tested as part of this study, but could form the basis for future research.

Though considered to be healthy, previous research of siblings of children with OCD found unaffected siblings to express higher rates of obsessive/unrealistic beliefs, inflated feelings of responsibility and overestimation of threat (Rector et al., 2009). Though the link between such variables and increased ERN was not examined as part of this study, it could certainly be the basis for future investigation, as would also be the study of the factors that may protect high-risk children with increased ERN from developing OCD (as may be the case in unaffected siblings scoring lower in assessments of unrealistic beliefs).

Finally, the neuroanatomical substrates of OCD are becoming increasingly defined by the exponential increase in evidence emerging from structural neuroimaging studies. However, there are at present no published reports of longitudinal studies examining the brain-based mechanisms underlying cognitive dysfunction among high-rirsk individuals who may eventually move on to develop OCD. Our findings demonstrate that increased ERN is a candidate trait marker for OCD, and may offer far-reaching insights into the etiology of OCD in high-risk siblings. The importance of the ERN for use as an endophenotype (or intermediate phenotype linking genetic predisposition to eventual OCD diagnosis) cannot be understated. Though at this time the shared genetic basis underlying increased ERN and OCD vulnerability has not been

determined, we are happy to report that genetics data was collected on each of the subjects included in this report, and plan to analyze the interaction of genotype and ERN expression as part of a future imaging study.

Figure 4.1. Response locked ERP waveforms at FCz and Cz comparing correct and error trial waveforms for OCD, Unaffected Siblings, and Healthy Comparison subjects. The ERN and CRN were measured at FCz and the early and late Pe were measured at Cz. For each panel, response onset occurred at 0ms and negative is plotted up.
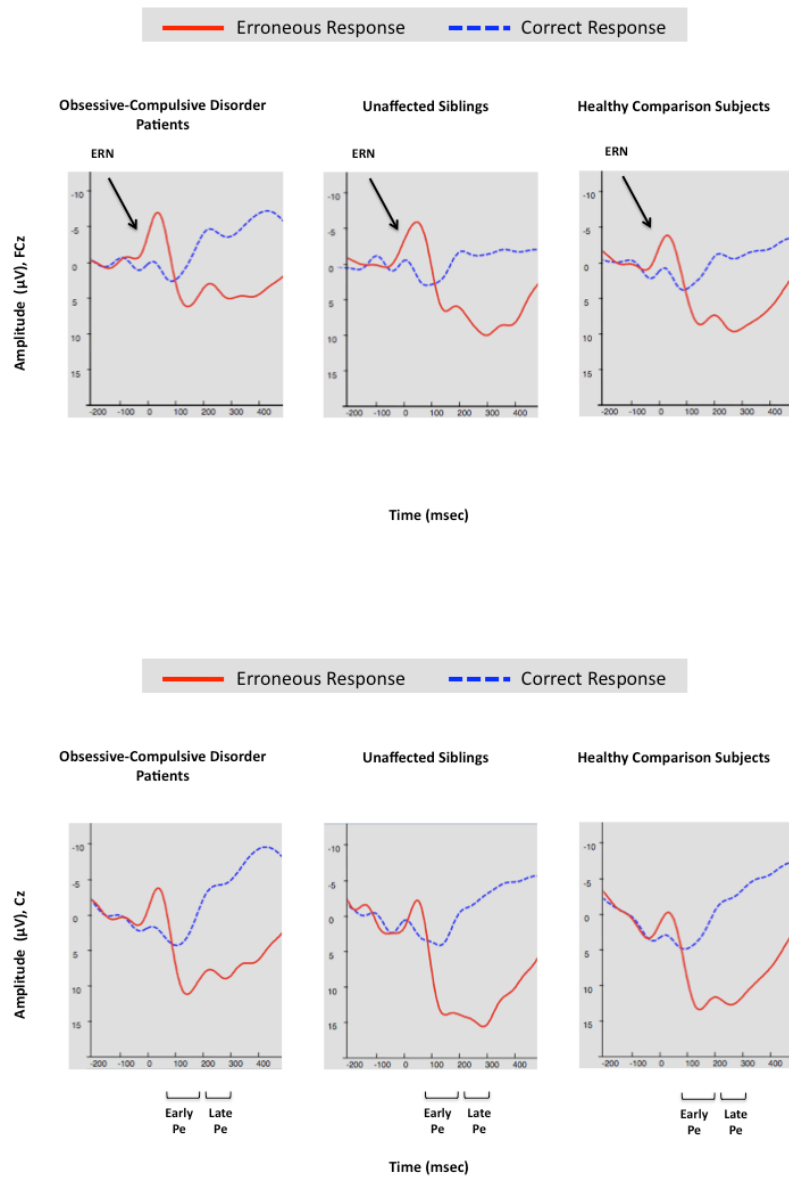
Table 4.1. Summary of ERP, Behavioral, and Clinical Data for OCD, Controls and Unaffected Siblings.

