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# Electrophysiological Endophenotypes in Autism Spectrum Disorder: A Family Study

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# A Family Study

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ABSTRACT

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Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder associated with altered neural connectivity and deficits in self-monitoring, response inhibition, and planning. One promising avenue of research to improve understanding of the symptoms and heritable nature of ASD may be the identification of neural endophenotypes of ASD. The error-related negativity (ERN) and post-error positivity (Pe), scalp-recorded event-related potentials (ERPs), reflect performance monitoring processes and may qualify as candidate endophenotypes of ASD. We collected ERP and behavioral data (error rates, response times) from 18 ASD probands and their families (mother, father, sibling) and 38 control youth and their parents to examine the utility of the ERN and Pe as endophenotypes of ASD. In order to examine differences based on group (ASD vs. control) and kinship (proband, sibling, mother, father), we conducted separate multiple regression analyses on behavioral and ERP data with group and kinship as predictors and families as clusters. We hypothesized that ASD probands would display reduced-amplitude ERN and impaired behavioral performance relative to control youth but no differences in Pe amplitude and that families of ASD probands would display reduced error minus correct (ΔERN) amplitudes and impaired behavioral performance relative to control families but no differences in ΔPe amplitude. We did not observe significant ERN amplitude group differences among ASD probands relative to control youth. Likewise, control youth did not differ from ASD probands on behavioral measures or Pe amplitudes. Analyses by family revealed that group and kinship did not significantly predict ΔERN amplitudes. However, fathers of ASD probands displayed significantly reduced ΔPe amplitudes relative to control fathers and parents displayed significantly larger ΔPe amplitudes and better performance than youth. Together, results do not provide sufficient evidence to support the ERN or Pe as an endophenotype or biomarker of ASD. These findings add to an overall heterogeneous literature on performance monitoring in ASD and point to the need for additional research to understand the state-related or trait-related factors that may contribute to ERN amplitudes in ASD.

Keywords: autism spectrum disorder, error-related negativity, post-error positivity, endophenotype

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# Electrophysiological Endophenotypes in Autism Spectrum Disorder: A Family Study

Autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by a constellation of psychological, cognitive, and neural symptoms. Diagnosis of ASD is based on the presence of social interaction impairments, including poor social and emotional reciprocity; communication deficits, often manifest in language delays or poor use of nonverbal communication; and inflexible, repetitive, or stereotypical behaviors (American Psychiatric Association, 2013). However, it is yet unclear why these symptoms co-occur and the functional impact and degree to which specific symptoms are present is heterogeneous across individuals on the autism spectrum (Minshew & Williams, 2007). Individual differences in symptom presentation are associated with substantial variability within the diagnosis of ASD, contributing to difficulty establishing meaningfully discriminatory diagnostic criteria that account for severity and differences in symptom presentation (Viding & Blakemore, 2007). As a result, research is needed to improve our understanding of the factors that contribute to ASD in order to guide diagnosis and treatment and establish distinct divisions among symptoms (Happé, Ronald, & Plomin, 2006; Liu & Takumi, 2014).

## Neural Abnormalities in ASD

Current theories suggest that impaired neural communication caused by abnormal white-matter connectivity may underlie the symptoms of ASD (Barnea-Goraly, Lotspeich, & Reiss, 2010; Belmonte et al., 2004; Griebling et al., 2010; Haznedar et al., 2000; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Wass, 2011). Functional neuroimaging studies reveal short-range white matter over-connectivity (Belmonte et al., 2004; Orekhova et al., 2007; Wass, 2011) coupled with impaired long-range connectivity between neural networks (Anderson et al., 2011;

Just et al., 2007; Kana, Keller, Minshew, & Just, 2007; Zikopoulos & Barbas, 2010), possibly initiated by early brain overgrowth (Belmonte et al., 2004; Courchesne et al., 2011; Redcay & Courchesne, 2005; Wass, 2011). Altered connectivity may result in inadequate integration of information between brain regions, resulting in overall neural inefficiency during complex, higher-level social and cognitive processes (Kana, Libero, & Moore, 2011; Minshew & Williams, 2006; Wass, 2011).

Studies suggest a link between abnormal connectivity and the social, communication, and restricted/repetitive behaviors of ASD. For example, disrupted limbic connectivity within the uncinate fasciculus and frontal and temporal thalamic projections is tied to impairments in socio-emotional functioning (Ameis & Catani, 2015) and increased corticostriatal functional connectivity is associated with difficulties in social interaction and communication as well as restricted interests/repetitive behaviors (Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013). Abnormal connectivity in ASD may lead to deficits in higher-level cognitive functions, such as theory of mind and executive functioning (Cheng, Rolls, Gu, Zhang, & Feng, in press; Christ, Kester, Bodner, & Miles, 2011; Just et al., 2007; Ozonoff, Pennington, & Rogers, 1991). Taken together, though disrupted neural connectivity is clearly implicated in the symptoms of ASD, the location and extent of disrupted connectivity is variable, as is the developmental course, possibly influencing the extensive heterogeneity in symptom presentation and severity in individuals with ASD (Viding & Blakemore, 2007).

**The Genetics of ASD**

Heritability studies suggest that ASD is the most heritable neurodevelopmental disorder (Bailey et al., 1995; Hallmayer et al., 2011), with estimates of up to 80% heritability (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010; Losh, Sullivan, Trembath, &

Piven, 2008) and concordance rates among monozygotic twins estimated at 70-90% compared to 10-30% in dizygotic twins (Bailey et al., 1995; Rosenberg et al., 2009). In addition, family members of affected individuals are 24 to 40 times more at risk for developing ASD than families without a history of ASD (Losh et al., 2008; Ozonoff et al., 2011). Even if they do not receive a formal diagnosis, unaffected family members of ASD probands (i.e., the affected individual) often display milder symptoms of ASD themselves, identified as the broader autism phenotype. Though findings are somewhat mixed (Hallmayer et al., 2011; Ronald & Hoeksma, 2010), additive genetic factors (i.e., the cumulative affect of variability in allelic genetic expression) may have a larger influence on ASD symptoms than non-shared environmental factors (Colvert et al., in press; Klei et al., 2012). The strong influence of genetic factors on ASD symptom presentation has also been observed among those with subclinical symptoms, suggesting genetic liability exists across severity levels of ASD symptomology (Colvert et al., in press). Thus, studies of heritability consistently indicate that genetics play a critical role in contributing to both clinical and subclinical symptoms of ASD.

Autism spectrum disorder is clearly heritable, but does not follow typical Mendelian patterns of inheritance and researchers have identified hundreds of genetic loci and chromosomal abnormalities tied to the disorder (Betancur, 2011; Gaugler et al., 2014; Li, Zou, & Brown, 2012). Many of the genetic variants implicated in ASD are involved in regulating general neuronal functioning, reinforcing the role of abnormal neuronal development in ASD (Liu & Takumi, 2014). For example, genome wide association studies (GWAS) have identified genetic loci involved in regulating synaptic membrane exocytosis (Kumar et al., 2010), binding amyloid and CREB precursor proteins (Barnby et al., 2005; Sutcliffe, Han, Amin, Kesterson, & Nurmi, 2003), regulating NMDA and glutamate receptors, and several other critical functions (see Li et

al., 2012 for a full review). Given that the genes currently tied to ASD are associated with general neural functions rather than specific processes it is unclear to what degree these genes influence specific symptomatic and neural outcomes. It may be that rare mutations contribute to liability for ASD diagnosis, but that common variation in genes (such as those noted above) explain a larger proportion of the heritability of ASD (Gaugler et al., 2014). Therefore, the unique functional consequences (e.g., stereotypical behaviors, impaired communication, etc.) of ASD are likely the result of complex gene-environment and gene-gene interactions that occur throughout the course of development (Betancur, 2011; Eapen, 2011; Hallmayer et al., 2011; Kiser, Rivero, & Lesch, 2015; Liu & Takumi, 2014; Risch et al., 1999).

**Endophenotypes: Bridging Genes and Behavior**

Given the heterogeneous symptom presentation and neural and genetic complexity of ASD, a key issue in ASD research is the identification of easily measurable processes that mediate genotype-behavior relationships. Researchers have suggested the utility of cognitive or neural endophenotypes as a way to link genes and behavior and better understand the nature of ASD (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011; Glahn, Thompson, & Blangero, 2007; Gottesman & Gould, 2003; Jeste & Nelson, 2009). According to National Institutes of Health Research Domain Criteria (RDoC) policy, endophenotypes are "relatively well-specified physiological or behavioral measures that are considered to occupy the terrain between disease symptoms and risk genotypes" (Insel & Cuthbert, 2009, p. 988). In other words, endophenotypes are internal processes (i.e., generally unobservable to the naked eye) that mediate gene-behavior pathways (Gottesman & Gould, 2003; Viding & Blakemore, 2007). Neuropsychological processes, cognitive measures, psychometric patterns, and patterns of neural activation have all been proposed as potential endophenotypes given that they are tied to genetic

causes but also contribute to symptom presentation (Miller & Rockstroh, 2013). It is important to note that although endophenotypes are conceptualized as meditational processes, they do not represent another level in a causal chain leading from genes to behavior. Rather, endophenotypes are a part of a causal network wherein disruption at one level can, by association, have an impact at other levels, influencing the etiology of a disorder (Cannon & Keller, 2006; Miller & Rockstroh, 2013). In this way, endophenotypes integrate psychological, biological, physiological, and genetic information (Viding & Blakemore, 2007) and may improve understanding of gene-behavior relationships by providing insight into possible mechanisms through which disorders occur (Glahn et al., 2007; Viding & Blakemore, 2007).

The use of endophenotypes may be particularly advantageous in ASD research by providing a way to link heterogeneity between behavioral presentation and genetic factors (Eapen, 2011; Jeste & Nelson, 2009). The current state of ASD research clearly indicates the complexity of the gene-behavior relationship, as no one factor has been identified as a primary cause of ASD symptoms. The conceptualization of endophenotypes is in-line with individual variability evident in ASD research, as it assumes that psychopathology is complex and the result of multi-faceted, reciprocal and recursive relationships that occur throughout development (Miller & Rockstroh, 2013). Additionally, endophenotypes may provide a way to identify homogeneous subgroups among those with ASD (de Geus, 2010; Eapen, 2011; Viding & Blakemore, 2007) or provide a sensitive measure of susceptibility in relatives without overt signs of the disorder (Viding & Blakemore, 2007). Again, because the definition of an endophenotype assumes a multi-causal network rather than one individual contributor (Miller & Rockstroh, 2013), endophenotypes may facilitate greater differentiation of the unique contributors that underlie ASD symptoms but result in individual symptom profiles. Thus, the identification of

endophenotypes is a critical step in building on previous research to advance our understanding of ASD.

Several criteria have been established for behaviors or neural activity to qualify as an endophenotype. A candidate endophenotype must be: 1) associated with a disorder, 2) heritable, 3) manifest independent of illness state (e.g., uniform before and after treatment), 4) co-occur with the disorder in families, and 5) present in the same form within families of affected individuals to a larger degree than the general population (Gottesman & Gould, 2003; Olvet & Hajcak, 2008). These criteria differentiate endophenotypes from biomarkers, as they imply that a potential endophenotype is more than a correlate with the disorder, is clearly heritable, and is not merely a state-dependent outcome with limited replicability (Gould & Gottesman, 2006; Miller & Rockstroh, 2013; Ritsner & Gottesman, 2009). A biomarker, on the other hand, detects pathophysiological features of a disorder but may not be tied to underlying genetic causes (Ritsner & Gottesman, 2009).

**Electrophysiological endophenotypes.** Recently, researchers have suggested the utility of event-related potentials (ERPs) as neural endophenotypes (de Geus, 2010; Glahn et al., 2007; Olvet & Hajcak, 2008). Event-related potentials are time locked markers of neural activity as measured by scalp-recorded electroencephalogram (EEG). Substantial evidence suggests that ERPs are heritable and thus stem from genetic processes (for a review, see de Geus, 2010). Due to the high temporal resolution of EEGs, ERPs can be used to signify specific cognitive, behavioral, and motor responses to internal processes or external stimuli (de Geus, 2010). Thus, ERPs are easily measurable indices that reveal information regarding the timing and processing stage impacted by a specific disorder (de Geus, 2010). In this way ERPs are ideal potential

endophenotypes, as they are influenced by genetics but are also directly tied to cognitive and neural processes.

*ERN*. One promising candidate for use as an endophenotypic marker in ASD is the error-related negativity (ERN; Olvet & Hajcak, 2008), an ERP associated with cognitive control and performance monitoring processes (Falkenstein, Hohnsbein, Hoormann, & Banke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Yeung, Botvinick, & Cohen, 2004). The ERN is a fronto-central negativity that appears approximately 50-100ms following an error response (Gehring et al., 1993; Yeung et al., 2004). Source localization studies suggest that the ERN is associated with activity in the anterior cingulate cortex (ACC) and may involve communication with several brain regions within the prefrontal cortex to facilitate top-down control (Bush, Luu, & Posner, 2000; Carter et al., 1998; van Veen & Carter, 2002a).

Several theories have been proposed to explain ERN generation (see Larson, Clayson, & Clawson, 2014 for a review). The conflict monitoring theory suggests that the ERN may represent response conflict between competing correct and incorrect responses (Botvinick, Carter, Braver, Barch, & Cohen, 2001; Yeung et al., 2004). From this perspective, the ERN is a reflection of performance monitoring processes used to evaluate contextual information to monitor and regulate goal-directed behaviors (Botvinick et al., 2001; Yeung et al., 2004; Yeung & Cohen, 2006). Alternatively, the ERN may represent a signal of error awareness when the expected correct response is inconsistent with the erroneous response that was selected (Falkenstein et al., 1991; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). The reinforcement learning theory of the ERN considers the role of dopamine in ERN generation, suggesting that the ERN is a signal that results from phasic dips in dopamine following an error (Holroyd & Coles, 2002). These decreases in dopamine result in disinhibition of the ACC,

signaling that an unexpected outcome has occurred and behavioral modification is required to improve performance in the future (Holroyd & Coles, 2002). Finally, the ERN may be more closely tied to affective responses when a motivationally salient outcome does not occur, with enhanced ERN amplitudes reflecting increased neural activity due to the aversive nature of an error (Chiu & Deldin, 2007; Proudfit, Inzlicht, & Mennin, 2013; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). Common among all of these theories is the underlying theme that enhanced ERN amplitudes are associated with activation of cognitive and affective processes involved in recognizing and utilizing contextual information following errors to then regulate performance and avoid error commission in the future (Olvet & Hajcak, 2008; South, Larson, Krauskopf, & Clawson, 2010).

*Pe.* The post-error positivity (Pe) is a positive-going ERP that typically co-occurs with the ERN. The Pe appears within 200-500ms of error commission and is typically more posteriorly located than the ERN, possibly representing activation in the rostral or dorsal ACC (Bush et al., 2000; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; van Veen & Carter, 2002b). Most research on the Pe suggests that it signifies error awareness or detection (Hajcak, McDonald, & Simons, 2004; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Steinhauser & Yeung, 2010), with larger amplitudes following trials in which individuals were aware of error commission (Endrass, Reuter, & Kathmann, 2007; O'Connell et al., 2009), though some inconsistencies have been observed (Herwig, Baumgartner, Kaffenberger, & Brühl, 2007). Most studies indicate a dissociation between the ERN and Pe, as the Pe purportedly acts more directly as an error signal utilized to initiate behavior change than the ERN (Nieuwenhuis et al., 2001). Thus, the ERN and Pe signify separate but related phases of the performance monitoring process.

**The ERN and Pe as potential endophenotypes.** Current research indicates that the ERN, but not the Pe, may qualify as an endophenotype of psychopathology (Olvet & Hajcak, 2008; Proudfit et al., 2013). Of note, considerably more research has been conducted on the ERN than the Pe in relation to the above criteria for a candidate endophenotype, with greater variability in findings related to the Pe. Research regarding the first criteria as an endophenotype suggests that ERN amplitude differences are associated with pathology such as depression, anxiety, obsessive-compulsive disorder (OCD), and, most importantly, ASD (Chiu & Deldin, 2007; Endrass, Klawohn, Schuster, & Kathmann, 2008; Hajcak, Franklin, Foa, & Simons, 2008; Hajcak, McDonald, & Simons, 2003; Henderson et al., 2006; Ruchsow et al., 2005; South et al., 2010). Research on the Pe is less consistent, with some studies indicating no significant group differences among individuals with OCD and depression relative to control participants (Chiu & Deldin, 2007; Endrass et al., 2010; Ruchsow et al., 2005) while another study indicated significantly reduced ΔPe (error minus correct trial Pe) among individuals with MDD relative to controls (Olvet, Klein, & Hajcak, 2010). Supporting the second criteria as an endophenotype, heritability estimates of both the ERN and Pe approach .50, implying that these waveforms are linked to genetic factors (Anokhin, Golosheykin, & Heath, 2008). Additionally, multivariate analyses revealed genetic overlap of more than 50% for the ERN and Pe, suggesting that they stem from similar genetic influences (Anokhin et al., 2008). Finally, in support of the third criteria, ERN amplitude differences remain stable after treatment, suggesting that the ERN remains constant regardless of illness state (Hajcak et al., 2008; Olvet & Hajcak, 2008). The Pe, however, changed among adults with ADHD following mindfulness-based cognitive therapy, with significantly increased Pe amplitudes putatively indicative of greater global cognitive and affective self-awareness (Schoenberg et al., 2014). Together, the ERN appears to meet the first

three criteria as an endophenotype, but research regarding the Pe suggests that it is not consistently associated with psychopathology and may not be reliable indicator of disease-related processes.