	Controls n=38 Mean (SD)	OCD n=19 Mean (SD)	Unaffected Siblings n=19 Mean (SD)
Demographic data			
Age (years)	13.99 (2.31)	13.82 (2.36)	13.68 (2.24)
Task performance data			
Accuracy	0.8935 (0.0440)	0.8705(0.0756)	0.8932 (0.0546)
Error reaction time	487.7978	361.7082 (61.0318)	385.5302 (101.1565)
Correct reaction time	416.3223	447.0854 (67.2036)	467.5340 (112.4061)
Post-error reaction	461.2059	471.9387	472.4393 (254.5408)
ICV	0.6720 (0.7788)	0.9066 (1.3910)	0.6719 (0.7803)
Clinical data			
Child Behavior Checklist			
Total score	6.6667 (5.2715)	28.5000 (22.6495)	8.6316 (4.7751)
Internalizing score	2.2857 (2.0986)	12.6500 (10.1633)	2.8421 (2.5876)
Externalizing score	1.6905 (1.8934)	6.0000 (7.7595)	2.5789 (2.5888)
Negative Affectivity	1.0476 (1.1677)	6.4000 (5.4134)	1.5263 (1.8964)
Withdrawn / Depressed	0.7143 (0.9948)	2.5500 (2.6052)	0.6316 (0.7609)
Anxiety	0.2381 (0.4844)	3.7000 (2.7928)	0.5789 (0.8377)
Obsessions and	0.6190 (0.7949)	5.8500 (4.2087)	0.9474 (1.4327)
Summary of the baseline-to-peak CRN, ERN, and Pe amplitude			
CRN at FCz	1.9163	1.0150 (5.5890)	1.1387 (4.9396)
ERN at FCz	-2.3751 (4.0692)	-5.2125 (5.3787)	-4.9132 (4.0956)
Early Pe at Cz	11.4646 (7.8966)	9.0758 (7.0257)	11.6319 (17.2762)
Late Pe at Cz	12.3441 (9.3999)	8.3721 (10.3676)	14.8305 (15.5195)

Table 4.2. Univariate Analysis of Variance for evaluating the effects of withdrawn behaviors on ERN amplitude. The CBCL withdrawn scale was observed to not significantly predict ERN amplitude.

Tests of Between-Subjects Effects

Dependent Variable:ERN_FCz

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	728.646[a]	24	30.360	2.056	.015
Intercept	16.787	1	16.787	1.137	.291
Covariate: Main Diagnosis	116.701	2	58.350	3.952	.025
Covariate: Block	277.038	18	15.391	1.042	.433
Covariate: Gender	1.717	1	1.717	.116	.735
Covariate: Drug Status	7.284	1	7.284	.493	.486
Covariate: Age (Years)	10.177	1	10.177	.689	.410
Withdrawn CBCL Score	35.152	1	35.152	2.381	.129
Error	752.957	51	14.764		
Total	2482.029	76			
Corrected Total	1481.603	75			

a. R Squared = .492 (Adjusted R Squared = .253)

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Chapter V

Error Processing Abnormalities in Autism Spectrum Disorders

Introduction

Autism Spectrum occurs in 1 in 150 children (Amaral et al., 2008). According to the American Pediatric Association, affected individuals are characterized by significantly impaired social interactions, communication deficits, and a restricted, repetitive pattern of interests and activities (2000). In addition, children with ASD display significant variation in behavioral impairment and often display co-occurring emotional and behavioral symptoms (EBS) (Gadow et al., 2004). About 50-80% of ASD youth present with a wide myriad of internalizing and externalizing behaviors, including anxiety, depression, impulsivity, attention problems, aggression, and rule-breaking behavior (Bauminger et al., 2010). Although these behaviors have been readily described in individuals with ASD for years (Bradley and Isaacs, 2006), the research community has yet to fully understand the mechanisms underlying comorbid EBDs in ASD (Pandolfi et al., 2012).

There is growing evidence of both structural and functional abnormalities of the anterior cingulate cortex (ACC) in ASD, which is involved in detecting errors and integrating affective response to negative outcomes (Mathalon et al., 2003). Furthermore, atypical ACC activation in ASD has been observed during a number of cognitive tasks (Ashwin et al., 2007; Kana et al., 2007; Kennedy et al., 2006). There is also evidence of altered metabolism (Kennedy et al., 2006; Levitt et al., 2003; Nakamura et al. 2011) and

reduced volume of the ACC in ASD (Haznedar et al., 2000). Increased error-related brain activity and ACC hyperactivity have been reported in children and adults with autism spectrum disorders (Solomon et al., 2009). To date, abnormal error processing has been examined in ASD to only a limited extent.

Current theory suggests that in ASD deficits in error processing and other related executive functions may contribute to social-cognitive impairments (Henderson et al., 2006) and higher-order repetitive behaviors in ASD (Mosconi et al., 2009). Specifically, in the Henderson study, children with increased ERN experienced greater social impairment, whereas in the Mosconi study, impaired inhibitory control during the antisaccade task was associated with greater RRB symptom severity. It is therefore of utmost importance to continue to better understand how error-processing works in ASD.

Error-processing can be studied by means of the error-related event-related potentials, including the error-related negativity (ERN), correct-related negativity (CRN), early positivity (early Pe) and late positivity (late Pe). The goal of the proposed study will be to explore the neural circuitry underlying error processing in ASD by means of these four error-related potentials.

The error-related negativity (ERN) is an event-related potential generated by the anterior cingulate cortex (ACC) that is both frontally-maximal and peaks about 0-100 ms after an erroneous response (Gehring et al., in press). It reflects early error-processing activity, specially the distress associated with having just made an incorrect response. The error-related negativity is followed by the error positivity, a slower positive complex peaking about 100 - 500 ms after an incorrect response (Shalgi et al., 2009). The error positivity is considered to consist of two separate waveforms, the early and late Pe (Arbel

and Donchin, 2009). The specific function of the early positivity (early Pe) and late positivity (late Pe) has been heavily debated, though it has been suggested that these components may reflect the conscious recognition and awareness that a mistake was made and the initiation of a mechanism involving the updating of working memory for the purpose of initiating learning mechanisms following error-commission (Shalgi et al., 2009).

The primary goal of the following study was to compare error-related brain activity – using the ERN, CRN and the early and late Pe – in 26 children with ASD and 26 carefully age-matched healthy comparison subjects performing a flanker task. Based on previous results reported by Henderson and collagues in a preliminary study with children with ASD, we predicted increased ERN in children ASD (Henderson et al., 2006). Efforts were made to find a link between ASD EBD symptomatology and error-related brain activity. Group differences were identified in the CRN, ERN, the early Pe, and the late Pe, between ASD and HC children, thus providing evidence for an overall atypical error-processing mechanism that may be associated with severe symptomatology in ASD.

Methods

Participants

Patients were recruited through the University of Michigan Autism and Communication Disorders Center, and had been referred there for possible ASD diagnosis. Comparison subjects were recruited from the surrounding community and all had previously been included in an analysis of error-related ERP components across

development (please refer to Chapter 2 in this dissertation). All participants lived with at least one English-speaking biological parent who was willing to participate in research and all were currently enrolled at school or were home-schooled, did not have a history of learning disability or grade retention. Participants were paid for their interviews and psychophysiological recordings.

All 52 participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version (Kaufman et al., 1997) and the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (Hanna, 2007). All participants were subject to exclusion if they had a history of mental retardation, head injury with a sustained loss of consciousness, or a chronic neurological disorder such as a seizure disorder. Furthermore, healthy comparison subjects were excluded if they had a raw score greater than 15 in the Social Communication Questionnaire, (scores ranged from 0-10, mean: 1.7308, standard deviation: 2.2901) (Constantino et al., 2003). ASD subjects were excluded if they had a lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar I disorder, conduct disorder, or substance-related disorder or a current diagnosis of obsessive-compulsive disorder, attention-deficit hyperactivity disorder, major depressive disorder, or anorexia nervosa; additional exclusion criteria included cognitive function < 85.

ASD diagnoses were confirmed using the Autism Diagnostic Interview-Revised, ADI-R (Rutter et al., 1995) and the Autism Diagnostic Observation Schedule, ADOS (Lord et al., 2000) administered by research reliable personnel. As is customary, the ADOS was scored using the standard algorithm in all ASD youth participating in the study. Meanwhile, ADOS data from 20 (out of n = 26) participants was also scored using

the recently "revised" algorithms; the use of the revised algorithm has only become widely used in recent years for research purposes, has shown improved diagnostic validity over the traditional algorithm, and includes additional items for coding restricted and repetitive behaviors (RRB) (Gotham et al., 2007).

Parents of all participants completed the Child Behavior Checklist (CBCL) (Achenbach, 1991). The CBCL provided raw scores for total behavioral problems, internalizing problems, and externalizing problems, as well as raw scores for syndrome subscales measuring negative affectivity (anxious/depressed symptoms), withdrawn behaviors (withdrawn/depressed symptoms), and anxiety. Additional parent-report measures of ASD symptom severity (including the Social Responsiveness Scale and the Repetitive Behavior Scale-Revised) were administered as well, but only to parents of children with ASD.

Only seven (of 26) ASD subjects were medicated at the time of assessment; patients were included in the study only if they were taking a stable dose of a selective serotonin reuptake inhibitor, antipsychotic, or mood stabilizer. Medications being taken (and number of patients taking the medication) were the following: fluoxetine (2), sertraline (1), paroxetine (1), aripiprazole (2), risperidone (2); only one child was on more than 1 medication (a combination of fluoxetine and risperidone) at the time of assessment.

It is worth emphasizing that previous studies have suggested that serotonergic antidepressants have no effect on error-related negativity amplitude (de Bruijn et al., 2006). The effects of aripiprazole and risperidone, if any, on error processing have not been determined yet, though haloperidol (another atypical antipsychotic) has been

observed to decrease ERN amplitude in healthy adults (Kenemans and Kahkonen, 2011; Zirnheld et al., 2004); given this, additional analyses were pursued in order to gage the differences in ERP components between children with ASD and healthy comparison subjects, while excluding those ASD children on medication.