Relatively few studies to date have examined the fifth criteria of an endophenotype, or whether ERN or Pe amplitude differences exist in unaffected first-degree family members. The few existing studies reveal similar patterns of ERN activation among probands and relatives of affected individuals compared to controls, providing compelling evidence that the ERN may serve as a useful endophenotype. For example, enhanced ERN amplitudes observed in OCD probands were also observed in siblings of individuals with OCD (Carrasco et al., 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011), reduced-amplitude ERN associated with substance use disorders were also observed among children whose parents had a substance use disorder (Euser, Evans, Greaves-Lord, Huizink, & Franken, 2012), reduced-amplitude ERN was seen in relatives of individuals with schizophrenia and probands (Simmonite et al., 2012), and reduced-amplitude ERN seen in ADHD probands were also observed among unaffected relatives (Albrecht et al., 2008; McLoughlin et al., 2009). In contrast, no difference in Pe amplitude was observed in relatives of probands with ADHD or schizophrenia (Albrecht et al., 2008; McLoughlin et al., 2009; Simmonite et al., 2012). Based on the current research, the ERN, but not the Pe, meets the fifth criteria of an endophenotype, as it appears to be present in the same from within families of affected individuals.

The methodology utilized within these studies of family and heritability and ERPs is variable, limiting the interpretability of the role of kinship (e.g., whether the individual is a sibling or parent) in ERN and Pe generation. For example, in the abovementioned studies of OCD and ADHD, affected individuals and "relatives" were either not related (McLoughlin et al.,

2009; Riesel et al., 2011) or were related in some but not all sibling pairs (Carrasco et al., 2013; Simmonite et al., 2012). Further, Euser et al. (2012) only included relatives without the comparison of affected probands. Only the study by Albrecht et al. (2008) examining children with ADHD included a full sample of related sibling pairs. Thus, although these studies suggest that the ERN may serve as a marker of susceptibility among unaffected relatives, no studies have examined ERN amplitudes within families of affected probands who also participated in the study. Full family studies are requisite to better understand how the ERN mediates the gene-symptom relationship.

**The ERN as an endophenotype of ASD.** Given the utility of endophenotypes in bridging the genetic and symptom/behavioral heterogeneity of ASD, it may be beneficial to examine the ERN as a potential endophenotype of ASD. As detailed below, there is some evidence that the ERN may qualify as a candidate endophenotype of ASD. The heritable nature of the ERN and relationship with neural and cognitive processes further support the ERN as an endophenotype of ASD, as the ERN may provide a way to link heterogeneity of symptoms in a way that accounts for genetic, neural, and cognitive aspects of ASD.

*ERN in ASD*. Research examining the ERN in individuals with ASD reveals significantly attenuated ERN amplitudes relative to typically developing controls (TDCs), putatively implying a reduced ability to evaluate conflicting information (Sokhadze et al., 2010; Sokhadze et al., 2012; South et al., 2010; Vlamings, Jonkman, Hoeksma, van Engeland, & Kemner, 2008). Imaging studies during cognitive control tasks reveal that the implementation of cognitive control required for response monitoring by the ACC may be impaired due to compromised neural structure (Simms, Kemper, Timbie, Bauman, & Blatt, 2009) and reduced connectivity between the ACC and both long-distance and neighboring brain regions such as the prefrontal

cortex (Agam, Joseph, Barton, & Manoach, 2010; Anderson et al., 2011; Courchesne et al., 2011; Thakkar et al., 2008; Zikopoulos & Barbas, 2010). Together, these studies suggest that cognitive control impairments in ASD are potentially tied to neural irregularities in the ACC and its concomitant connections.

Other studies of the ERN in individuals with ASD reveal inconsistent differences between ASD youth and TDCs. Groen et al. (2008) observed no differences in ERN amplitudes among children with sub-threshold symptoms of ASD relative to TDCs and children with ADHD. In contrast, *larger* ERN amplitudes were observed among children with ASD with higher VIQ scores relative to TDC children (Henderson et al., 2006). More recent research adds to these studies by suggesting that individual characteristics may play a critical role in contributing to ERN generation in ASD. For example, although no group differences were observed in ERN amplitudes between youth with ASD relative to TDCs, larger ERN amplitudes were associated with greater severity of parent-reported symptoms of ASD (McMahon & Henderson, 2014). Similarly, ΔERN (the difference between ERN amplitudes on correct and error trials) amplitude differences between youth with ASD and TDC youth were not observed during a basic facial processing task, but larger ΔERN amplitudes were observed during a more complex task, possibly suggesting reduced processing efficiency in ASD in complex social contexts (McMahon & Henderson, 2014). In sum, the majority of studies indicate differences in ERN amplitudes between youth with ASD and TDCs, though individual differences may play a critical role in mediating and/or moderating ERN amplitude differences.

*Pe in ASD.* Research on the Pe in individuals with ASD is limited but overall reveals no significant Pe differences among individuals with ASD relative to TDCs. Across four separate studies, children and adults with ASD displayed no significant differences in Pe amplitude

(Groen et al., 2008; Santesso et al., 2011; Sokhadze et al., 2010; South et al., 2010). Only one study by Vlamings et al. (2008) revealed significantly reduced-amplitude Pe in ASD compared to TDCs, possibly indicative of overall reduced error awareness or allocation of attention to errors. Taken together, the bulk of the current research on the Pe in ASD points to intact neural indices of error awareness.

*Performance monitoring in unaffected relatives.* The nature of performance monitoring in family members of ASD probands remains largely unexplored, as no studies to date have examined ERN amplitudes in relatives of ASD probands. Nevertheless, there is substantial evidence of genetic liability in family members, supporting the possibility of the ERN as a neural endophenotype. Unaffected relatives display impairments in joint attention, communication, and social interaction (Bishop, Maybery, Wong, Maley, & Hallmayer, 2006; Dawson et al., 2002; Ruser et al., 2007; Sucksmith, Roth, & Hoekstra, 2011; Sumiyoshi, Kawakubo, Suga, Sumiyoshi, & Kasai, 2011). Cognitively, family members also display deficits in planning (Delorme et al., 2007; Nydén, Hagberg, Goussé, & Rastam, 2011; Ozonoff, Rogers, Farnham, & Pennington, 1993) and the ability to organize information (Sumiyoshi et al., 2011), although other studies report no significant differences in these areas (Sucksmith et al., 2011; Wong, Maybery, Bishop, Maley, & Hallmayer, 2006). Likewise, on tasks assessing several different domains of functioning, researchers have observed commonalities in neural activation between ASD probands and their relatives, including gray matter volume increases and decreases, atypical frontal activation, lack of expected neural differentiation to congruent and incongruent biological actions, and increased trait-related neural activity (Ahmed & Vander Wyk, 2013; Belmonte, Gomot, & Baron-Cohen, 2010; Kaiser et al., 2010; Peterson et al., 2006). As a whole, studies of neural activation and cognitive variables in non-affected family members suggest the

presence of similar global cognitive and neural deficits observed in ASD probands. It is unclear whether differences in ERN amplitude are reflective of cognitive or neural impairments resulting from ASD or whether differences in ERN amplitude represent heritable markers tied to a genetic predisposition for ASD (de Geus, 2010).

In sum, the ERN may qualify as an endophenotype of ASD. Current ERP research suggests that differences in ERN amplitude among individuals with ASD may be tied to cognitive and neural deficits that underlie the symptoms of the disorder. As a result, the ERN appears to meet the first criteria for an endophenotype of ASD. The heritable nature of the ERN and ASD suggest that the ERN may also account for genetic commonalities that are associated with neural abnormalities and symptom presentation in individuals with ASD. Evidence that the underlying neural structures and cognitive functions signified by the ERN are altered in ASD probands and families of individuals with ASD further supports a putative relationship between ERN amplitudes and genes associated with ASD. Thus, in the current study, we sought to determine whether the ERN qualifies as an endophenotype of ASD by measuring neural activation during performance monitoring processes ASD probands, non-affected relatives of ASD probands, and control families. Identifying easily measurable endophenotypes of ASD is an important step in understanding the gene-behavior relationship of ASD, as it may lend insight into causal networks that underlie symptom presentation (de Geus, 2010). Greater understanding of these factors can lead to improved diagnostic classification and treatment specificity. Further, though the focus of this project is specific to ASD, identifying the utility of the ERN as an endophenotype will benefit research on other psychological disorders and extend knowledge of the utility of ERPs. The specific aims and hypotheses of this study are presented below.

## Specific Aims and Hypotheses

Aim 1: To identify the presence of subthreshold symptoms of ASD in unaffected relatives of ASD probands compared to control families.

Hypothesis 1: Guided by past research (Sucksmith et al., 2011), we predicted that unaffected family members of ASD probands would display a higher degree of ASD symptoms than control families as manifest by measures of ASD symptoms and the broader autism phenotype. Further, we predicted that differences in ASD symptoms would be present based on kinship status (i.e., whether the participant is a mother, father, or sibling), with ASD siblings showing the highest level of subthreshold symptoms, followed by fathers of ASD probands and mothers of ASD probands.

Aim 2: To replicate previous findings that youth with ASD display reduced performance monitoring ERPs relative to TDC youth (Sokhadze et al., 2010; Sokhadze et al., 2012; South et al., 2010; Vlamings et al., 2008) and examine whether dysfunctional behavioral [error rates and response times (RTs)] and ERP (e.g., ERN) markers of performance monitoring were evident in parents and siblings of ASD probands to a greater degree than control families.

Hypothesis 1**:** ASD probands would display reduced-amplitude ERN and decreased behavioral modification (longer RTs on error trials, greater error rates) relative to TDC youth, replicating previous research indicating that the ERN meets the first criteria as a potential endophenotype of ASD (Sokhadze et al., 2010; Sokhadze et al., 2012; South et al., 2010; Vlamings et al., 2008). Groups would not differ in Pe amplitude.

Hypothesis 2**:** ERN amplitudes would differ based on family and kinship status (i.e., whether the subject is a mother, father, sibling, or proband). Families of ASD probands would display similar electrophysiological and behavioral patterns as seen in ASD probands (i.e., less negative

ERN amplitudes), indicating that irregular ERN amplitudes and impaired behavioral responses were evident to a greater degree in unaffected relatives of youth with ASD. Pe amplitudes would not differ based on group or kinship status.

Hypothesis 3: Increased levels of ASD symptomology would be associated with a greater degree of electrophysiological and behavioral impairment in performance monitoring, solidifying that these impairments were associated with ASD.

## Method

### Participants

The Brigham Young University Institutional Review Board (IRB) approved all study procedures. After complete description of the study to subjects, written informed consent was obtained. Autism spectrum disorder probands and participating families of ASD probands were recruited from referrals to the Brigham Young University Comprehensive Clinic, community advertisement, and (with previous consent provided) an existing research participant pool of individuals with ASD. Control families were recruited via advertisement throughout the local community and Brigham Young University campus.

For our study purposes we collected data from biological family members that included a male ASD proband or a male TDC, along with the youths' mother, father, and one male sibling (see Figure 1). All youth participants were males between the ages of 10 and 17 years, native English speakers, and had a gestation over 34 weeks. We chose to include only male ASD probands, ASD siblings, and TDCs as studies indicate potential sex differences in the amplitude of the ERN and other cognitive control ERPs (Clayson, Clawson, & Larson, 2011; Larson, South, & Clayson, 2011; Moser, Moran, Schroder, Donnellan, & Yeung, 2013). Also, the sex of the proband may not increase the risk that siblings will receive a diagnosis of autism or the

broader autism phenotype (Goin-Kochel, Abacchi, & Constantino, 2007; Ozonoff et al., 2011; Pickles et al., 2000), decreasing the likelihood that selecting only males biased our results. However, there is evidence of increased risk for ASD diagnosis or the broader autism phenotype in male siblings compared to female siblings (Ozonoff et al., 2011; Piven et al., 1990; Szatmari & Jones, 1998), thus enhancing our ability to detect subthreshold symptoms of autism by only including male participants. We chose to use only children over age 10 in order to reduce age-related differences in cognitive processing between siblings. Several studies indicate that inhibitory control systems are not fully developed until age 10, at which time children begin to perform more similar to adults (Ridderinkhof, van der Molen, Band, & Bashore, 1997; Rueda et al., 2004).

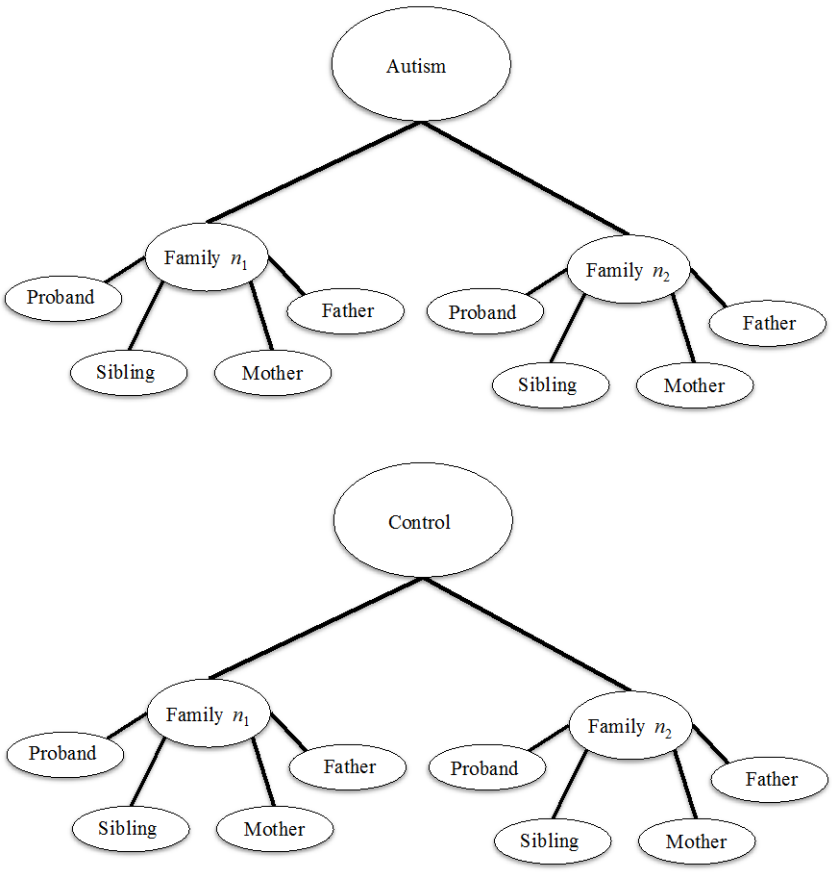


*Figure 1.* Study design.

Initial study enrollment included 180 participants from 42 families. For a full summary of participant dropout and exclusion, see Figure 2. Ultimately, there were 148 participants who met full inclusion criteria (73 ASD probands/relatives, 75 TDCs/relatives). Of those who met full inclusion criteria, 134 participants (61 ASD probands/relatives, 73 TDCs/relatives) had full data for both behavioral (i.e., RT and error rate data) and ERP measures. One sibling of an ASD proband did not have behavioral data due to computer malfunction in behavioral recording and eight participants (six ASD probands/relatives, two controls) did not have ERP data due to the commission of six or fewer error trials or excessive noise artifact (Olvet & Hajcak, 2009b). Demographic information for youth and adult participants as a function of ASD and proband status is in Tables 1 and 2.

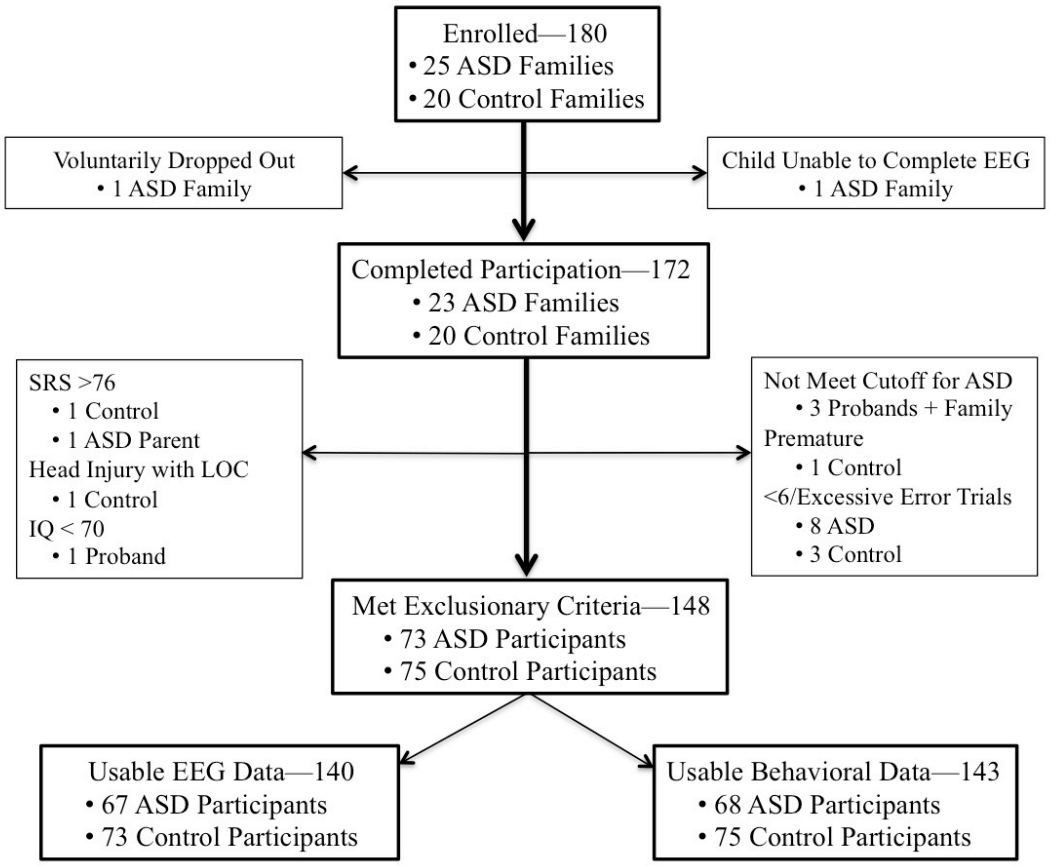


*Figure 2.* Participant flowchart.