The ASD group consisted of 26 pediatric patients who were age-matched to 26 comparison subjects. Within the ASD group, 14 had a diagnosis of autism (e.g. "high-functioning autism"), 6 had a diagnosis of Asperger Syndrome and 6 had a diagnosis of PDD-NOS. An original sample of 30 children was recruited for the study; while ERP data was collected for all children in the study, four were lost to follow-up (i.e. interview measures were not collected), hence the children were subsequently dropped from the study sample. As shown in Table 1, the average age of the ASD patients was 13.7 years (range, 8.7 – 17.0) and the average age of the HC was 14.1 years (range 10.0 – 18.6); there were no group differences in age ($t(50)=.45378$, p=.50365). The ASD group had 21 males, whereas the comparison group had 19 males.

Task

Participants performed a modified Eriksen flanker task in which arrows appeared on a personal computer display with congruent (e.g., →→→→→) and incongruent (e.g., →→←→→) conditions. They were instructed to respond as quickly and accurately as possible to the central arrow target, while ignoring the adjacent arrows, by pressing one of two buttons indicating the direction of the middle arrow (i.e., right versus left). The stimuli remained on the screen for 250 msec, with the interval between consecutive stimuli lasting 1500 msec.

Procedure

Each participant was seated 0.65 meters directly in front of the computer monitor and told to place equal emphasis on speed and accuracy in responding. Following a practice block of 32 trials, each subject completed 8 blocks of 64 trials for a total of 512 trials. The subjects were told to place equal emphasis on speed and accuracy in their responses. Performance feedback was provided after every block to yield error rates of approximately 10%, ensuring an adequate number of trials for stable error-related waveforms.

Electrophysiological Recording, Data Reduction, and Analysis

The EEG was recorded from DC-512 Hz using scalp electrodes, two mastoid electrodes, and four EOG electrodes using the BioSemi ActiveTwo system, an EEG active-electrode sensor system that is well-tolerated by children because it does not require scalp abrasion. Data were recorded referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode. A nylon mesh cap was used with sensors embedded in it. EEG data were screened for artifacts using visual inspection as well as automated artifact rejection algorithms in the Matlab-based analysis software EEGLAB. Eye movement artifacts were corrected using the Gratton regression procedure (Gratton et al., 1989).

Behavioral measures included accuracy expressed as a percentage errors out of all trials. Average reaction times on error and correct trials were calculated separately. Reaction times were analyzed with group as a between-subject factor and response type as a within-subject factor. Reaction time after errors were evaluated to determine if there were group differences in post-error behavioral adjustments.

The error-related negativity and both error positivity components were quantified using mean amplitude measures relative to a pre-response baseline -200 to -50 msec. The mean amplitude of the error-related negativity was computed at Cz in a window from 0 to 100 msec following the incorrect response on error trials; measurements were made at Cz given that the difference between ERN and CRN was largest at this electrode. The correct response negativity consisted of the same measure computed on correct response trials. The mean amplitude of the early error positivity was computed at Cz in a window from 100 msec to 200 msec following the incorrect response and the mean amplitude of the late error positivity in a window from 250 msec to 350 msec following the incorrect response; measurements were made at Cz given that the difference between error and correct waveforms at their respective time windows was largest at this electrode.

Separate analyses of the error-related negativity and both error positivity components were conducted with a repeated-measure analysis of variance and Student's t-tests; furthermore, these analyses were corrected for multiple comparisons using Tukey's test statistic. Statistical significance for all clinical comparisons were evaluated using chi-square tests, followed by two-sided Monte Carlo simulations for the purpose of confirming significance.

Correlation analyses involving Pearson correlation coefficients were performed in order to determine the relationship between task-related behavioral measures (including accuracy and reaction time) and error-related ERP component amplitude. Additional analyses using the Spearman's rank correlation coefficient were performed in order to determine the relationship between CBCL clinical measures (i.e. did not follow a normal distribution) and ERP component amplitudes. CBCL measures that significantly

correlated with ERP component amplitudes were next included as part of an univariate analysis of variance, for the purpose of addressing whether these measures could effectively predict error-related negativity and error positivity amplitudes. All behavioral and clinical measures were statistically evaluated using SPSS 19, whereas event-related potential measures were analyzed using custom software written in C and in Matlab, as well as the Matlab-based EEGLAB software package (http://www.sccn.ucsd.edu/eeglab/). All statistical tests were two-tailed with the alpha level set at 0.05.

Results

Preliminary Analyses

Clinical, behavioral and ERP measures were examined for skewness and outliers. Both ERP and task-related behavioral measures satisfied assumptions of parametric statistics, although four outliers were identified while evaluating ERN values across the 52 children in the sample (3 ASD and 1 HC, with ERN values greater than +/- 3 std. devs. from each group's mean). For all ERP analyses pursued in this chapter, results were first evaluated by including the entire n = 52 sample, followed by analyses excluding the four outliers. Group differences across the CBCL measures were analyzed with methods other than standard parametric tests, given that this data was heavily skewed, and characterized by an over-abundance of zero values.

Behavioral Data

Behavioral data for participants are presented in **Table 1**. There were no group differences in accuracy (t(50)=1.050, p>.05), reaction time during error (t(50)=1.283,

p>.05) or correct trials ($t(50)$=1.502, p>.05), or post-error slowing ($t(50)$=1.377, p>.05) between ASD children and the healthy comparison subjects, though children with ASD were slower to respond during error and correct trials, in comparison to the HC. Overall, participants were faster on error than correct trials (F = 44.346, df = 1, 50, p<.001). No main effect of group and no interaction between group and response type for reaction time reached significance (p = 0.158 and 0.708, respectively).

Clinical Data

Means and standard deviations for the CBCL subscales are presented in **Table 1**. Additional parent- and self-reported measures of ASD symptom severity (including the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule, the Social Responsiveness Scale, and the Repetitive Behavior Scale-Revised) cognitive function, and anxiety (including the Spence Children's Anxiety Scale) are summarized in **Table 2.**

Analyses showed that children with ASD presented with greater psychopathology across most behavioral dimensions of interest, including the total CBCL score (χ^2=19.133, p<.001), total internalizing score (χ^2=11.909, p<.001), total externalizing score (χ^2=13.696, p<.001), total withdrawn score (χ^2=10.501, p<.001), and total anxiety problems score (χ^2=6.715, p<.05). No significant differences were observed in total negative affectivity score (χ^2=3.837, p>0.05), between ASD and healthy comparison subjects.

Error-related Potential Data

As highlighted in **Figure 1** and summarized in **Table 1,** group differences were identified in all four error-related ERP components studied in this study. Post-hoc tests

were carried out between groups using the Tukey adjustment for multiple comparisons. After correcting for multiple comparisons, children with ASD had a more negative CRN ($t(50) = 3.233$, p<0.05) and ERN at Cz ($t(50) =2.416$, p<0.05), in comparison to HC subjects. In addition, ASD children had a less positive early Pe ($t(50) = 3.151$, p<0.05) and late Pe at Cz ($t(50) =2.820$, p<0.05), in comparison to the HC group. Group differences remained significant after removal of four outlier datapoints (i.e. CRN: $t(46)$ =2.711, p<0.05; ERN: $t(46)$ =2.827, p<0.05; Early Pe: $t(46)$ =2.735, p<0.05; Late Pe: $t(46)$ =2.351, p<0.05).

In addition, when removing all 7 ASD children who were on medication from the previous analyses, there was still a significant difference in all 4 ERPs between ASDs and HCs (children with ASD continued to have a more negative CRN, $t(50) = 2.700$, p<0.05, and ERN: $t(50) = 2.461$, p<0.05; children with ASD continued to have a less positive Early Pe: $t(50) = 2.707$, p<0.05, and Late Pe: $t(50) = 3.238$, p<0.05).

Error-related negativity amplitude at electrode Cz was significantly correlated with accuracy among HC children (HC: $r = -.518$, p<0.05, $n = 26$); when considering the ASD children only, the trend did not endure ($r = -.135$, p>0.05, $n = 26$). Removal of four outliers did little to affect these results (HC: $r = -.446$, p<0.05, $n = 25$; ASD: $r = .140$, p>0.05, $n = 23$). In HC subjects, but not ASD, greater early Pe amplitude significantly correlated with greater accuracy ($r = -.5109$, p = 0.008), longer reaction times during correct ($r = -.4470$, p = 0.022) and error trials ($r = -.5045$, p = 0.009), and greater post error slowing ($r = -.4704$, p = 0.015); findings remained significant even after removal of an outlier.

Correlations with Symptom Severity (CBCL)

When considering all 52 subjects, only the total CBCL score and the withdrawn symptom severity score ($r = -.313$, $p<0.05$ and $r = -.302$, $p<0.05$, respectively) significantly correlated with ERN amplitude (i.e. greater symptom severity corresponded with larger ERN amplitude). However, the correlation only remained significant at a trend-level after removal of four outlier children ($p = 0.093$).

An univariate analysis of variance was carried out in order to evaluate whether withdrawn symptom severity significantly predicted ERN amplitude. Given that the withdrawn scale is embedded within the CBCL total scale, the CBCL total scale was not included as an independent variable in this analysis. Additional CBCL scores did not significantly correlate with ERN, CRN, or early and late Pe amplitude, and were therefore not included in subsequent analyses.

Univariate Analysis of Variance (CBCL Scales)

As summarized in **Table 3**, the withdrawn scale did not significantly predict ERN amplitude, including when age, diagnosis, drug status, and gender were added as nuisance covariates. Findings did not change when 4 outliers were excluded from this analysis (model $p>0.05$).

Correlations with Symptom Severity (ASD-Only Scales)

Additional parent- and self-reported measures of ASD symptom severity (including the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule, the Social Responsiveness Scale, and the Repetitive Behavior Scale-Revised) are presented in **Table 2.** None of these measures significantly correlated with error-related component amplitude, and were therefore not included in subsequent analyses.