Table 1

*Summary Demographic and Neuropsychological Data for Youth Groups*

| | ASD Probands | | | ASD Siblings | | | Control Youth | | |
|---|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range |
| Age | 13.50 | 1.38 | 11-16 | 12.13 | 1.93 | 10-16 | 12.66 | 2.16 | 10-17 |
| FSIQ | 105.72 | 15.79 | 76-140 | 113.19 | 11.68 | 79-128 | 111.84 | 9.06 | 86-132 |
| VIQ | 102.11 | 17.01 | 72-137 | 110.13 | 9.65 | 88-128 | 110.58 | 10.80 | 85-135 |
| PIQ | 108.61 | 13.53 | 86-133 | 114.19 | 14.81 | 76-136 | 110.87 | 9.63 | 91-129 |
| DS Raw[3] | 13.06 | 3.64 | 6-19 | 14.38 | 3.42 | 10-21 | 15.26 | 3.67 | 7-25 |
| DS Standard | 6.41 | 3.12 | 1-11 | 8.13 | 3.20 | 3-15 | 8.60 | 3.17 | 1-16 |
| TMT A Raw[4] | 26.59 | 6.16 | 17-37 | 29.40 | 7.69 | 17-44 | 26.89 | 8.53 | 13-50 |
| TMT B-Raw | 84.85 | 59.78 | 33-300 | 73.15 | 25.38 | 48-137 | 75.52 | 47.40 | 28-300 |
| SCARED | 19.87 | 13.11 | 4-41 | 10.46 | 10.32 | 0-38 | 6.66 | 5.84 | 0-25 |
| ADOS-G | 12.89 | 3.79 | 7-21 | - | - | - | - | - | - |
| SCQ | 18.67 | 6.62 | 7-34 | 2.77 | 2.28 | 0-7 | 3.34 | 2.32 | 0-8 |
| SRS | 77.56 | 8.52 | 63-98 | 48.33 | 11.36 | 38-72 | 45.24 | 6.33 | 37-64 |
| AQ | - | - | - | 10.08 | 6.91 | 0-25 | 11.97 | 5.13 | 3-30 |

*Note.* FSIQ = full scale intelligence quotient, VIQ = verbal intelligence quotient, PIQ = perceptual intelligence quotient, DS = Digit Span, TMT = Trail Making Test, SCARED = Screen for Child Anxiety Related Disorders, ADOS-G = Autism Diagnostic Observation Schedule-Generic, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale, AQ = Autism Spectrum Quotient.

[3]We utilized the Digit Span subtest from the Wechsler Memory Scales, 3rd Edition for all adult and child participants. As a result, age-based norms were not available for children under 16. We utilized norms from the Wechsler Intelligence Scale for Children, 4th Edition to approximate standard scores for youth below age 16.

[4]The adult version of the TMT A and TMT B was utilized for youth and parents.

Table 2

*Summary Demographic and Neuropsychological Data for Adult Groups*

| | ASD Fathers | | | ASD Mothers | | | Control Fathers | | | Control Mothers | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range |
| Age | 42.50 | 4.73 | 37-51 | 40.00 | 4.12 | 34-49 | 44.37 | 6.56 | 36-56 | 41.83 | 5.46 | 33-51 |
| Education | 15.81 | 3.15 | 12-22 | 15.65 | 2.29 | 12-20 | 17.90 | 2.83 | 12-25 | 15.11 | 1.71 | 11-18 |
| FSIQ | 117.13 | 9.20 | 100-130 | 112.67 | 8.89 | 98-126 | 120.58 | 8.93 | 101-133 | 114.72 | 8.07 | 100-133 |
| VIQ | 110.67 | 8.65 | 95-125 | 108.22 | 10.81 | 92-127 | 116.79 | 10.53 | 93-131 | 111.67 | 8.12 | 98-133 |
| PIQ | 120.40 | 11.87 | 99-136 | 114.22 | 8.09 | 100-127 | 120.05 | 9.20 | 99-136 | 114.33 | 8.18 | 101-131 |
| DS-Raw | 19.13 | 4.84 | 11-27 | 16.39 | 2.77 | 12-22 | 20.22 | 4.26 | 13-27 | 17.87 | 3.19 | 13-25 |
| DS Standard | 11.67 | 3.42 | 6-17 | 9.56 | 1.85 | 7-14 | 12.61 | 2.91 | 7-17 | 10.18 | 2.30 | 7-16 |
| TMT A Raw | 21.47 | 4.49 | 15-31 | 19.15 | 5.58 | 13-31 | 22.23 | 7.15 | 13-41 | 18.77 | 5.41 | 12-28 |
| TMT A T-Score | 54.47 | 7.19 | 43-68 | 57.76 | 11.67 | 41-78 | 55.67 | 11.98 | 35-80 | 62.53 | 11.63 | 46-89 |
| TMT B Raw | 50.63 | 13.53 | 30-72 | 45.63 | 14.77 | 28-75 | 49.16 | 19.31 | 31-108 | 45.36 | 14.43 | 28-75 |
| TMT B T-Score | 54.33 | 9.22 | 41-70 | 55.24 | 10.17 | 38-75 | 56.06 | 11.07 | 30-72 | 58.53 | 9.60 | 38-73 |
| BDI | 6.44 | 5.54 | 0-17 | 4.94 | 4.53 | 0-15 | 4.74 | 4.68 | 0-17 | 7.22 | 7.28 | 0-22 |
| STAI-State | 32.67 | 8.87 | 20-50 | 28.71 | 7.40 | 20-43 | 26.16 | 6.19 | 20-42 | 29.22 | 8.29 | 20-49 |
| STAI-Trait | 35.56 | 8.88 | 22-48 | 33.88 | 8.60 | 20-52 | 32.16 | 6.48 | 23-49 | 34.78 | 10.67 | 20-59 |
| SRS-II | 48.00 | 7.05 | 37-61 | 44.27 | 5.70 | 36-55 | 41.61 | 6.23 | 36-65 | 44.12 | 5.67 | 38-54 |
| AQ | 16.25 | 6.63 | 9-32 | 12.41 | 6.97 | 6-33 | 44.37 | 6.56 | 9-26 | 13.94 | 5.47 | 5-25 |
| BAPQ | 2.60 | 0.66 | 1.19-3.42 | 2.39 | 0.74 | 1.61-4.42 | 2.57 | 0.58 | 1.72-3.64 | 2.45 | 0.42 | 1.72-3.11 |

(continued)

*Note.* FSIQ = full scale intelligence quotient, VIQ = verbal intelligence quotient, PIQ = perceptual intelligence quotient, DS = Digit Span, TMT = Trail Making Test, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, SRS = Social Responsiveness Scale, AQ = Autism Spectrum Quotient, BAPQ = Broader Autism Phenotype Questionnaire.

No control families reported a first-degree relative with ASD and no parents or siblings of ASD probands reported a suspected or formal diagnosis of an ASD. Several participants had neurological conditions, including one control mother with multiple sclerosis, one mother of an ASD proband with stroke, one ASD sibling with apraxia, and one TDC youth with a history of skull fracture. In addition, 28 participants reported previous psychological diagnoses, including 13 ASD probands, 5 ASD siblings, 2 TDCs, 4 mothers of ASD probands, 3 fathers of ASD probands, and 1 control mother. A chi-square test examining psychological diagnosis (any diagnosis, no diagnosis) x Group (ASD proband, ASD sibling, TDC youth, mother of an ASD proband, father of an ASD proband, control mother, control father) indicated significant group differences in the presence of a psychological diagnosis ($\chi^2 = 48.19$, $p < .001$), with significantly more ASD probands with secondary psychological diagnoses. Psychological diagnoses included: ADHD, learning disabilities, major depressive disorder, anxiety, OCD, and PTSD. Twenty-four participants were taking psychoactive medications at the time of participation (7 ASD probands, 5 ASD siblings, 6 mothers of ASD probands, 1 father of an ASD proband, 2 TDCs, 2 control mothers, 1 control father). Groups significantly differed in the use of psychoactive medications ($\chi^2 = 21.59$, $p = .001$), with greatest use of medication among ASD probands.

**Clinical Diagnosis and Assessment**

**Measures administered to all participants[1].** See Table 3 for an overview of the tests administered. The Trail Making Test A and B (adult version) and digit span (DS) forward and backward were administered to assess levels of attention and processing speed. Intellectual functioning was determined using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

**Parent-report youth measures.** Parents provided demographic information about their children. The Social Communication Questionnaire (SCQ) was given to parents of TDCs and ASD probands to either rule out ASD diagnosis or help confirm ASD diagnosis, respectively. The SCQ is designed to measure communication and social functioning, with scores of 12 or higher indicative of ASD (Corsello et al., 2007). Social functioning was evaluated in youth using the parent-report version of the Social Responsiveness Scale, Second Edition (SRS-II), a measure designed to assess subthreshold levels of social impairment across a continuum of social functioning (Constantino et al., 2003), with scores 76 or above indicative of levels of social impairment (Constantino, Zhant, Frazier, Abbacchi, & Law, 2010). To assess the broader autism phenotype in siblings and all TDC youth, parents completed the youth version of the Autism Spectrum Quotient (AQ; Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006), a measure that assesses social and communication skills, imagination, attention to detail, and

[1] We were unable to obtain any survey measures for one ASD proband, three ASD siblings, and one mother of an ASD proband. Only the SRS-II was completed for one ASD proband and another ASD proband had excessive missing responses on the SCQ. We initially administered the first version of the SRS to all participants but were unable to obtain an updated SRS-II from eight participants. We utilized the first version of the SRS to determine whether each participant met cutoff criteria for participation but excluded them from all SRS-II analyses. Neuropsychological tests were not administered to one father of an ASD proband, one control father, one control mother, and one TDC sibling. DS scores were missing from two TDCs and TMT A scores were missing from one ASD sibling due to timer malfunction. One father of an ASD proband did not complete IQ testing.

attention switching/tolerance of change. Scores of 30 or above indicate the presence of ASD symptoms (Baron-Cohen et al., 2006). Parents of TDC and ASD youth completed the Screen for Child Anxiety Related Disorders (SCARED), a measure of anxiety (Birmaher et al., 1997).

Table 3

*Summary of Measures Administered*

| Domain | Tests Administered | Participants Assessed |
|---|---|---|
| Broader Autism Phenotype | BAPQ | Parents |
| | AQ | Parents, ASD siblings, TDC youth |
| Autism Diagnosis | ADOS-G | ASD probands |
| | SCQ | All youth |
| | SRS-II | All participants |
| Emotional/Behavioral Functioning | SCARED | All youth |
| | BDI-II | All parents |
| | STAI | All parents |
| | WASI | All participants |
| Cognitive Functioning | Digit Span | All Participants |
| | TMT A & B | All Participants |

*Note.* BAPQ = Broader Autism Phenotype Questionnaire, AQ = Autism Spectrum Quotient, ADOS-G = Autism Diagnostic Observation Schedule-Generic, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale, SCARED = Screen for Child Anxiety Related Disorders, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, WASI = Weschler Abbreviated Scales of Intelligence, TMT = Trail Making Test.

**Adult measures.** All parents provided self-reported demographic information. Parents also reported their spouse's behavior on the adult informant-report version of the SRS-II. To assess the broader autism phenotype, all adults completed the Broader Autism Phenotype Questionnaire (BAPQ; Hurley, Losh, Parlier, Reznick, & Piven, 2007), a questionnaire that

measures aloof and rigid personality characteristics and pragmatic language problems. The BAPQ is adequately sensitive and specific (>70% for all subscales) at identifying phenotypic characteristics of ASD in adults with genetic connections to ASD (Hurley et al., 2007). All parents also completed the adult version of the AQ (Baron-Cohen, Wheelright, Skinner, Martin, & Clubley, 2001) with scores of 32 or above indicative of the presence of ASD symptoms (Baron-Cohen et al., 2001). Previous studies of the AQ indicate that parents of ASD probands score higher than parents of TDCs, suggesting this measure is a reliable indicator of ASD characteristics (Wheelright, Auyeung, Allison, & Baron-Cohen, 2010). Finally, all parents completed the Beck Depression Inventory-II (Beck, 1996), and State-Trait Anxiety Inventory (Spielberger, Gorusch, Lushene, Vagg, & Jacobs, 1983).

**Autism diagnosis.** Autism diagnostic status was assessed in all youth participants to either confirm or rule-out ASD. Mental health providers, psychiatrists, or physicians in the community previously diagnosed all probands with ASD. Diagnosis was confirmed among probands using the Diagnostic and Statistical Manual of Developmental Disorders-IV (DSM-IV) criteria based on information from the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000), a measure designed to assess current functioning in the domains of social interaction, communication, play, and creativity (Lord et al., 2000). The ADOS-G is a well-established valid and reliable measure as indicated by excellent internal consistency, test-retest reliability, and accurate differentiation between individuals with ASDs compared to non-spectrum individuals (Lord et al., 2000). The ADOS-G was administered by Mikle South or by Ann Clawson who both received specific diagnostic training for ADOS administration and scoring. Inclusion as an ASD proband required meeting ADOS total cut-off score for ASD of 7 and either a score above 12 on the Social Communication Questionnaire (SCQ) or a score of 76

or above on the Social Responsiveness Scale, Second Edition (SRS-II). Siblings and TDC youth scored below 76 on the SRS-II, suggesting they likely did not display severely elevated levels of ASD symptoms suggestive of functional impairment (Kaiser et al., 2010)[2].

**Experimental Task**

All participants completed a modified Eriksen flanker task (Eriksen & Eriksen, 1974) to elicit behavioral and error responses similar to a task successfully used to study performance monitoring by our lab in previous studies of individuals with ASD (South et al., 2010). Participants were presented with a five-letter array with the letters 'H' or 'S' (e.g., HHHHH, SSSSS, HHSHH, SSHSS) and instructed to respond to the middle (target) letter as quickly and accurately as possible with a right-hand middle or index finger button press. The task included three blocks of 200 trials for 600 total trials; 50% of the trials were incongruent (e.g., HHSHH, SSHSS) and 50% were congruent (e.g., SSSSS, HHHHH). Previous research suggests that this task is developmentally appropriate for comparison in youth and adults, as both Ridderinkhof et al. (1997) and Rueda et al. (2004) found that by 10 years of age children are less susceptible to response competition and display conflict scores similar to adults.

Stimuli were presented in white against a black background on a 17-inch computer monitor approximately 24 inches from the participant's head. Response types (i.e., H or S target letters) were counterbalanced across participants. Flanker stimuli were presented 100ms before target stimuli, which remained on the screen for 600ms. The inter-trial interval varied randomly between 800ms and 1200ms. Participants completed 24 practice trials while they were observed

[2] One youth with ASD was missing both SRS-II and SCQ scores and three siblings were missing SRS-II scores. ADOS-G scores were obtained from the ASD proband (total score of 21), indicating that he clearly displayed symptoms of ASD above the diagnostic threshold. All of these participants were retained in analyses in order to maintain statistical power.

by an experimenter to ensure adequate understanding; the practice task was repeated until participants achieved at least 70% accuracy.

**EEG Recording and Reduction**

Electroencephalogram was recorded using a 128-channel geodesic sensor net and Electrical Geodesics, Inc. (EGI; Eugene, OR) amplifier system (20K nominal gain, bandpass = .10-100Hz). Recordings from the 128 scalp sites were initially referenced to the vertex electrode and digitized continuously at 250Hz with a 24-bit analog-to-digital converter. Following manufacturer guidelines, impedances were maintained below 50kΩ. Data were average-re-referenced off-line and digitally low-pass filtered at 30Hz. Bad channels were identified as channels with less than a .4 absolute correlation with neighboring channels. Bad channels were also identified on a trial-by-trial basis if they had a difference of 100μv from the minimum/maximum values for that trial or if they differed 30μv or more from neighboring channels. Trials with more than 10% bad channels were removed from analyses, and a channel marked bad on more than 20% of trials was considered globally bad. Eye blinks were removed using independent component analysis and saccades were removed using principal components analysis with promax rotation on EEGLAB (Delorme & Makeig, 2004) and the ERP PCA Toolkit (Dien, 2010). Eye blink components in the current data were compared to two blink templates; a manually generated template and a template automatically generated based on the current data. Components that correlated at .9 with either template were removed from the data (Dien, Michelson, & Franklin, 2010). For saccades, components that correlated at .8 with a manually generated template were removed from the data. Movement artifact was identified for removal on an individual trial basis using a temporal PCA. Activity with an amplitude difference greater than 200μv was removed from analyses (Dien, 2010).

Individual-subject ERP data were segmented according to participant response and calculated separately for correct and incorrect trials. In order to ensure reliability of ERP and behavioral analyses, participants with less than six error trials were excluded from analyses (Olvet & Hajcak, 2009a). Epochs of interest spanned from 400ms pre-response to 800ms post-response and were baseline adjusted from -400 to -200ms. Error-related negativity/correct-response negativity (CRN) amplitudes were calculated as the average negative amplitude from 15ms pre- and 15ms post-peak using a window between 0-150ms. We chose to utilize this adaptive mean procedure (i.e., averaging 15 ms around a peak) for the ERN/CRN, as this procedure has been recommended to reduce bias in developmental populations where there is a greater likelihood of variability in peak latency (Clayson, Baldwin, & Larson, 2013). Error-related negativity and correct-response negativity amplitudes were extracted as the average of electrodes FCz, 7, 106, and Cz (see Figure 3). Pe amplitudes were extracted using a window from 200-400ms and calculated as the mean amplitude across electrodes 54, 55, 78, 79, 61, and Pz (see Figure 3). Windows and electrode locations were chosen based on examination of the current data and previous studies suggesting that the ERN/Pe are fronto-centrally located (Falkenstein et al., 2000; Gehring et al., 1993; Larson, South, Clayson, & Clawson, 2012). We utilized an ROI-based approach for electrode selection, as research indicates that averaging across multiple electrodes improves reliability of ERP measurement (Baldwin, Larson, & Clayson, in press; Huffmeijer, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2014). To capture the difference between error and correct trials and further isolate error-related activity, we also calculated ΔERN and ΔPe scores by subtracting correct trial ERPs from error trial ERPs. For all behavioral and electrophysiological data errors of omission were excluded from analyses because there is no clear point at which errors are made to measure ERPs.

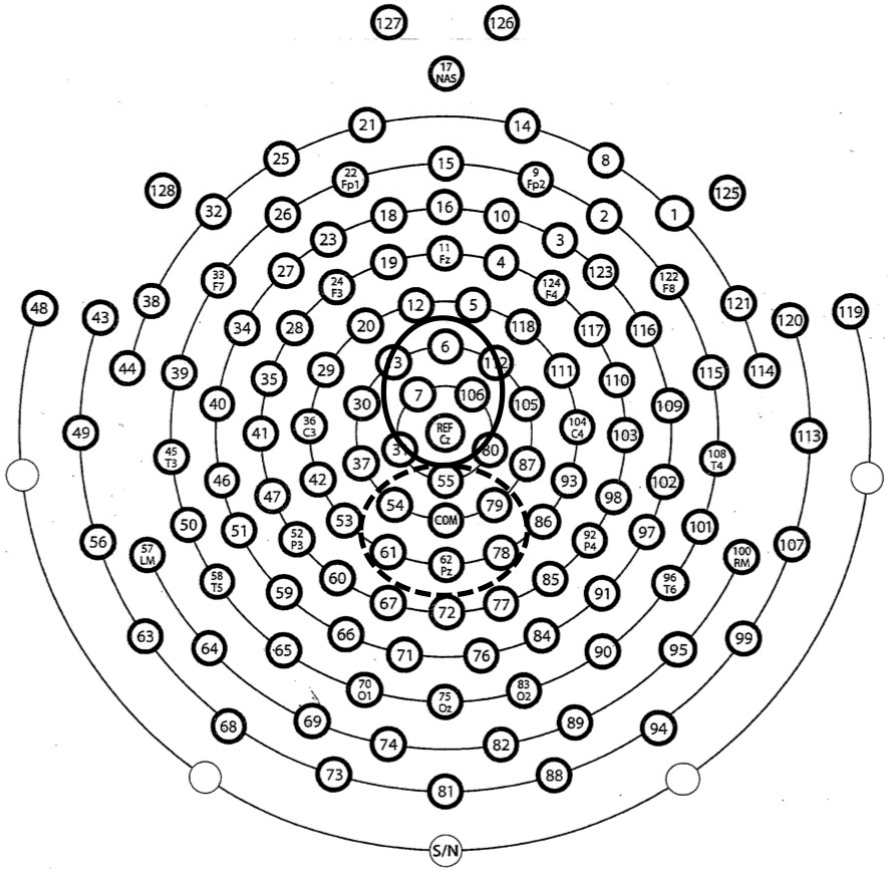


*Figure 3.* Layout of the 128-channel geodesic sensor net. The solid line outlines the fronto-central electrodes averaged for ERN analyses. The dashed line outlines the more posterior electrodes averaged for Pe analyses.

**Statistical Analysis**

Statistical analyses were completed with both SPSS 22 (IBMCorp., 2013) and STATA 13.1 (StataCorp, 2013) analysis software. All symptom measures (e.g., AQ, SRS, BAPQ), behavioral data (i.e., RTs and error rates) and ERP data were examined for outliers by group (ASD, control). Outliers were fenced to 2.5 interquartile ranges from the median. Response time data were negatively skewed and not normally distributed as indicated by the Shapiro-Wilk test of normality (Razali & Wah, 2011). Thus, RT data were log transformed. To ensure there

were no group differences in signal-to-noise ratios, all ERP measures were initially analyzed using one-way ANOVAs on background noise estimates, number of trials corrected for ocular artifact, and number of trials retained for single subject averaging (Clayson et al., 2013). Non-significant differences between groups for trial number and noise analyses suggest similar noise and/or trial counts.

**Demographic and neuropsychological data.** We initially compared ASD and control groups to determine if there were any differences in demographic and neuropsychological data. Descriptive statistics were computed for demographic characteristics (age, years of education). One-way ANOVAs were conducted separately for parents and youth to examine demographic, psychological (BDI, STAI, SCARED), and neuropsychological variables (WASI, TMT A and B, DS). Significant ANOVAs were decomposed using the Tukey Honestly Significance test in order to maintain alpha levels while completing multiple comparisons. Given that groups did not have equivalent sample sizes, we utilized a harmonic mean procedure.

Unless otherwise noted, for all statistical analyses parent groups included mothers of ASD probands, fathers of ASD probands, control mothers, and control fathers. Youth groups included ASD probands, ASD siblings, TDC probands, and TDC siblings. TDC probands were included in order to facilitate analysis by kinship status. One TDC from each control family was randomly selected as the "proband" and one as the "sibling."

**Regression analyses.** We utilized the following procedures for all regression analyses unless otherwise specified below. To examine differences in dependent variables by group (ASD/ASD relative, control) and kinship (mother, father, sibling, proband), we included group, kinship, and a Group x Kinship interaction as independent variables. Previous research indicates that including kinship and Group x Kinship interactions as regression terms is advantageous in

determining familial aggregation of a trait, facilitating an examination of the unique affect of kinship on the dependent variables of interest (Lee, Rebora, Valsecchi, Czene, & Reilly, 2013). Participants were dummy coded separately by group (ASD/ASD relative, control) with ASD participants and their relatives as the reference group, and by kinship status (mother, father, sibling, proband) with either probands as the reference group or mothers as the reference group.

For all regression analyses, families were included as clusters in order to account for non-independence of residuals due to shared genetic and environmental effects within families (Ari & Güvenir, 2002). Clustering allowed us to account for possible correlations within families while still examining differences between families. Robust standard errors were estimated using the Huber-White sandwich estimator in STATA for clustered data in order to account for nonindependence of observations due to family membership (Lee et al., 2013). The variance inflation factor (VIF) was reported as a measure of multicollinearity (Kleinbaum, Kupper, Muller, & Nizam, 2007).

**Aim 1, hypothesis 1.** *To determine whether subthreshold symptoms of ASD differed based on kinship status among unaffected relatives of ASD probands compared to control families*. Separate linear regressions were conducted with SRS-II, BAPQ, and AQ as dependent variables. The independent variable of kinship differed based on the dependent variable, as all measures were not administered to all participants due to age/diagnosis. For the SRS-II, which was administered to all participants, the independent variable of kinship included mother, father, sibling, and proband. For the AQ, which was only administered to control families and relatives of ASD probands, kinship only included mother, father, and sibling. For the BAPQ, which was only administered to parents, kinship included mothers and fathers only. We also included years

of education as a predictor for BAPQ given the presence of significant group differences based on educational attainment.

**Aim 2, hypothesis 1.** *To test whether ASD probands displayed reduced-amplitude ERN, Pe, and impaired behavioral modification relative to TDC youth.* We conducted robust ANOVAs on electrophysiological and behavioral data. Robust ANOVAs were utilized to reduce potential assumption violations due to outliers, distribution non-normality, and homogeneous error variance assumed in traditional ANOVAs (Keselman, 1998; Keselman, Wilcox, & Lix, 2003). Robust ANOVAs included winsorized covariances, bootstrapping, and use of the Welch-James statistic. For bootstrapping, the number of iterations was 50,000 and the seed for number generation was 1000 (Dien, Franklin, & May, 2006; Dien et al., 2010). For all ANOVAs the TDC youth were combined into one group, meaning they were not divided into separate groups based on probands and siblings in order to replicate previous studies and examine group differences independent of kinship (Henderson et al., 2006; South et al., 2010). For the ERN and Pe, robust ANOVAs included Group (ASD proband, TDC youth) and Accuracy (error, correct). For RTs and error rates, ANOVAs included Group (ASD proband, TDC youth) and Congruency (congruent, incongruent).

**Aim 2, hypotheses 2.** *To determine whether behavioral and ERP response differences were evident to a greater degree in unaffected relatives of youth with ASD compared to control families.* Generally following the procedures employed by Bramon et al. (2004) in a family study of the mismatch negativity in schizophrenia, linear regression was utilized to examine group differences in ERP and behavioral measures. Regressions were conducted separately for the following dependent variables: incongruent error rates, incongruent RTs, ΔERN, and ΔPe. We chose to utilize difference scores for ERP measures in order to isolate error-related activity

(i.e., subtracting out the activity that was common to correct and error responses) and reduce the number of comparisons. In addition to the independent variables noted above, in order to determine whether increased levels of ASD symptomology were associated with a greater degree of electrophysiological and behavioral impairment, we also included SRS-II as an independent variable in all regressions.

**Aim 2, hypotheses 3.** *To examine whether increased levels of ASD symptomology would be associated with a greater degree of electrophysiological and behavioral impairment.* In order to examine the relationship between ERP and behavioral measures and symptoms of ASD, we conducted zero-order correlations between incongruent error rates, incongruent RTs, ΔERN, ΔPe, SRS-II, BAPQ, and AQ. Further, past research suggests that internalizing symptoms, as indicated by measures of anxiety symptomology, are related to enhanced ERN amplitudes (Amodio, Master, Yee, & Taylor, 2008; Moser et al., 2013; Ruchsow et al., 2007; Weinberg, Olvet, & Hajcak, 2010) and may play a role in explaining ERN generation in ASD (Henderson et al., 2015). Thus, we also included SCARED scores for youth participants and STAI-State and STAI-Trait scores for adults. Finally, Henderson et al. (2006) also observed significantly larger ERN amplitudes among children with higher VIQ scores, so we included VIQ scores in our correlations.

## Results

### Demographic Data

**Youth.** Demographic, neuropsychological, and symptom measures for youth are displayed in Table 1. As noted above, group differences for measures of autism symptoms are included in the regression analyses. ASD probands and siblings and TDC probands and siblings did not significantly differ on age, $F(3, 68) = 1.46$, $p = .23$, or years of education, $F(3, 62) =$

0.56, $p = .64$. However, youth significantly differed on measures of anxiety, $F(3, 63) = 8.07$, $p < .001$. These group differences were primarily driven by ASD probands, who displayed significantly higher levels of anxiety than other participants. Specifically, post-hoc testing revealed significant mean differences between ASD probands and ASD siblings ($M = 9.41$, $p = .03$), TDC probands *(*$M = 13.21$, $p < .001$), and TDC siblings ($M = 13.23$, $p < .001$). No mean differences were significant between TDC siblings and ASD siblings ($M = -3.81$, $p = .64$), TDC siblings and TDC probands ($M = -0.02$, $p = 1.00$), and TDC probands and ASD siblings ($M = -3.80$, $p = .66$). In sum, demographics were similar between groups with the exception of anxiety where ASD probands displayed higher levels of anxiety relative to the other youth groups, but TDC and ASD siblings did not differ.

**Parents.** Demographic, neuropsychological, and symptom measures for parents are displayed in Table 2. Parents of children with ASD and parents of TDC children did not significantly differ in age or on measures of anxiety and depressive symptoms ($Fs < 2.11$, $ps > .11$). However, parent groups did significantly differ in years of education, $F(3, 66) = 4.31$, $p = .001$. Group differences were driven by higher levels of educational attainment among control fathers, as mean differences were significantly higher in control fathers than control mothers ($M = 2.78$, $p = .85$) and significantly higher in control fathers than mothers of ASD probands ($M = 2.25$, $p = .06$). Mean differences were not significant between fathers of ASD probands and control fathers ($M = -2.08$, $p = .08$), fathers of ASD probands and control mothers ($M = 0.70$, $p = .85$) or mothers of ASD probands ($M = 0.17$, $p = 1.0$). Mothers of ASD probands did not display mean differences in years of education relative to control mothers ($M = 0.54$, $p = .92$).

**Neuropsychological Data**

**Youth.** Mean FSIQ scores were above average for siblings and TDC youth and slightly above average for ASD probands (see Table 1), suggesting that all youth groups were generally functioning at or above normative levels. All youth groups did not significantly differ on FSIQ, VIQ, PIQ, DS, or TMT A and B ($Fs < 2.13$, $ps > .11$).

**Parents.** Analyses of FSIQ among mothers of ASD probands, fathers of ASD probands, control fathers, and control mothers revealed significant group differences, $F(3, 66) = 2.78$, $p = .05$, and approached significance for VIQ, $F(3, 66) = 2.58$, $p = .06$. Group differences were not present for PIQ scores, $F(3, 66) = 2.36$, $p = .08$. Control fathers displayed significantly higher FSIQ ($M = 7.91$, $p = .04$) and VIQ scores ($M = 8.57$, $p = .04$) than mothers of ASD probands. No other mean differences were significant between groups for FSIQ or VIQ ($Ms > 0.17$, $ps < 1.0$. Parents did not significantly differ on TMT A and B t-scores, $Fs < 1.76$, $ps > .17$. Finally, groups differed on DS standard score, $F(3, 64) = 4.85$, $p = .004$, with significantly lower scores in control mothers relative to control fathers ($M = -2.44$, $p = .05$) and mothers of ASD probands relative to control fathers ($M = -3.06$, $p = .01$). Fathers of ASD probands did not display significant mean differences from control fathers ($M = .94$, $p = .74$), control mothers ($M = 1.49$, $p = .39$), or mothers of ASD probands ($M = 2.11$, $p = .11$). Taken together, significant differences were observed between control fathers and mothers of ASD probands/control mothers on FSIQ, VIQ and DS. These differences may be attributable to higher levels of education attainment in control fathers relative to control mothers and mothers of ASD probands as noted above.

**ERP Data**

Youth and parent groups did not significantly differ on background noise estimates, number of trials retained for analysis, or number of trials corrected for ocular artifact for correct and error trials (youth: $Fs < 2.15$, $p > .10$, adults: $Fs < 2.65$, $p = .06$; see Tables

Table 4

*ERP and Behavioral Summary Data for Youth*

| | ASD Probands | | | ASD Siblings | | | Control Youth | | |
|---|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range |
| ERN | -1.08 | 1.89 | -3.46-2.21 | -0.81 | 1.73 | -3.42-2.02 | -1.09 | 2.52 | -6.80-3.65 |
| CRN | 0.43 | 1.56 | -2.04-2.87 | 1.35 | 1.79 | -1.73-3.97 | 0.89 | 2.00 | -2.90-6.24 |
| Pe | 3.08 | 1.60 | 0.98-6.48 | 4.34 | 2.78 | -0.74-10.09 | 5.09 | 3.32 | -0.67-12.85 |
| Pc | 0.05 | 1.77 | -3.35-2.79 | 0.04 | 2.36 | -4.20-3.88 | 0.52 | 2.01 | -3.95-4.82 |
| RT Incongruent | 445.16 | 33.65 | 372.04-509.18 | 454.70 | 32.78 | 396.33-519.81 | 460.06 | 41.06 | 356.92-524.47 |
| RT Congruent | 419.28 | 32.22 | 356.79-464.31 | 427.90 | 34.22 | 382.68-493.44 | 422.07 | 40.84 | 301.14-493.37 |
| Error Incongruent | .36 | .15 | .15-.73 | .34 | .11 | .15-.56 | .31 | .14 | .06-.61 |
| Error Congruent | .19 | .11 | .07-.41 | .20 | .11 | .03-.46 | .15 | .11 | .02-.36 |
| Correct Trials | 321.31 | 158.65 | 165-771 | 306.07 | 94.85 | 177-511 | 315.39 | 177.66 | 95-522 |
| Error Trials | 78.50 | 50.21 | 18-162 | 65.00 | 24.41 | 24-116 | 56.78 | 31.07 | 11-135 |

*Note.* ERN = error-related negativity, CRN = correct-related negativity, Pc = post-correct positivity, Pe = post-error positivity, RT = response time.

4 and 5). All participants included in ERP analyses had at least six error trials for averaging, suggesting an adequate number of trials were retained for reliable analyses (Olvet & Hajcak, 2009b). Means and standard deviations for all ERP and behavioral data are presented in Table 4 and Table 5.

Table 5

*ERP and Behavioral Summary Data for Adults*

| | ASD Fathers | | | ASD Mothers | | | Control Fathers | | | Control Mothers | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measure | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range | *M* | *SD* | Range |
| ERN | -1.89 | 3.24 | -9.93-2.20 | -2.32 | 2.93 | -9.03-1.83 | -1.99 | 2.32 | -6.89-1.59 | -1.55 | 2.25 | -7.56-1.56 |
| CRN | 1.42 | 0.96 | 0.11-2.93 | 0.51 | 1.90 | -4.82-3.84 | 1.42 | 1.50 | -2.45-4.18 | 0.62 | 1.86 | -2.27-4.48 |
| Pe | 3.17 | 2.54 | 0.18-9.04 | 2.66 | 2.13 | 0.72-7.86 | 2.66 | 2.46 | -1.32-7.84 | 2.89 | 2.62 | -1.37-10.99 |
| Pc | 1.02 | 1.31 | -0.87-3.27 | 0.89 | 1.48 | -0.82-5.26 | 0.87 | 1.52 | -1.12-4.50 | 0.50 | 1.33 | -2.22-2.88 |
| Incongruent RT | 483.02 | 45.06 | 409.28-584.69 | 467.58 | 39.22 | 392.94-561.54 | 480.62 | 29.61 | 422.88-527.39 | 476.09 | 33.34 | 412.38-540.44 |
| Congruent RT | 432.67 | 47.01 | 346.59-520.29 | 415.26 | 38.27 | 349.86-496.08 | 422.92 | 29.06 | 372.24-476.77 | 424.85 | 36.28 | 330.52-487.51 |
| Incongruent Error | .25 | .14 | .05-.57 | .20 | .12 | .50-.39 | .20 | .11 | .08-.51 | .19 | .10 | .04-.33 |
| Congruent Error | .08 | .07 | .00-.23 | .06 | .04 | .01-.16 | .06 | .05 | .01-.25 | .06 | .05 | .00-.22 |
| Correct Trials | 378.29 | 84.60 | 214-504 | 452.06 | 51.17 | 342-542 | 441.21 | 69.91 | 287-541 | 428.11 | 69.91 | 287-541 |
| Error Trials | 48.29 | 26.94 | 7-117 | 45.41 | 35.43 | 10-146 | 37.21 | 16.57 | 10-64 | 40.28 | 23.76 | 7-77 |

*Note.* ERN = error-related negativity, CRN = correct-related negativity, Pc = post-correct positivity, Pe = post-error positivity, RT = response time.