Discussion

The purpose of this study was to describe the CRN, ERN and early and late Pe in a well-characterized sample of 26 pediatric patients with ASD and 26 age-matched comparison subjects. Group differences were identified in the CRN, ERN, the early Pe, and the late Pe, between ASD and healthy comparison subjects; however, we approach the enhanced CRN finding (in the ASD sample) with extreme caution, specially given that the presence of broad slow positive wave overlapping with the CRN may have influenced our measurements of the CRN. Future studies with more precise methodologies for measuring the CRN (including PCA and time frequency analyses) may help better sort the relationship between this component and age.

Also, while several studies have shown that high-accuracy subjects tend to display larger ERN amplitude (Hajcak et al., 2003; Pieters et al., 2007), this relationship was only observed in healthy comparison subjects alone and not in our sample of ASD children. Given that there were no group differences in accuracy between the ASD and healthy comparison children, it is possible that children with ASD make use of alternative mechanisms for keeping up task-related accuracy; this finding may be in fact be reflective of an alternative cognitive style for processing errors in ASD; further research will be required to further understand this phenomenon.

Parent- and child-report measures of emotional and behavioral disorders and autistic symptom severity were also measured in order to identify the clinical correlates associated with atypical ERP component manifestation; results indicated that an overall atypical error-processing mechanism underlies severe symptomatology in ASD. When considering all 52 subjects, increased ERN amplitude significantly correlated with

increasing withdrawn score. These findings are in line with previous studies that reported increased error-related brain activity among individuals reporting high levels of internalizing behaviors and behavioral inhibition (Amodio et al., 2008; Boksem et al., 2006; Hajcak et al., 2003; Hajcak et al., 2004; McDermott et al., 2009; Olvet and Hajcak, 2008).

Our study came with two key limitations. First, approximately 7 (out of n = 26) ASD subjects were under medication while participating in our study. There was much variability in the range of medications being taken by each of these subjects (including mood stabilizers and antidepressants), thus making it impossible to evaluate the effects of each of these specific medication classes on error-processing and the ERN. Such an analysis may be the subject for future research.

In addition, the ASD sample in our study was largely heterogeneous, and there was much variation in the specific spectrum-related diagnoses represented across this sample. Specifically, within this study's ASD sample, 14 children had a diagnosis of autism (e.g. "high-functioning autism"), 6 had a diagnosis of Asperger Syndrome and 6 had a diagnosis of PDD-NOS. Given that data was only collected in n = 6 PDD-NOS and n = 6 Asperger children, it was not possible to determine whether there are differences in error-processing across the sub-diagnoses included under the ASD spectrum. We suspect that this too could be further addressed in a study with a larger ASD sample.

Finally, it has not escaped us that, in the same line as the OCD vs Unaffected sibling study presented on Chapter 3 of this dissertation, it would certainly benefit the field to introduce a study on ASD and their siblings. Already, there is evidence to support the presence of atypical cognition in siblings with ASD, who experience a greater risk for

developing ASD that the general population (Constantino et al., 2006; Constantino et al., 2011; Hughes et al., 1999; Orsmond and Seltzer, 2007). Findings showing increased ERN in ASD siblings may help substantiate the claim of the ERN as a potential endophenotype in ASD. Future studies may aim to address the gap in the literature.