**Aim 1, Hypothesis 1**

*To determine whether subthreshold symptoms of ASD differed based on kinship status among unaffected relatives of ASD probands compared to control families.*

**SRS-II.** Findings of the regression model are summarized in Table 6. Variance inflation factor scores indicated that no independent variables were multicollinear for the SRS-II. The overall model was significant, $F(7, 36) = 63.45$, $p < .001$, and accounted for 74% of the variance in SRS-II scores. Group status significantly predicted SRS-II scores, with significantly higher SRS-II scores among ASD families compared to control families. Kinship was also a significant predictor. Mothers, fathers, and siblings all displayed significantly lower SRS-II scores than probands. Importantly, Group x Kinship interactions were significant. ASD mothers displayed significantly higher SRS-II scores than control mothers, ASD fathers displayed significantly higher scores than control fathers, and ASD siblings displayed significantly higher scores than TDC siblings. Thus, results followed the expected pattern, with higher levels of ASD symptoms among ASD probands and unaffected relatives of ASD probands relative to control families.

**AQ.** See Table 6 for regression findings. No independent variables were multicollinear for the AQ. The overall model was significant, $F(5, 38) = 2.47$, $p = .05$, and accounted for 15% of the variance. However, no individual predictors were significant, including group and kinship for fathers and siblings. The interaction between kinship and group was also not significant for fathers or siblings.

**BAPQ.** See Table 6 for regression findings. No independent variables were multicollinear. The overall model was not significant, $F(4, 37) = 1.39$, $p = .26$, and accounted for 6% of the variance. No predictors were significant, including group and kinship. The interaction between kinship and group was also not significant.

Table 6

*Regression Model for Symptom Measures*

| Variables | $R^2$ | *p*-value | *B* | Robust *SE* | *t*-value | *p*-value | VIF |
|---|---|---|---|---|---|---|---|
| **DV: SRS-II** | .74 | <.01 | | | | | |
| Group | | | -34.6 | 2.33 | -14.86 | <.01 | 3.76 |
| Kinship | | | | | | | |
| Mothers | | | -33.3 | 2.37 | -14.05 | <.01 | 3.04 |
| Fathers | | | -29.56 | 2.59 | -11.41 | <.01 | 3.22 |
| Siblings | | | -29.23 | 4.74 | -6.17 | <.01 | 3.51 |
| Group x Kinship | | | | | | | |
| Control Mothers | | | 34.42 | 2.84 | 12.14 | <.01 | 3.46 |
| Control Fathers | | | 27.87 | 2.91 | 9.56 | <.01 | 3.80 |
| Control Siblings | | | 33.03 | 4.93 | 6.71 | <.01 | 4.25 |
| **DV: AQ** | .15 | .05 | | | | | |
| Group | | | 1.65 | 2.08 | 0.80 | .43 | 2.91 |
| Kinship | | | | | | | |
| Fathers | | | 3.89 | 2.73 | 1.42 | .16 | 2.80 |
| Siblings | | | -2.22 | 2.44 | -0.91 | .37 | 3.04 |
| Group x Kinship | | | | | | | |
| Control Fathers | | | -.26 | 3.33 | -0.08 | .94 | 3.56 |
| Control Siblings | | | .22 | 2.87 | 0.08 | .94 | 3.89 |
| **DV: BAPQ** | .06 | .26 | | | | | |
| Years of Education | | | -0.05 | 0.03 | -1.96 | .06 | 1.20 |
| Group | | | 0.04 | 0.21 | 0.17 | .86 | 2.01 |
| Kinship | | | | | | | |
| Fathers | | | 0.22 | 0.28 | 0.78 | .44 | 2.12 |
| Group x Kinship | | | | | | | |
| Control Fathers | | | 0.04 | 0.33 | 0.11 | .92 | 3.40 |

*Note.* *SE* = standard error, VIF = variance inflation factor, SRS = Social Responsiveness Scale, AQ = Autism Spectrum Quotient, BAPQ = Broader Autism Phenotype Questionnaire.

In summary, we observed significant group differences in ASD symptoms as measured by the SRS-II that followed the predicted direction of significantly greater symptoms in ASD probands and relatives compared to control families. Contrary to predictions, groups did not differ on measures of the broader autism phenotype as measured by the AQ and BAPQ.

**Aim 2, Hypothesis 1**

*To test whether ASD probands displayed reduced-amplitude ERN, Pe, and impaired behavioral modification relative to TDC youth.*

**ERN.** The Group x Accuracy robust ANOVA examining ERN amplitudes among ASD probands and all TDC youth revealed a significant main effect of accuracy, with significantly more negative amplitudes on error trials relative to correct trials, $T_{WJt}/c(1.0, 28.5) = 61.77$, $p < .001$. The main effect of group was not significant, $T_{WJt}/c(1.0, 26.2) = 0.32$, $p = .58$. Importantly, the Accuracy x Group interaction was not significant, $T_{WJt}/c(1.0, 28.5) = 0.87$, $p = .36$, suggesting that no significant group differences were observed for the ERN.

**Pe.** The main effect of accuracy was significant, with more positive Pe amplitudes on error trials than correct trials, $T_{WJt}/c(1.0, 34.0) = 69.38$, $p < .001$. The main effect of group was not significant, $T_{WJt}/c(1.0, 24.1) = 1.15$, $p = .29$. The Group x Accuracy interaction was also not significant, $T_{WJt}/c(1.0, 34.0) = 1.27$, $p = .26$. Thus, group differences were not observed for Pe amplitude.

**Behavioral data.** For error rates, robust ANOVAs revealed a significant main effect of congruency, $T_{WJt}/c(1.0, 36.1) = 153.21$, $p< .001$. The main effect of group and Group x Congruency interaction were not significant, $T_{WJt}/c(1.0, 25.9) = 0.23$, $p = .64$; $T_{WJt}/c(1.0, 36.1) = 0.80$, $p = .38$, respectively. For RTs, the main effect of congruency was significant, $T_{WJt}/c(1.0,$

24.9) = 81.86, $p < .001$. The main effect of group and Group x Congruency interaction were not significant, $T_{WJt}/c(1.0, 27.0) = 0.19$, $p = .67$; $T_{WJt}/c(1.0, 24.9) = 0.14$, $p = .71$, respectively.

In summary, we did not replicate previous findings of significant group differences for ERN amplitudes (Sokhadze et al., 2010; South et al., 2010; Vlamings et al., 2008) and we did not observe group differences for behavioral measures or amplitude of the Pe ERP.

**Aim 2, Hypotheses 2**

*To determine whether behavioral and ERP response differences were evident to a greater degree in unaffected relatives of youth with ASD compared to control families.*

**ΔERN.** See Figures 4-7 for waveforms and scalp maps according to group. Findings of the regression models for all ERPs are summarized in Table 7. Although we initially planned to include SRS-II as a predictor in our regressions, analyses revealed that the SRS-II was highly related to group, leading to significant multicollinearity in our regressions (VIFs for group ranging from 9.91-10.03). Thus, we chose to exclude SRS-II as a predictor for ERP and behavioral regressions. After removing the SRS-II, VIF scores for ΔERN, ΔPe, RTs, and error rates suggested that no independent variables were multicollinear in all analyses. The overall ΔERN model was not significant, $F(7, 37) = 1.21$, $p = .32$, and accounted for 6% of the variance in ΔERN scores. Group was also not a significant predictor. Kinship was not a significant predictor among mothers, fathers, or siblings relative to probands, and no interactions between kinship and group were significant.

**ΔPe.** See Figures 4 and 8-10 for waveforms and scalp maps according to group. The model for ΔPe amplitudes was significant, $F(7, 37) = 9.38$, $p < .001$, and accounted for 23% of the variance in ΔPe. The effect of group approached significance. The effect of kinship was

significant for mothers and fathers but not siblings. Interactions between group and kinship were only significant for fathers.

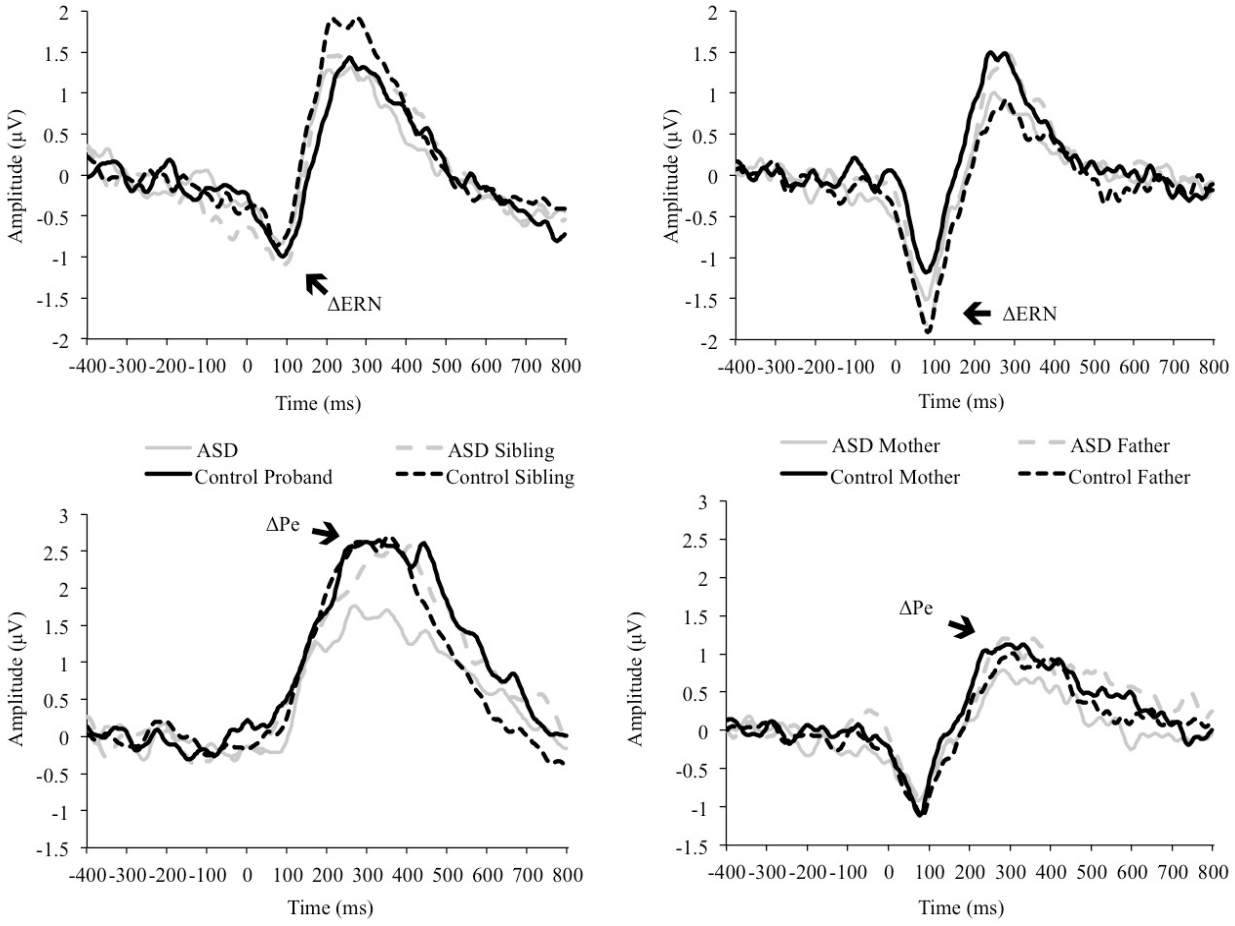


*Figure 4.* ΔERN and ΔPe amplitudes by youth and adult groups. ΔERN amplitudes were averaged over electrodes FCz, 7, 106, Cz. ΔPe amplitudes were averaged over electrodes 54, 55, 78, 79, 61.

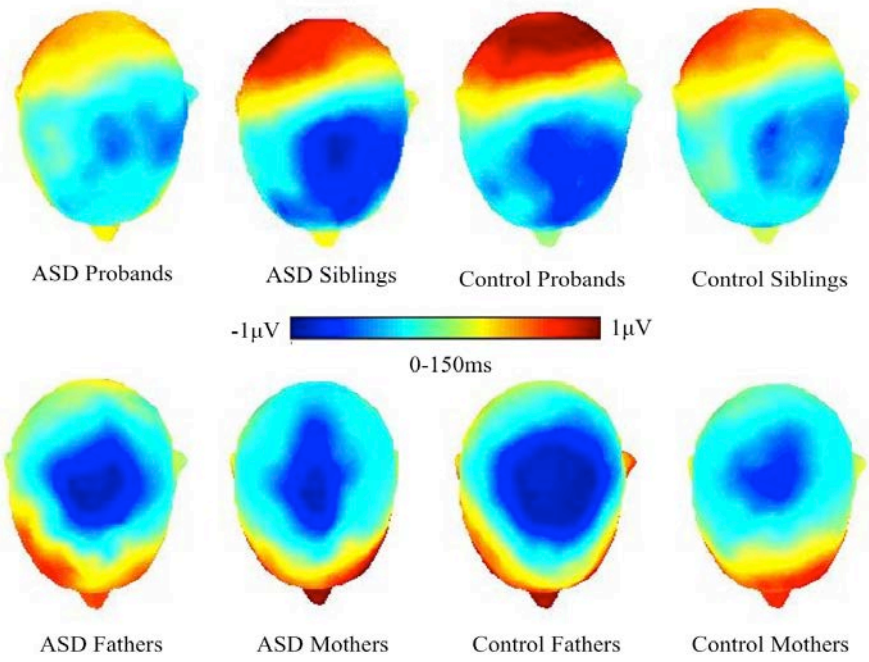


*Figure 5.* ΔERN amplitude topographical maps by youth and adult groups. Scalp maps represent the average from 0-150ms.

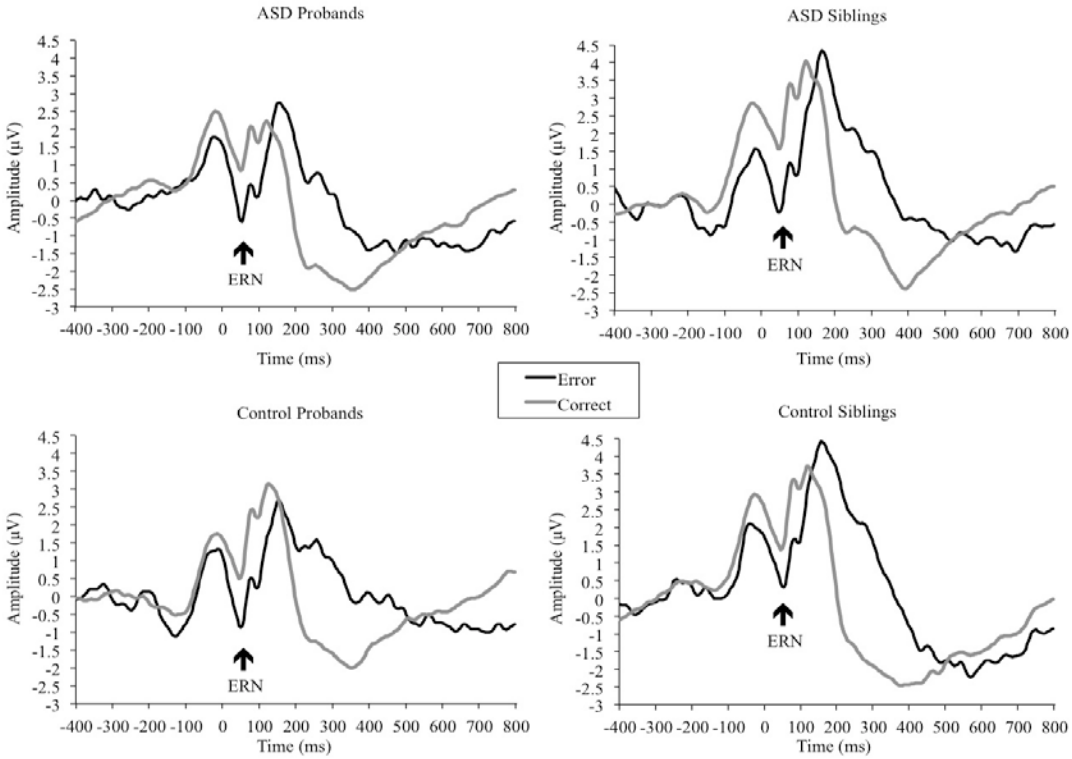


*Figure 6.* ERN and CRN amplitudes by youth group. Averaged over electrodes FCz, 7, 106, Cz.