Figure 5.1. Response locked ERP waveforms at Cz comparing correct and error trial waveforms for ASD and Healthy Comparison subjects. For each panel, response onset occurred at 0ms and negative is plotted up. After correcting for multiple comparisons, children with ASD had a more negative CRN ($t(50)$ = 3.233, p<0.05) and ERN at Cz ($t(50)$ =2.416, p<0.05), in comparison to HC subjects. In addition, ASD children had a less positive early Pe ($t(50)$ = 3.151, p<0.05) and late Pe at Cz ($t(50)$ =2.820, p<0.05), in comparison to the HC group.
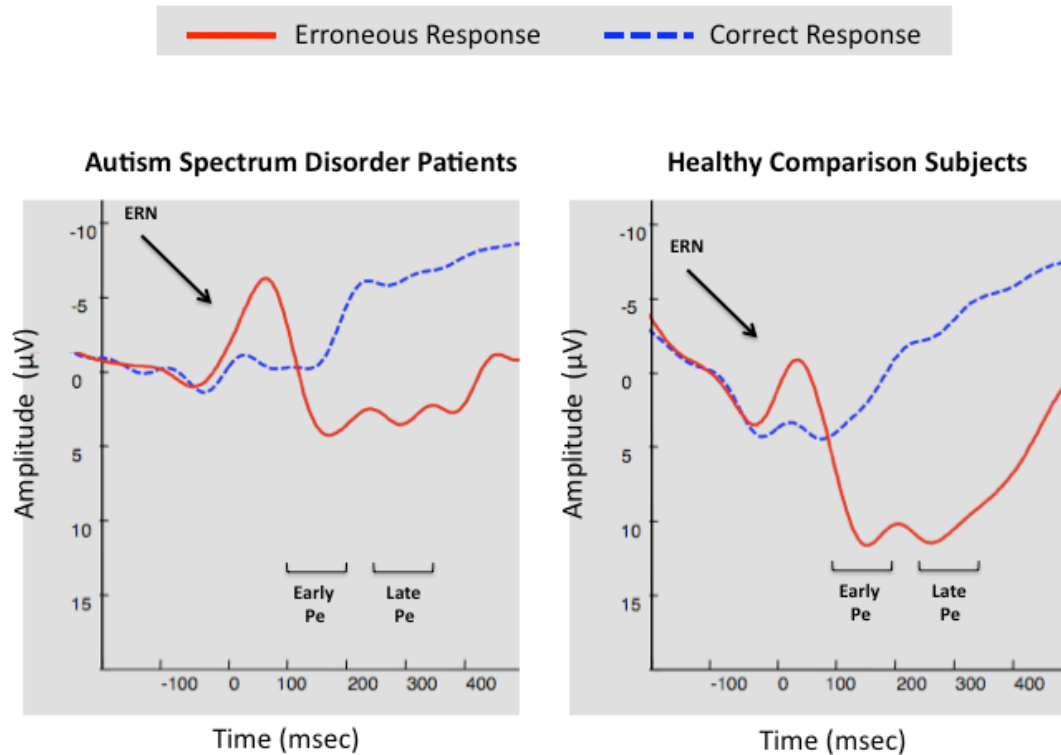
Table 5.1. Demographic, Performance, Clinical, and ERP Data (Summary) for Autism Spectrum Disorder (ASD) and Healthy Comparison participants.

	HC, n=26	ASD, n=26
	Mean	Mean
Demographic Data		
Age (years)	14.1 (2.500)	13.7 (2.200)
Task Performance Data		
Accuracy	0.892 (.050)	0.910 (.071)
Error reaction time (msec)	404.831 (138.194)	457.205 (132.206)
Correct reaction time (msec)	478.426 (102.018)	522.926 (134.309)
Post-error reaction (msec)	452.638 (175.262)	525.701 (206.075)
Clinical Data		
Child Behavior Checklist		
Total score	7.800 (5.708)	45962 (22.284)
Internalizing score	2.680 (2.249)	11.692 (6.620)
Externalizing score	2.160 (2.192)	10.231 (8.155)
Negative Affectivity	1.320 (1.249)	5.462 (3.733)
Withdrawn / Depressed	.0.840 (1.143)	4.077 (2.682)
Anxiety	.320 (0.557)	3.000 (2.433)
ERP Measures		
CRN at Cz	1.837 (5.083)	-3.315 (6.341)
ERN at Cz	-2.611 (6.482)	-7.774 (8.761)
Early Pe at Cz	13.403 (7.592)	6.216 (8.809)
Late Pe at Cz	12.593 (8.309)	5.653 (10.256)

Table 5.2. Descriptives of additional parent- and self-reported measures of ASD symptom severity (including the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule, the Social Responsiveness Scale, and the Repetitive Behavior Scale-Revised) cognitive function, and anxiety (including the Spence Children's Anxiety Scale).

Clinical Measure	Mean (Standard	Range
Autism Diagnostic Interview-Revised (ADI-R)		
ADI-R Social	17.35 (5.58)	8-26
ADI-R Verbal	14.32 (4.00)	6-22
ADI-R	7.65 (2.83)	2-14
ADI-R	5.95 (2.33)	3-11
Autism Diagnostic Observation Schedule (ADOS)		
ADOS Social	10.4 (4.57)	2-20
ADOS	3.9 (1.97)	0-8
Cognitive Function		
Verbal Cognitive	104.5 (28.85)	27-150
Non Verbal	107.2 (14.55)	81-137
Spence Children's Anxiety		
Total Score	29.96 (14.20)	7-65
Social Responsiveness Scale		
Total Score	88.04 (30.68)	11-138
Social Awareness	13.15 (9.36)	4-56
Social Cognition	16.62 (7.84)	2-43
Social	32.42 (10.71)	10-54
Social Motivation	16.19 (8.39)	4-48
Autistic	19.96 (11.56)	5-68

Table 5.3. Univariate Analysis of Variance for evaluating the effects of withdrawn behaviors on ERN amplitude. The CBCL withdrawn scale was observed to not significantly predict ERN amplitude.

Tests of Between-Subjects Effects

Dependent Variable:ERN

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	442.937[a]	5	88.587	1.416	.237
Intercept	34.069	1	34.069	.545	.464
Covariate: Drug Status	48.022	1	48.022	.768	.386
Covariate: Gender	31.281	1	31.281	.500	.483
Covariate: Diagnosis	113.969	1	113.969	1.822	.184
Covariate: Age (mos)	7.617	1	7.617	.122	.729
Withdrawn CBCL Score	34.333	1	34.333	.549	.463
Error	2814.464	45	62.544		
Total	4712.256	51			
Corrected Total	3257.401	50			

a. R Squared = .136 (Adjusted R Squared = .040)

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Chapter VI

Conclusion

Over the last two decades, increased interest in the characterization of error-related ERP components in healthy and psychiatric adult populations has resulted in the improved understanding of error-processing and its correlates to everyday function. The error-related negativity has been proposed as a potential endophenotype for internalizing disorders (Olvet and Hajcak, 2008). The ERN may be useful for further improving our comprehension of the link between genetic risk and disease onset in a number of disorders, including anxiety, OCD, and ASD.