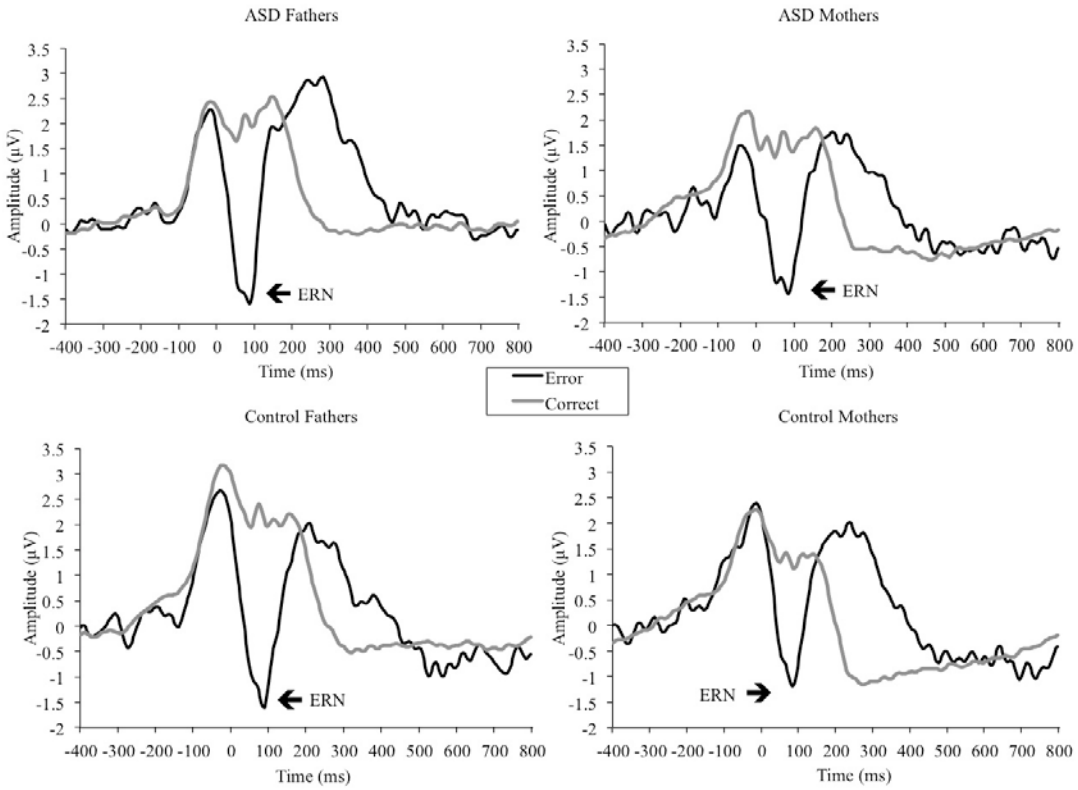


*Figure 7.* ERN and CRN amplitudes by adult group. Averaged over electrodes FCz, 7, 106, Cz.

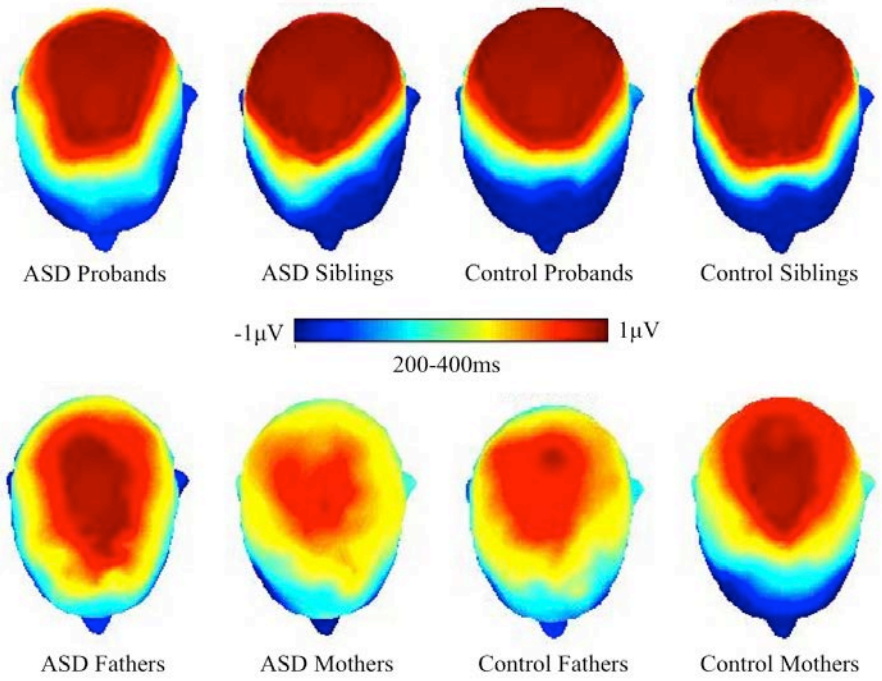


*Figure 8.* ΔPe amplitude topographical maps by youth and adult groups. Scalp maps represent the average from 200-400ms.

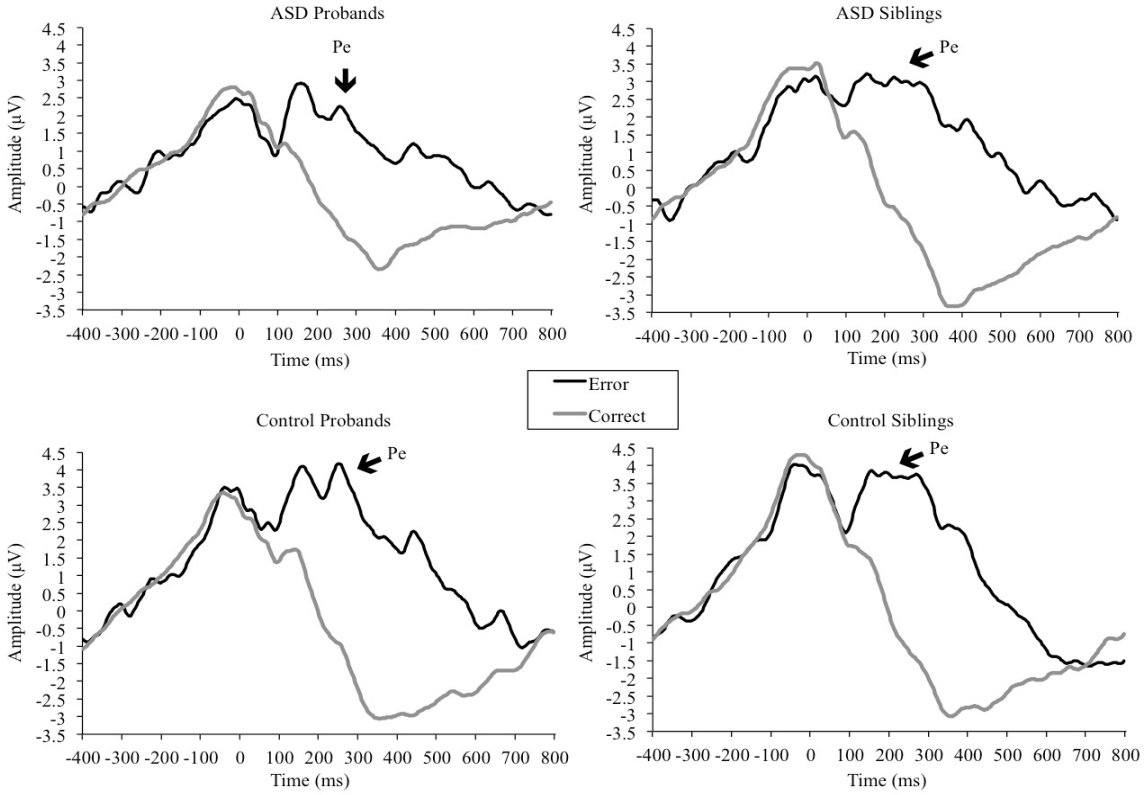


*Figure 9.* Pe and Pc amplitudes by youth group. Averaged over electrodes 54, 55, 78, 79, 61.

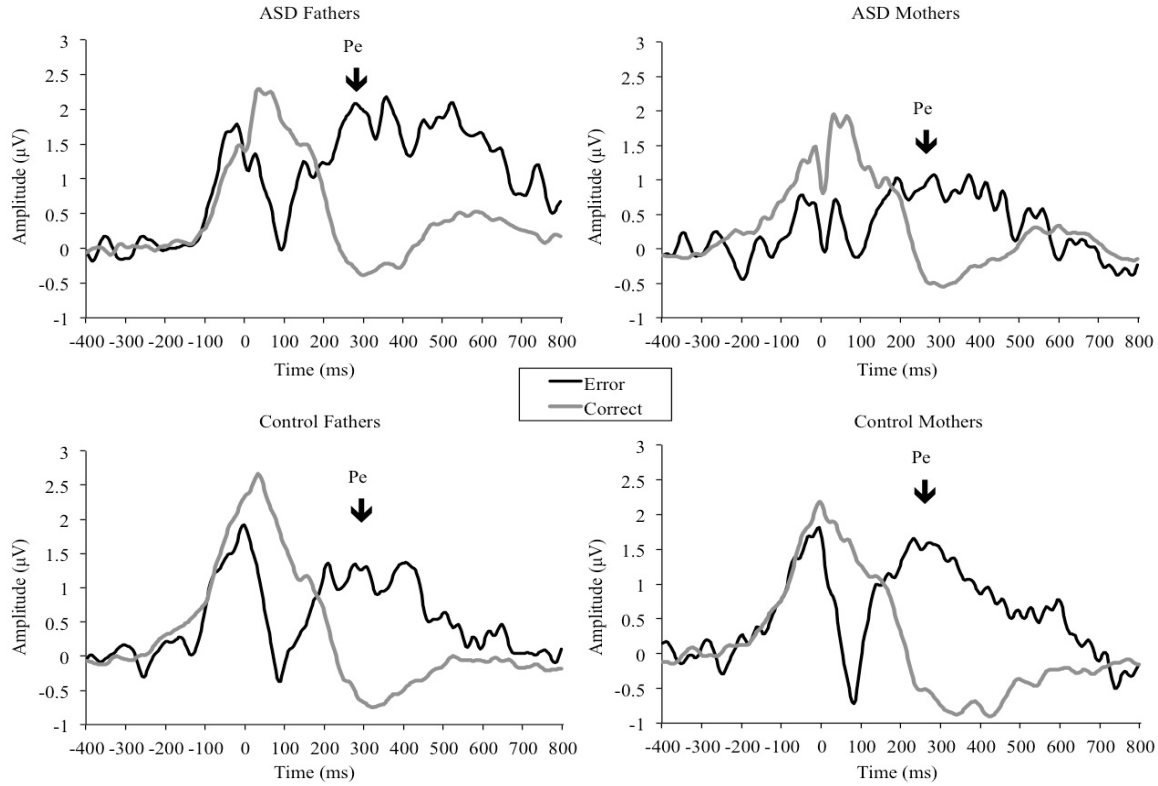


*Figure 10.* Pe and Pc amplitudes by adult group. Averaged over electrodes 54, 55, 78, 79, 61.

Table 7

*Regression Model for ERP Measures*

| Variables | $R^2$ | *p*-value | *B* | Robust *SE* | *t*-value | *p*-value | VIF |
|---|---|---|---|---|---|---|---|
| **DV: ΔERN** | .06 | .322 | | | | | |
| Group | | | -0.38 | 0.31 | -1.22 | .229 | 4.07 |
| Kinship | | | | | | | |
| Mothers | | | -0.40 | 0.30 | -1.33 | .190 | 3.15 |
| Fathers | | | -0.63 | 0.42 | -1.50 | .142 | 3.34 |
| Siblings | | | -0.24 | 0.23 | -1.07 | .293 | 3.29 |
| Group x Kinship | | | | | | | |
| Control Mothers | | | 0.63 | 0.51 | 1.23 | .227 | 3.68 |
| Control Fathers | | | 0.17 | 0.52 | .32 | .750 | 4.01 |
| Control Siblings | | | 0.46 | 0.37 | 1.26 | .214 | 3.93 |
| **DV: ΔPe** | .23 | .001 | | | | | |
| Group | | | 1.01 | 0.52 | 1.93 | .061 | 4.07 |
| Kinship | | | | | | | |
| Mothers | | | -0.92 | 0.28 | -3.25 | .002 | 3.15 |
| Fathers | | | -0.62 | 0.30 | -2.08 | .045 | 3.34 |
| Siblings | | | 0.74 | 0.44 | 1.67 | .103 | 3.29 |
| Group x Kinship | | | | | | | |
| Control Mothers | | | -0.64 | 0.51 | -1.18 | .245 | 3.68 |
| Control Fathers | | | -1.14 | 0.57 | -2.00 | .052 | 4.01 |
| Control Siblings | | | -0.64 | 0.67 | -0.95 | .349 | 3.93 |

*Note.* *SE* = standard error, ERN = error-related negativity, Pe = post-error positivity, VIF = variance inflation factor.

**Behavioral data.** See Figure 11 for bar graphs depicting error rates and RTs by group. Regression findings are summarized in Table 8. The model for error rates was significant, $F(7, 37) = 9.47$, $p < .001$, and accounted for 21% of the variance in incongruent trial error rates. Group was not a significant predictor. However, kinship was significant for mothers and fathers but not siblings. Finally, no interactions between group and kinship were significant. The model for RTs was significant, $F(7, 38) = 2.66$, $p = .02$, accounting for 11% of the variance in incongruent RTs. Group was not a significant predictor and the Group x Kinship interaction was not significant. However, kinship was significant for mothers and fathers, but not siblings.

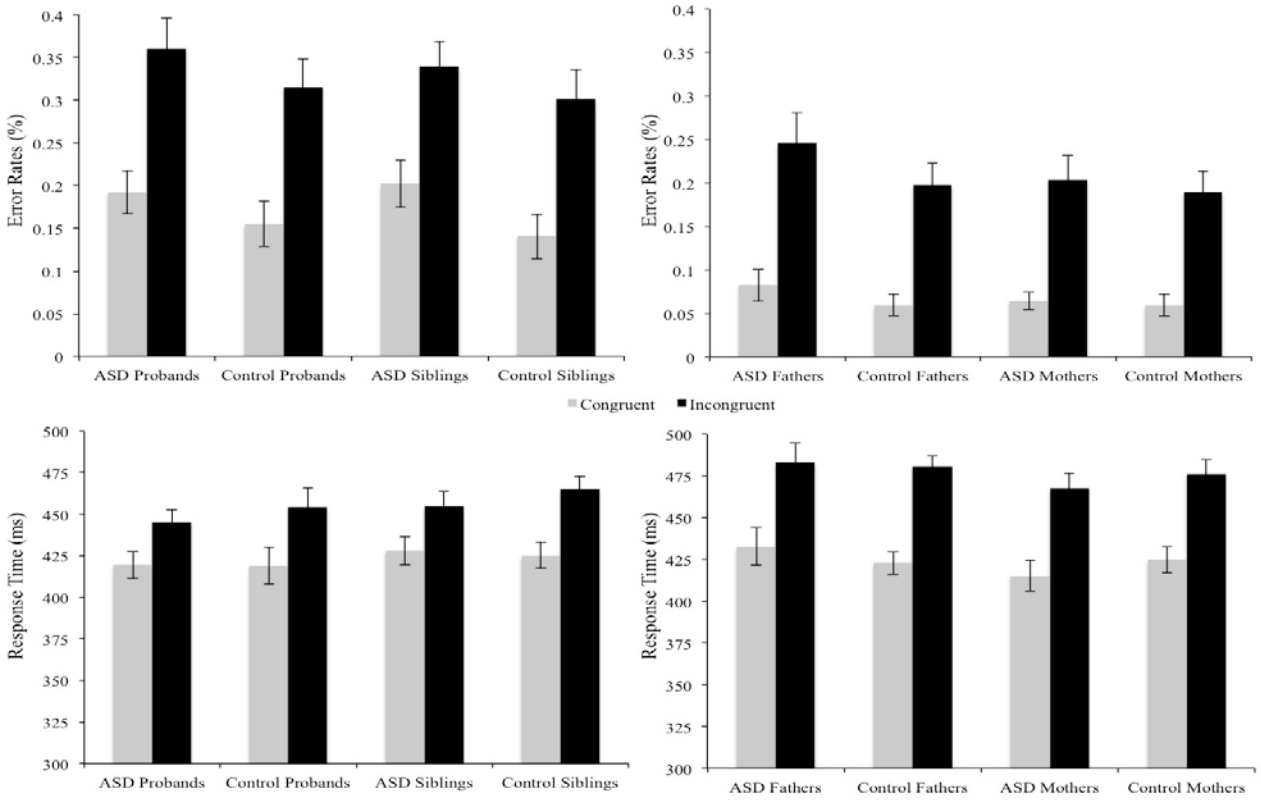


*Figure 11.* Behavioral data as a function of group and trial type. Error bars represent the standard error.

Table 8

*Regression Model for Behavioral Measures*

| Variables | $R^2$ | *p*-value | *B* | Robust *SE* | *t*-value | *p*-value | VIF |
|---|---|---|---|---|---|---|---|
| **DV: Incongruent Errors** | .21 | <.01 | | | | | |
| Group | | | -0.045 | .05 | -0.91 | .37 | 3.93 |
| Kinship | | | | | | | |
| Mothers | | | -0.156 | .03 | -5.28 | <.01 | 2.99 |
| Fathers | | | -0.115 | .04 | -2.76 | .01 | 3.11 |
| Siblings | | | -0.021 | .04 | -0.52 | .61 | 3.22 |
| Group x Kinship | | | | | | | |
| Control Mothers | | | 0.031 | .05 | 0.61 | .54 | 3.49 |
| Control Fathers | | | -0.002 | .05 | -0.06 | .96 | 3.72 |
| Control Siblings | | | 0.007 | .06 | 0.11 | .91 | 3.91 |
| **DV: Incongruent RTs** | .11 | .02 | | | | | |
| Group | | | 0.008 | 0.01 | 0.55 | .58 | 3.93 |
| Kinship | | | | | | | |
| Mothers | | | 0.211 | 0.01 | 1.99 | .05 | 2.99 |
| Fathers | | | 0.035 | 0.01 | 2.62 | .01 | 3.11 |
| Siblings | | | 0.009 | 0.01 | 0.84 | .41 | 3.22 |
| Group x Kinship | | | | | | | |
| Control Mothers | | | 0.001 | 0.02 | 0.05 | .96 | 3.49 |
| Control Fathers | | | -0.009 | 0.02 | -0.50 | .62 | 3.72 |
| Control Siblings | | | 0.002 | 0.02 | 0.14 | .89 | 3.91 |

*Note.* *SE* = standard error, RT = response time, VIF = variance inflation factor.

**Aim 2, Hypotheses 3**

*To examine whether increased levels of ASD symptomology would be associated with a greater degree of electrophysiological and behavioral impairment.*

Pearson's correlations are presented in Table 9. Incongruent RTs and incongruent error rates were not significantly associated with any variables except SRS-II scores, with higher SRS-II scores predicting poorer behavioral performance (lower RTs, higher error rates). Autism symptoms were not significantly related to ΔERN amplitudes, but lower AQ and BAPQ scores were significantly related to enhanced ΔPe amplitudes. Contrary to expectations, anxiety was not significantly related to ΔERN or ΔPe amplitudes among youth. Among adults, higher state anxiety was associated with enhanced ΔERN amplitudes and lower levels of trait anxiety were related to more positive ΔPe amplitudes.

Taken together, regressions examining group differences in ERP and behavioral measures of performance monitoring partially followed predictions. No differences were observed in ΔERN amplitude. ΔPe amplitude differed between ASD and control groups; mothers and fathers differed from probands. For behavioral data, mothers and fathers displayed faster RTs and less error rates than probands. Overall, individuals with higher levels of ASD symptoms responded slower and made more errors, and higher levels of the broader autism phenotype were significantly related to reduced ΔPe amplitudes. Higher state anxiety predicted enhanced ΔERN and higher trait anxiety predicted enhanced ΔPe amplitudes among adults.

**Supplementary Analyses**

It is possible that including group as a predictor in regressions limited our ability to understand the role of ASD symptomology and ERP generation, as limiting analyses to current diagnostic definitions may reduce our ability to identify the influence of dimensional ASD symptoms on ERP amplitudes (Miller & Rockstroh, 2013). Thus, we conducted regressions on ΔERN and ΔPe amplitudes as dependent variables without group as a predictor. Independent

Table 9

*Pearson's Correlations for ERPs, Behavioral, and Psychological Measures*

| | ΔERN | ΔPe | Incongruent RTs | Incongruent Errors |
|---|---|---|---|---|
| SRS-II | .070 | -.081 | -.198* | .288** |
| AQ | .102 | -.311** | .011 | .002 |
| BAPQ | .104 | -.341** | -.002 | .111 |
| SCARED | -.003 | -.273* | -.085 | .221 |
| STAI-State | .293* | -.204 | .150 | .202 |
| STAI-Trait | .196 | -.330** | -.018 | -.012 |
| VIQ | .015 | -.001 | .063 | -.155 |

*Note*. ERN = error-related negativity, Pe = post-error positivity, RT = response time, SRS = Social Responsiveness Scale, AQ = Autism Spectrum Quotient, BAPQ = Broader Autism Phenotype Questionnaire, SCARED = Screen for Child Anxiety Related Disorders, STAI = State-Trait Anxiety Inventory, VIQ = verbal intelligence quotient.

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

variables in regressions included SRS-II scores and kinship. As in previous analyses, we estimated robust standard errors and included clustering by family.

See Table 10 for regression results. No predictors were multicollinear for ΔERN or ΔPe analyses. The model for ΔERN amplitudes was not significant, $F(4, 36) = 1.73$, $p = .17$, and explained 6% of the variance. Kinship and SRS-II were not significant predictors. The model for ΔPe was significant, $F(4, 36) = 11.50$, $p < .01$, and explained 24% of the variance. In addition, SRS-II was a significant predictor, with larger SRS-II scores associated with decreased ΔPe amplitudes. Kinship was a significant predictor for mothers and fathers but not siblings. Thus, analyses without group as a predictor remained consistent with ΔERN analyses but revealed a significant relationship between symptoms of ASD and ΔPe amplitudes.

Table 10

*Regression Model for ERP Measures Without Group as a Predictor*

| Variables | $R^2$ | *p*-value | *B* | Robust SE | *t*-value | *p*-value | VIF |
|---|---|---|---|---|---|---|---|
| **DV: ΔERN** | .06 | .165 | | | | | |
| SRS-II | | | 0.006 | 0.01 | 0.73 | .47 | 1.32 |
| Kinship | | | | | | | |
| Mothers | | | -0.004 | 0.32 | -0.01 | .99 | 1.83 |
| Fathers | | | -0.524 | 0.29 | -1.81 | .08 | 1.83 |
| Siblings | | | 0.055 | 0.22 | 0.25 | .81 | 1.69 |
| **DV: ΔPe** | .01 | <.001 | | | | | |
| SRS-II | | | -0.028 | 0.01 | -2.08 | .05 | 1.32 |
| Kinship | | | | | | | |
| Mothers | | | -1.643 | 0.40 | -4.12 | <.001 | 1.83 |
| Fathers | | | -1.669 | 0.43 | -3.90 | <.001 | 1.83 |
| Siblings | | | 0.151 | 0.42 | 0.36 | .72 | 1.69 |

*Note.* *SE* = standard error, ERN = error-related negativity, Pe = post-error positivity, VIF = variance inflation factor.

## Discussion

Due to the substantial heterogeneity in symptom presentation and complex genetic profile, the use of endophenotypes is particularly important in ASD research. Endophenotypes may elucidate mechanisms that mediate genes and symptoms and thereby represent unique etiological paths to ASD. Thus, we sought to identify whether the ERN and Pe qualify as electrophysiological endophenotypes of ASD by comparing ERP and behavioral (error rates, RTs) data among ASD probands and their families relative to control families. Our results do no provide sufficient evidence to support the ERN as an endophenotype of ASD, as we did not observe expected group differences in ERN amplitude between ASD youth and control youth.

Additionally, group and kinship did not predict ΔERN amplitudes within family-based ΔERN analyses. Our results also confirm that the Pe is not an endophenotype of ASD, as we did not observe significant group differences between ASD probands and TDCs but did see group differences among fathers of ASD probands relative to control fathers. The implications of these findings are discussed in relation to ASD specifically and the ERN/Pe as endophenotypes of pathology more broadly.

**The ERN: Neural Endophenotype or Biomarker?**

In contrast to our predictions and previous research (Sokhadze et al., 2010; Sokhadze et al., 2012; South et al., 2010; Vlamings et al., 2008), we did not observe significant group differences in ERN amplitude when comparing ASD probands to TDC youth. These findings suggest that the ERN does not meet the first criteria as an endophenotype of ASD, as ERN amplitude differences were not associated with ASD and thus may not reflect underlying deficits in cognitive functioning and neural development.

The current finding of no group differences in ERN amplitude adds to an overall mixed literature on ERN amplitudes and error processing in ASD. While the preponderance of studies reveal attenuated ERN amplitudes in ASD youth (Sokhadze et al., 2010; Sokhadze et al., 2012; South et al., 2010; Vlamings et al., 2008) and adults (Santesso et al., 2011) relative to TDCs, two studies among youth with ASD reveal a lack of group differences in ERN amplitudes relative to TDC children (Henderson et al., 2015) and children with ADHD (Groen et al., 2008). Greater-amplitude ERNs were observed in one study, but only when comparing ASD youth who had the highest VIQ scores to TDCs (Henderson 2006). Thus, while several studies point to ERN amplitude differences in ASD relative to controls, this pattern of results has not been replicated in all samples.

Also, within our sample, heightened levels of ASD symptoms as measured by the SRS-II were not significantly correlated with ERN amplitudes in ASD, further bringing into question the relationship between ERN amplitudes and the symptomatic behaviors of individuals with ASD. The relationship between ASD symptom measures and deficits in error processing has not been consistently observed in the literature. Indeed, multiple studies report no significant correlations between symptom measures and ERN amplitudes or fractional anisotropy (FA) within the ACC (Barnea-Goraly et al., 2010; Groen et al., 2008; Noriuchi et al., 2010; South et al., 2010; Vlamings et al., 2008). Other studies report that higher levels of social impairment and/or repetitive behaviors are related to reduced ERN amplitudes and reduced FA in the ACC (Santesso et al., 2011; Thakkar et al., 2008) or, alternatively, that higher parent-reported symptoms are associated with enhanced ERN amplitudes (Henderson et al., 2015). These differences may reflect heterogeneity in ASD diagnosis and symptom presentation; all studies included high functioning participants that may have presented with varying levels of severity of social, communication, and restricted/repetitive behavior deficits. It may be that overall symptom levels are less influential on ERN amplitudes than the specific nature of symptoms (e.g., social or communication vs. restricted and repetitive behavior) or pattern of symptom presentation (e.g., degree of social deficits relative to deficits in stereotyped behaviors).

In order to test whether ERN amplitude differences were present in relatives of ASD probands, we examined the ΔERN in families of ASD probands relative to controls. Even with the use of methods to specifically differentiate the effects of kinship and shared familial genetics, group and kinship did not significantly predict ΔERN amplitude. These results indicate that the ERN does not relate to kinship status in ASD and thus does not meet all criteria necessary to qualify as a candidate endophenotype of ASD. In addition, the lack of differences in ASD

probands relative to TDCs suggest that the ERN also does not qualify as a diagnostic biomarker of ASD, as it appears that altered ERN amplitudes are neither specific indicators of disease diagnosis nor genetic liability for ASD (Ritsner & Gottesman, 2009).

**The Pe: Marker of Autism Symptoms?**

In-line with our hypotheses, we observed no differences in Pe amplitude between ASD probands and TDCs. A lack of group differences in Pe amplitude is consistent with the preponderance of previous studies in individuals with ASD compared to controls (Groen et al., 2008; Santesso et al., 2011; Sokhadze et al., 2010; South et al., 2010) and in studies comparing individuals with other forms of psychopathology to controls (Chiu & Deldin, 2007; Endrass et al., 2010; Ruchsow et al., 2005). Similar Pe amplitudes among ASD probands and TDCs suggest that youth with ASD do not display differences in neural indices of error awareness used to signal and initiate subsequent behavior change (Hajcak et al., 2004; Nieuwenhuis et al., 2001; Steinhauser & Yeung, 2010). Further, a lack of group differences suggests that the Pe is not consistently associated with diagnosis of ASD and thus does not qualify as an endophenotype or biomarker of the disorder (Ritsner & Gottesman, 2009).

Contrary to predictions, group and kinship status were significant predictors of ΔPe amplitude. Group x Kinship interactions were only significant for fathers, with significantly more positive ΔPe amplitudes in control fathers relative to fathers of ASD probands, pointing to reduced error awareness. Some evidence suggests that fathers of ASD probands may display overall heightened levels of the broader autism phenotype (De la Marche et al., 2012) as well as executive functioning deficits such as planning and attentional flexibility (Hughes, Leboyer, & Bouvard, 1997) or set-shifting (Wong et al., 2006). Thus, fathers of ASD probands may display a reduced ability to flexibly attend to and monitor their behavior, resulting in altered neural

indices of error awareness. However, because this pattern was not observed in ASD probands, these findings again suggest that the Pe is likely not an endophenotype or biomarker of ASD but may point to underlying neural and/or cognitive abnormalities in fathers of ASD probands representative of an overall genetic risk toward symptoms of ASD. In other words, the Pe may reflect some degree of clinical symptomology but is not directly linked to clinical manifestations of ASD and is thus not reliably tied to ASD diagnosis (Ritsner & Gottesman, 2009).

Mothers and fathers also displayed significantly larger ΔPe amplitudes than youth, possibly due to more mature prefrontal neural development and enhanced neural efficiency (Segalowitz & Dywan, 2009). This pattern of results has not been consistently observed in studies of Pe amplitudes across development (Ladouceur, Dahl, & Carter, 2007; Santesso, Segalowitz, & Schmidt, 2006; Wiersema, van der Meere, & Roeyers, 2007). However, all previous studies included adults who were younger than adults in the current sample (typically within ages 20-30) and may thus not capture developmental contrasts between youth and older adults.

**Implications for ASD**

Taken together, our findings suggest that the ERN and Pe do not qualify as endophenotypes of ASD. The ERN was not significantly different between ASD probands and TDC youth, suggesting it does not meet the first criteria as an endophenotype. Likewise, no group differences were observed in relatives of ASD probands compared to control families, suggesting that the ERN also does not meet the fifth criteria as an endophenotype. Based on our correlational analyses and evidence of a relationship between ASD symptoms and ERN amplitudes in past research, it is yet unclear whether ERN amplitude differences are directly related to symptoms of ASD (e.g., traits) or whether they are associated with state-related

processes not specific to ASD (e.g., internalizing symptoms, broader cognitive dysfunction, response to treatment; Gould & Gottesman, 2006). Given the variability of previous findings and lack of group differences in the current study it is likely that these state- or trait-related differences play a role in ERP generation and may explain significant group differences observed in some but not all studies of the ERN in ASD.

Likewise, the Pe does not appear to qualify as an endophenotype of ASD. We did not observe any group differences in Pe amplitude between ASD probands and TDCs, suggesting that the Pe is not reliably associated with ASD diagnosis. Interestingly, kinship and group did predict ΔPe amplitudes among fathers of ASD probands relative to control fathers and ASD symptoms were significantly correlated with ΔPe amplitudes. The relationship between heightened levels of ASD symptoms and reduced ΔPe amplitudes suggests that the Pe may reflect underlying traits of ASD such that the presence of subthreshold social, communication, and repetitive/restricted behaviors may reduce overall error awareness. However, because changes in Pe amplitude were not associated with clinically significant manifestations of ASD, the Pe is not a reliable diagnostic indicator.

One possible confound to our ability to identify the relationship between ASD symptoms and ERP amplitudes may have been our reliance on group as a predictor in all regressions (Miller & Rockstroh, 2013; Volkmar & McPartland, 2014). Groups were defined based on DSM-IV diagnostic criteria for ASD. Using DSM-based diagnostic distinctions permitted examination of the differences between ASD probands/relatives and controls but may have led us to rely too heavily on categorical distinctions between normal functioning and clinical diagnosis. In a discussion about the limitations of using current categorical diagnostic distinctions in endophenotype research, Gould and Gottesman (2006) suggested that:

> DSM approaches provide a partially validated mechanism whereby physicians can provide reliable diagnoses, communicate amongst themselves and report their findings to insurance providers. However, disease heterogeneity implicit in the current classification schema, and the imprecise quantification of the behaviors being described, makes it difficult to even partially deconstruct such 'diseases' within model organisms. (p. 113)

Thus, although the use of DSM categorical distinctions has substantial clinical utility, it may limit research aimed at understanding the underlying etiological mechanisms of disorders.

The limitation of utilizing DSM diagnostic criteria is particularly pertinent in ASD research due to the high diagnostic heterogeneity, diversity of symptom presentation, and variability of symptom severity (Happé et al., 2006). There has been considerable debate amongst clinicians and researchers regarding diagnosis of ASD, particularly amongst individuals with ASD who are higher functioning and thus similar to those included in the current project and past research on the ERN in ASD (Lord & Bishop, 2015; Lord & Jones, 2012; Volkmar & McPartland, 2014; Volkmar & Reichow, 2013). Also, current diagnostic criteria for ASD do not include cognitive deficits (e.g., deficits in executive functioning) that may be especially relevant in identifying whether the ERN is an endophenotype of ASD (Leung, Vogan, Powell, Anagnostou, & Taylor, 2015; Miller & Rockstroh, 2013). Thus, although these ASD diagnostic distinctions are based on research and currently utilized by clinicians, relying on current definitions of ASD may have limited our ability to deconstruct the heterogeneity of ASD and identify neural deficits that underlie symptoms of ASD regardless of diagnostic status.

Due to the heterogeneity of ASD diagnosis and limitations of current ASD diagnostic criteria, we conducted additional supplementary analyses in which we removed group as a predictor in regressions and only examined the relationship between dimensional measures of

ASD symptoms (SRS-II scores), kinship, and ΔERN amplitudes. Again, SRS-II scores and kinship were not significant predictors of ΔERN amplitudes, suggesting that even when removing group status, ASD symptoms did not predict ΔERN amplitudes. These findings reinforce that the ERN is not an endophenotype of ASD, as ERN amplitudes do not appear to be related to dimensional aspects of ASD symptoms.

Interestingly, analyses on ΔPe amplitudes without group as a predictor did reveal that ASD symptoms and kinship predicted ΔPe amplitudes, with higher SRS-II scores related to significantly smaller ΔPe amplitudes. Correlations with ΔPe amplitude similarly indicated a negative relationship between measures of the broader autism phenotype (AQ, BAPQ), with higher scores associated with significantly reduced ΔPe amplitudes. The relationship between Pe amplitude and the broader autism phenotype suggests that regardless of diagnosis, the social deficits and repetitive, restricted behaviors characteristic of ASD are associated with electrophysiological indicators of reduced error awareness. Reduced error awareness during performance monitoring may contribute to poor behavioral flexibility and modification, resulting in impaired social and emotional reciprocity and increased behavioral inflexibility. Alternatively, anxiety may play a role in our results, as reduced ΔPe amplitudes were also significantly associated with increased levels of trait anxiety in both adults and youth. Individuals with heightened levels of ASD symptoms may be more aware of their subthreshold social or behavioral deficits and feel increased concern about others' evaluations, leading to heightened levels of anxiety. Elevated levels of anxiety may tax attentional systems, reducing overall error awareness (Eysenck, Derakshan, Santos, & Calvo, 2007). Thus, it may be that the specific combination of heightened levels of ASD symptoms and elevated trait anxiety reduce error awareness.

**Future Directions: The ERN as an Endophenotype**

The findings of the current study have implications for a larger discussion of the utility of the ERN and Pe as endophenotypes of psychopathology. As outlined previously, studies of the Pe are inconsistent and generally suggest that the Pe does not qualify as a biomarker or endophenotype of psychopathology. Thus, the following discussion will focus primarily on the ERN.

There is growing dialogue about the utility of the ERN as an endophenotype (Manoach & Agam, 2013; Moser et al., 2013; Olvet & Hajcak, 2008; Proudfit et al., 2013). Most research on the ERN to date has explored the first criteria as an endophenotype, or whether the ERN is associated with particular diagnoses. However, despite extensive research on the relationship between the ERN and various state- and trait-related conditions (Clayson, Clawson, & Larson, 2012; Moser, Hajcak, & Simons, 2005; Olvet & Hajcak, 2012; Pailing & Segalowitz, 2004), there is considerable within-subject and between-subject variability, bringing into question the nature of the relationship between the ERN and psychopathology. The current study adds to a mixed literature in which some, but not all psychological conditions are associated with changes in ERN amplitude (e.g., Chiu & Deldin, 2007; Endrass et al., 2008; Groen et al., 2008; Hajcak et al., 2003; Henderson et al., 2015; Ruchsow et al., 2006; South et al., 2010). Important questions must be addressed in order to determine whether the ERN is best characterized as an endophenotype or biomarker, including how particular symptoms are related to increases or decreases in ERN amplitudes and to what degree environmental factors mediate the relationship between ERN amplitude and symptom presentation (Proudfit et al., 2013).