The goal of this dissertation was to further enlighten our understanding of the ERN across a number of pediatric populations. At this point, it is possible to take a step back, and re-evaluate the potential for the ERN as a possible endophenotype for OCD, ASD, and anxiety. The reader is reminded about the 3 criteria for a trait to attain "endophenotype status." These were presented in the introduction to this dissertation and are further addressed here in light of the findings revealed by this dissertation.

Criteria 1: Endophenotypes are characterized by their association to disease, but are not influenced by changes in disease-related state levels in symptom severity. As evidenced throughout this dissertation, elevated ERN amplitude was observed in children with OCD (Chapter 3 and 4), anxiety (Chapter 3), and autism (Chapter 5). The presence of elevated ERN amplitude across all three disorders may be reflective of a shared subset of genes responsible for bringing about this specific physiological signature and

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eventually paving the way towards disease. In healthy individuals, increased ERN amplitude has been associated with the presence of 1-2 copies of the 5-HTTLPR short variant (Fallgatter et al., 2004) and the presence of the Met/Met versus Val+ polymorphism of the catechol-*O*-methyltransferase (COMT) gene (Mueller et al., 2011). Similar analyses have yet to be carried out in patient groups. Future patient studies may consider using the ERN as a target of analyses aiming to elucidate the genes that bring about increased ERN in OCD, anxiety, and autism.

Also in line with Criteria 1 is the fact that, as previously shown in a wide array of adult studies, the ERN did not appear to change as a function of disease-specific symptom severity (for example, increasing OC symptom severity did not correspond with increased ERN, as evidenced in Chapters 3 and 4 of this dissertation). Previous studies have looked into comparing the ERN in OCD pediatric and adult samples (before and after CBT and SSRI treatment, respectively; please refer to (Hajcak et al., 2008; Stern et al., 2010). Whether the ERN changes in anxiety and autism as a by-product of effective pharmacological or behavioral intervention remains a mystery, and may be a suitable research question to be addressed in future research studies.

Criteria 2: Endophenotypes must also be heritable and present in individuals at genetic risk for a particular disorder (including first degree relatives, such as siblings and offspring). As reported in Chapter 4, elevated ERN amplitude was observed in both pediatric patients with OCD and their unaffected siblings, further confirming the possibility of the ERN serving as an endophenotype mediating the link between genetic predisposition and atypical brain activity. Our findings were in line with a recent report that addressed the same question, albeit in adults (Riesel et al., 2011).

Criteria 3: Endophenotypes are, according to theory, present before disorder onset. They remain static throughout development or, alternatively, change over the years in a way that is well characterized and understood (Iacono and Malone, 2012). It is still unknown to us the number of unaffected siblings (whose data was presented in Chapter 4) who will eventually develop OCD. Although not directly tested in Chapter 4, our research group does plan to revisit the unaffected siblings that participated in our study, for the purpose of determining if any eventually developed OCD. This study will enable us to model if increased ERN, compounded with greater genetic risk, eventually paves the way towards disease onset among unaffected siblings of children with OCD. In this way, we will be able to further validate the use of the ERN as an endophenotype, by evidencing whether OCD patients do express an elevated ERN prior to disease onset.

Criteria 3 does bring up an interesting point: as mentioned by Iacono in a recent manuscript on the use of endophenotypes in alcoholism research, it is possible that endophenotypes may remain static throughout development, or alternatively, change over the years in a way that is very specific and well-understood. As highlighted in Chapter 2 of this dissertation, it appears that the ERN changes (i.e. decreases in amplitude) across healthy development. Current research on the ERN could benefit from the use of longitudinal research designs for the purpose of better characterizing the changes in the ERN across atypical development. It is possible that, if able to reliably predict a specific atypical pattern of change in the ERN across development in psychiatric populations (such as OCD or anxiety), it may be possible to use this *change in the ERN* as a more effective marker for disease risk, as opposed to just the presence of an elevated ERN

earlier in childhood (Iacono and Malone, 2012). To our knowledge, the use of a *changing marker* as an endophenotype has not been considered within the field of ERP research.

In sum, this dissertation aimed to characterize a series of error-related ERP components across a number of pediatric healthy and patient groups. Findings seemed to further validate the use of the ERN as a potential endophenotype in psychiatric research. Further research on the expression of ERPs across development will definitely shed light not only on the complexities of ACC function across the lifespan, but also how differential expression of ACC activity, along with other (currently unknown) factors, bring about internalizing psychopathology in youth.

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