Despite claims that the ERN does in fact qualify as an endophenotype in some ways like differentiating groups (Manoach & Agam, 2013; Olvet & Hajcak, 2008; Proudfit et al., 2013),

few studies have explored criteria necessary to differentiate whether the ERN is better characterized as a biomarker (Lenzenweger, 2013; Miller & Rockstroh, 2013). Although there is some variability in the definition of a biomarker (Strimbu & Tavel, 2010), biomarkers are broadly defined as "indicator[s] of the presence or extent of a biological process that is directly linked to the clinical manifestations and outcomes of a particular disease (Ritsner & Gottesman, 2009, p. 5-6)." Unlike endophenotypes, biomarkers need not be tied to genetic causes and are better conceptualized as correlates associated with a disorder (Gould & Gottesman, 2006; Lenzenweger, 2013; Miller & Rockstroh, 2013). Also, because biomarkers may not fall within the causal chain from genotype to symptoms, biomarkers can be influenced by state-related factors such as mood or response to treatment (Lenzenweger, 2013). Thus, in order to differentiate an endophenotype from a biomarker, it is critical to examine whether a candidate endophenotype is manifest consistently independent of illness state and whether it demonstrates patterns of heritability within families.

There is currently relatively little research examining whether ERN amplitude differences are manifest independent of illness state, or before and after treatment. Most discussion of the stability of the ERN before and after psychopathology treatment rests on only one study that found no significant changes in ERN amplitudes among children with OCD before and after treatment that successfully reduced OCD symptoms (Hajcak et al., 2008), but no research to date has attempted to replicate study findings in the same population or in other populations. In fact, Sokhadze, El-Baz, Sears, Opris, and Casanova (2014) observed changes in ERN amplitude that suggest the ERN might not remain stable following treatment. Specifically, the authors observed increased ERN amplitudes among children with ASD relative to waitlist comparison subjects following 18 sessions of repetitive Transcranial Magnetic Stimulation that successfully reduced

symptoms such as irritability, hyperactivity, and stereotypic behaviors. Given that biomarkers do not always remain stable following treatment, it is critical to determine whether ERN amplitudes change following reductions/increases in symptom presentation or whether they remain stable once an individual crosses over a diagnostic threshold.

Second, additional family studies are also needed to reestablish the heritability of the ERN, determine whether altered ERN amplitudes co-occur with the disorder in families, and determine whether altered ERN amplitudes are present in the same form within families of affected individuals. This is particularly critical in differentiating whether the ERN is an endophenotype or biomarker, as endophenotypes are associated with pathways from genes to symptoms but biomarkers may not be as directly tied to genetic risk (Ritsner & Gottesman, 2009). As noted previously, the methodology in most family studies does not fully permit an examination of the role of kinship status (e.g., Albrecht et al., 2008; Riesel et al., 2011; Simmonite et al., 2012). The current study is an important first step in examining the ERN within biologically related families, but additional research within families is necessary to understand the heritable nature of the ERN and determine the ways in which ERN amplitudes may signify links between genetics and symptom presentation.

In order to reconcile variability within ERN research and determine whether the ERN is indeed an endophenotype, we suggest exploring an additional sixth criterion that has been proposed for a candidate endophenotype: reliability and specificity of measurement (Chan & Gottesman, 2008; Miller & Rockstroh, 2013). According to this criterion, candidate endophenotypes should have high sensitivity, meaning that they should be associated with a disorder more strongly than other conditions (Lenzenweger, 2013; Miller & Rockstroh, 2013). The findings of the present study and other current research on the ERN reveal inconsistent

relationships between the ERN and DSM-based diagnostic categories, highlighting the importance of utilizing research that considers dimensional measures of pathology. Examining endophenotypes based on categorically defined groups can lead to the tendency to explain results based on diagnosis, creating a cyclical situation in which a diagnostic "label becomes an explanation" (Volkmar & McPartland, 2014, p. 196) and thereby validates current diagnostic criteria instead of providing new information. Also, a more dimensional view of pathology is consistent with RDoC criteria and may permit researchers to account for underlying traits and syndromes rather than arbitrary distinctions between disorders, thereby acknowledging that there are multiple etiological pathways to a set of symptoms (Gould & Gottesman, 2006). A more dimensional approach applied to the ERN, as was attempted in supplementary analyses in the current study, may facilitate an enhanced understanding of the pathways that lead to differential neural activation during performance monitoring (Gould & Gottesman, 2006), resulting in a broader understanding of the overlap between disorders (Miller & Rockstroh, 2013).

The lack of sensitivity to DSM-based diagnostic criteria may not disqualify the ERN as a plausible endophenotype, but rather indicate that the ERN is associated with common symptoms that underlie multiple conditions. Two theories regarding the relationship between underlying traits and ERN generation have recently been proposed that have promise in determining whether the ERN is an endophenotype. In a meta-analysis of the relationship between ERN amplitudes and anxiety, Moser et al. (2013) proposed that the enhanced ERN amplitudes in anxiety might reflect compensatory error-monitoring processes related to heightened levels of anxious apprehension. According to this theory, anxious apprehension, or worry, interferes with attention to goal-directed behaviors by reducing processing efficiency and heightening response conflict following an error, resulting in enhanced ERN amplitudes (Moser et al., 2013).

Alternatively, Proudfit et al. (2013) proposed that the ERN signifies broader trait-based levels of threat sensitivity, with larger-amplitude ERN associated with greater sensitivity to threat. In this way, the ERN acts as a risk marker for the development of pathology and may be associated with specific compensatory strategies to reduce/increase threat sensitivity, including worry (Proudfit et al., 2013). While both theories propose different mechanisms through which anxiety leads to changes in ERN amplitudes, they similarly suggest that underlying levels of internalizing symptoms affect performance monitoring.

The compensatory error-monitoring and threat-sensitivity theories of ERN generation and functional significance are dimensional in nature, as underlying levels of threat sensitivity or anxious apprehension may result in various symptoms manifest differently based on an individual's environment (e.g., learning experiences) or genetic risk. Differences in genetic and environmental factors may mask the relationship between categorical diagnoses and ERN amplitude, explaining current variability in ERN amplitudes across diagnoses (Proudfit et al., 2013). The next step in ERN research should be to examine these hypotheses to determine how ERN amplitudes are related to genetic risk for anxious apprehension or threat sensitivity and whether variability in ERN amplitudes signify environmentally derived differences on an etiological pathway to symptom presentation. Greater understanding of the relationship between internalizing symptoms and ERN amplitudes may lend important insight into whether the ERN qualifies as an endophenotype of broader traits that underlie psychopathology.

**Anxiety and the ERN in ASD**

Given that ERN amplitudes may reflect underlying dimensional trait levels of anxiety, we explored the relationship between ERN amplitudes and internalizing symptoms among participants. Individual levels of internalizing symptoms (e.g., anxiety) have been tied to more

negative (i.e., greater) ERN amplitudes and may influence ERN presentation in ASD where anxiety is a frequent comorbidity (Vasa & Mazurek, 2015). The role of individual differences in state/trait levels of anxiety and comorbid anxiety diagnoses may also in part explain variability in the literature on ERN amplitudes in ASD.

Although ASD probands displayed significantly higher levels of parent-reported anxiety than both TDC youth and ASD siblings, we did not observe significant correlations between SCARED scores and ERN amplitudes in ASD probands alone or in all youth, similar to our previous work (South et al., 2010). A lack of relationship between anxiety and ASD suggests that underlying levels of internalizing symptoms may not be related to ERN generation in ASD and thus may partially explain the lack of group differences in the current sample of ASD youth relative to control youth. However, our sample only included two ASD probands who reported comorbid anxiety disorders, possibly limiting our ability to detect the influence of clinical levels of anxiety on ERN amplitude among youth with ASD.

In contrast, among adults we did observe significant correlations between state levels of anxiety and ERN amplitudes, with significantly higher levels of state anxiety related to enhanced ERN amplitudes. The relationship between state-based changes in affect and ERN amplitudes is not yet clear, as specific state-based manipulations of anxiety do not always relate to changes in ERN amplitudes (Moser et al., 2013). The threat-sensitivity theory attempts to account for differences in the literature by proposing that individual levels of threat sensitivity may determine the degree to which the ERN is influenced by state-related changes in anxiety by altering the affective value of errors (Proudfit et al., 2013). Individuals with higher levels of worry may interpret errors as being more threatening, leading to an enhanced ERN (Proudfit et

al., 2013). Although the measures of anxiety in the current study were not designed to measure worry, our findings reinforce the general role of anxiety in ERN generation.

**Behavioral Performance**

In addition to examining ERP indices of performance monitoring, we also examined behavioral measures. In contrast to our hypotheses, we did not observe significant differences in RTs or error rates when comparing ASD probands to TDCs. The lack of group differences in behavior is not surprising given the lack of group differences in neural activation and adds further support for overall intact performance monitoring processes in our sample of high functioning youth with ASD relative to control youth.

In behavioral analyses accounting for family and kinship, we did not observe differences in performance by group or in Group x Kinship interactions. However, parents performed better than youth, with significantly faster RTs and significantly reduced error rates. These findings are not unexpected given that greater neural maturity in adults may result in more efficient information processing and behavioral responses (e.g., Santesso et al., 2006; Wiersema et al., 2007).

**Future Directions**

This study represents an important step in ASD research and research on the ERN and Pe as endophenotypes. Our findings lead to several suggestions for future research in ASD to understand discrepancies within the literature regarding ERN amplitudes and ASD diagnosis, to explore the ways in which the Pe reflects underlying traits of ASD, and to examine possible etiological pathways to neural activation in ASD.

Further research is requisite in order to elucidate if and how ERN and Pe amplitude differences relate to the symptoms of ASD. As noted, specific combinations of severity across

social, communication, and restricted/repetitive behavior symptoms may influence ERN and Pe amplitudes to varying degrees. Also, given the variability in the literature, it is likely that other factors mediate or moderate the relationship between ASD symptoms and performance monitoring. These moderating factors may be either state-related factors or trait-based differences. Thus, we suggest exploring state-based manipulations as well as more trait-based factors, such as the role of cognitive deficits, comorbid psychological conditions, and alterations in neural connectivity as potential factors that modulate ERN and Pe amplitudes in ASD. Accounting for state- and trait-based factors in this way may also reveal diagnostic subgroups that are generally masked by whole-group analyses.

Future research should also examine the role of task complexity on ERN/Pe generation and behavior in ASD. If theories of connectivity in ASD are correct, individuals with ASD may have increasing difficulty with tasks that involve greater cognitive demand. Examining cognitive and neural processes during tasks of varying levels of complexity that tap into different skills (e.g., social and emotional functioning, executive functioning) may reveal whether individuals with ASD have a threshold of ability above which they are unable to perform at the same level as TDCs. Further, incorporating ERP research with measures of neural connectivity (e.g., DTI) may further reveal if and when individuals with ASD utilize compensatory neural activity between neural regions to achieve similar performance.

Another important consideration for future research is conducting more studies that specifically examine whether the ERN is sensitive to a more general underlying trait, such as those proposed in the compensatory error-monitoring hypothesis or the threat-sensitivity hypotheses. Researchers should apply both theories to ASD specifically by measuring worry or threat-sensitivity in order to understand to what degree anxiety influences the ERN in ASD. It

may be particularly beneficial to compare ERN amplitudes among individuals with anxiety, ASD probands, and ASD probands with comorbid anxiety disorders in order to determine whether clinical levels of anxiety differentially affect ASD-related performance monitoring abilities and neural processes. It is possible that anxiety enhances an already reduced ERN in ASD, resulting in ERNs that, at times, appear comparable to TDCs.

Finally, the observed relationship between Pe amplitudes and symptoms of ASD should be explored further. If reduced Pe amplitudes are related to symptoms of ASD, future research should explore what specific symptoms influence Pe amplitudes (e.g., social deficits, communication deficits, reduced executive functioning, etc.) and to what degree these symptoms must be present to significantly alter error awareness. Given that Pe amplitudes were also significantly correlated with anxiety, it may be that the specific interaction between heightened levels of anxiety and subthreshold symptoms of ASD be associated with reduced error awareness.

**Limitations**

Several limitations should be considered when interpreting the results of the current study. First, our study had a substantial amount of missing data due to participant dropout, excessive movement artifact during EEG acquisition, low rates of error commission, and missing surveys from families. The missing data in our study resulted in relatively small groups for each cell during analyses. Excessive movement artifact in part reflects challenges of EEG data acquisition among children with ASD who may have greater difficulty remaining still and may experience increased discomfort during net application due to sensory sensitivities. The nature of the task may have also played a role, as it is possible that we did not obtain high enough error rates for some participants due to the ease of the task. We attempted to utilize a task that was

cognitively demanding and that had enough trials to challenge adult participants but that did not exceed levels appropriate for youth participants. Determining an appropriate level of difficulty for both adult and youth participants is an important consideration moving forward, particularly as additional research is conducted to include comparisons within families.

Second, our sample of individuals with ASD was high functioning, with IQs in the average to above-average range. Overall levels of intellectual functioning may play a role in ERN generation, as differences in overall cognitive capacity may influence the efficiency of performance monitoring. Henderson et al. (2006) observed a significant relationship between ERN amplitudes and VIQ scores, with enhanced ERN amplitudes observed among children with higher VIQ scores. The relationship between VIQ and ERN amplitudes was not replicated in the current study or past studies (South et al., 2010; Vlamings et al., 2008). Research consistently suggests that overall IQ is predictive of long-term outcomes in ASD (Magiati, Tay, & Howlin, 2014) and may underlie some of the heterogeneity in symptom presentation and severity. The relationship between IQ and functional outcomes in ASD may indicate that the sample of children and adults included in the current study represents a separate, distinct portion of the ASD population. The lack of group differences in neural activation observed among these individuals may not be representative of the overall population of individuals with ASD.

Similarly, we did not observe the expected pattern of symptoms of the broader autism phenotype among relatives of ASD probands. Regression analyses examining group and kinship differences on the AQ and BAPQ were not significant, suggesting that relatives of ASD probands included in the current study may not have displayed heightened levels of the broader autism phenotype as observed in other samples (Hurley et al., 2007; Ingersoll, Hopwood, Wainer, & Donnellan, 2011; Sasson et al., 2013). Indeed, average AQ and BAPQ scores among

mothers and fathers of ASD probands and ASD siblings did not meet established cutoffs of 32/30 (females/males) or 3.15, respectively, for the broader autism phenotype (Baron-Cohen et al., 2006; Baron-Cohen et al., 2001; Hurley et al., 2007). However, in regressions examining SRS-II scores we did observe the expected pattern of significantly higher levels of ASD symptoms among individuals with ASD relative to all other groups and among unaffected relatives of ASD probands relative to control families. Thus, relatives of ASD probands did not display differences on measures of the broader autism phenotype but did display differences on a dimensional measure of ASD symptoms, possibly suggesting that our sample of unaffected ASD relatives were higher functioning and displayed overall fewer subthreshold symptoms of ASD.

Lower than anticipated levels of ASD symptoms seen in relatives may in part reflect measurement error. We utilized different rating sources for the AQ/BAPQ and SRS-II among parents. The AQ and BAPQ involved self-report ratings of behavior, while SRS-II scores involved spouse-report ratings of behavior. Previous research documents differences based on the rater, suggesting that observed discrepancies may reflect differences in self-perception of symptoms (Hurley et al., 2007; Seidman, Yirmiya, Milshtein, Ebstein, & Levi, 2011). In addition, though the concurrent validity of the AQ, SRS, and BAPQ has been previously established in a non-clinical sample (Ingersoll et al., 2011), no studies have examined the concurrent validity in a sample that included unaffected relatives of ASD probands. Ingersoll et al. (2011) suggested that "the BAPQ is more closely related to the defining features of the [broader autism phenotype], whereas the SRS-A is more closely related to peripheral features of the phenotype, and may be indicative of psychopathology more generally" (p. 1654). Thus, the observed discrepancy between SRS-II and AQ/BAPQ scores may also reflect overall greater levels of pathology in ASD relatives rather than greater symptoms of ASD severity.

Finally, a large proportion of participants in the current study were taking psychotropic medications at the time of study participation. There is some evidence that medication use may influence ERN amplitudes (Barnes, O'Connell, Nandam, Dean, & Bellgrove, 2014; de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004; de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006; Groen et al., 2008; Riba, Rodriguez-Fornells, Münte, & Barbanoj, 2005). Previous research in ASD also suggests some differences based on medication status (Henderson et al., 2006), though this has not been replicated in all studies (Santesso et al., 2011; South et al., 2010). Thus, it is possible that psychotropic medication use influenced the observed findings.

**Conclusion**

In summary, this is the first study to examine the ERN and Pe in biologically related families, permitting an examination of the role of heritability and kinship status. We utilized group and kinship as predictors in regressions in order to examine differences in the familial aggregation of ERN amplitudes and included families as clusters in order to account for shared variance due to family membership. Results only partially followed predictions. Error-related negativity and Pe amplitudes among youth with ASD were not significantly different from control youth, and group and kinship status did not predict ΔERN amplitudes or ΔPe amplitudes. Thus, we did not find support for the ERN or Pe as endophenotypes or biomarkers of ASD, though the Pe may be influenced by symptoms of ASD. Similarly, group and kinship did not predict behavioral data aside from significantly better performance in adults relative to youth, regardless of group status. Our findings suggest the need for additional studies of the ERN as an endophenotype of pathology that determine the reliability and specificity of the ERN in relation to dimensional, syndrome-based components of pathology.

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