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ORIGINAL PAPER

Electrophysiological Endophenotypes and the Error-Related Negativity (ERN) in Autism Spectrum Disorder: A Family Study

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Abstract We examined the error-related negativity (ERN) as an endophenotype of ASD by comparing the ERN in families of ASD probands to control families. We hypothesized that ASD probands and families would display reduced-amplitude ERN relative to controls. Participants included 148 individuals within 39 families consisting of a mother, father, sibling, and proband. Robust ANOVAs revealed non-significant differences in ERN amplitude and behavioral performance among ASD probands relative to control youth. In subsequent multiple regression analyses group and kinship (proband, sibling, mother, father) did not significantly predict ΔERN (error minus correct ERN) or behavioral performance. Results do not provide evidence for the ERN as an endophenotype of ASD. Future research is needed to examine state- or trait-related factors influencing ERN amplitudes in ASD.

Keywords Autism spectrum disorder · Error-related negativity · Cognitive control · Endophenotype

Introduction

Autism spectrum disorder (ASD) is characterized by social interaction impairments, communication deficits, and repetitive or stereotyped behaviors. The functional impact and degree to which specific symptoms are present is heterogeneous across individuals with ASD (Minshew and Williams 2007), pointing to a complex etiology. Research suggests that impaired neural communication associated with abnormal white-matter connectivity may underlie ASD symptoms (Wass 2011; Barnea-Goraly et al. 2010; Griebling et al. 2010). Although ASD is highly heritable, it does not follow typical Mendelian patterns of inheritance and there are hundreds of genetic loci and chromosomal abnormalities in ASD, suggesting that gene–environment and gene–gene interactions also contribute to symptom presentation (Li et al. 2012; Gaugler et al. 2014). Given the complex etiology of the disorder, there is significant variability in symptom presentation between individuals (Minshew and Williams 2007).

A key issue in ASD research is the identification of measurable processes that mediate genotype–behavior relationships and underscore symptom heterogeneity. 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 (Glahn et al. 2007; Jeste and Nelson 2009; Bosl et al. 2011; Gottesman and Gould 2003). 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 and 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 and Gould 2003; Viding and Blakemore 2007). 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

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families, and (5) present in the same form within families of affected individuals to a larger degree than the general population (Gottesman and Gould 2003; Olvet and Hajcak 2008). These criteria differentiate endophenotypes from biomarkers, as biomarkers are correlates of a disorder, are not clearly heritable, and are often state-dependent outcomes (Miller and Rockstroh 2013; Ritsner and Gottesman 2009).

The error-related negativity (ERN), an event-related potential (ERP), may qualify as an endophenotype of ASD. The ERN is a fronto-central negativity that peaks 50–100 ms following the commission of errors and has been localized to the caudal anterior cingulate cortex (ACC) using dipole modeling (Gehring et al. 1993; Bush et al. 2000; van Veen and Carter 2002). Theories of ERN generation suggest it is associated with cognitive control and performance monitoring—aspects of executive functioning necessary to flexibly regulate behavior to meet goals and respond to environmental changes (Larson et al. 2014; Olvet and Hajcak 2008). Indeed, in one study ERN amplitudes were associated with measures of cognitive flexibility and executive control, suggesting that enhanced performance monitoring (larger-amplitude ERN) may be tied to greater cognitive flexibility and executive control (Larson and Clayson 2011).

Evidence that the underlying neural structures and cognitive functions signified by the ERN are altered in ASD supports a putative relationship between ERN amplitudes and the characteristic deficits of ASD. For example, several neuroimaging studies point to decreased metabolism and disrupted connectivity in the ACC of individuals with ASD (Balsters et al. 2016; Haznedar et al. 2000; Hoffmann et al. 2016; Solomon et al. 2015; Zhou et al. 2016). Further, neural abnormalities in the ACC have been related to less flexible learning, stereotyped behaviors/restricted interests, and social deficits, pointing to a possible link between abnormal ACC functioning and ASD symptom presentation (Balsters et al. 2016; Haznedar et al. 2000; Hoffmann et al. 2016; Solomon et al. 2015; Zhou et al. 2016; Thakkar et al. 2008). Cognitively, individuals with ASD consistently demonstrate difficulties with cognitive flexibility and behavioral monitoring—aspects of executive functioning employed during performance monitoring. It is, therefore, possible that reduced performance monitoring in ASD represents an executive functioning deficit in internal behavioral monitoring, contributing to difficulty with aspects of flexible and adaptive functioning, such as theory of mind, empathy, or restricted/repetitive behaviors (Hűpen et al. 2016). As a result, the ERN may signify abnormalities in neural and executive functioning that contribute to core features of ASD.

Previous research provides some support that the ERN is associated with ASD diagnosis and, thus, may meet the first criterion as an endophenotype of ASD. Specifically, some studies suggest attenuated ERN amplitudes in those with ASD relative to typically developing controls (South et al. 2010; Sokhadze et al. 2010, 2012; Vlamings et al. 2008). Correlations have also been identified between reduced-amplitude ERN and poorer social skills (Henderson et al. 2006; Hűpen et al. 2016; Santesso et al. 2011; South et al. 2010), though no studies have explicitly explored the relationship between ERN amplitudes and stereotyped/restricted symptoms or executive functioning in ASD (Hűpen et al. 2016). Other studies, however, reveal inconsistent differences between ASD youth and controls, including no differences in ERN amplitudes (Groen et al. 2008; Henderson et al. 2015), and larger ERN amplitudes among ASD youth with higher VIQ scores relative to control children (Henderson et al. 2006) and among youth during an emotional processing task relative to control youth (McMahon and Henderson 2014). It is possible that individual differences (e.g., IQ) or the nature of the task may explain variability in the ASD and ERN literature. Importantly, the majority of studies indicate differences in ERN amplitudes between youth with ASD and controls, and it has been suggested that reduced amplitude ERN points to difficulty with internal performance monitoring in ASD, although we acknowledge the mixed findings (Hűpen et al. 2016).

The ERN also appears to meet the second and third criteria as an endophenotype. Supporting the second criterion, heritability estimates of the ERN approach 0.50, implying that the ERN is linked to genetic factors (Anokhin et al. 2008). No studies to date have examined the third criterion in ASD, though ERN amplitude differences remained stable after treatment of anxiety disorders, suggesting that the ERN remains constant regardless of illness state (Hajcak et al. 2008; Olvet and Hajcak 2008). Together, the ERN appears to meet the first three criteria as an endophenotype. The heritable nature of the ERN and relationship with neural and cognitive processes highlight the utility of 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.

Regarding the fourth criterion of an endophenotype, no studies have examined ERN amplitudes in relatives of ASD probands. Nevertheless, there is substantial evidence of genetic liability in family members that may affect ERN generation. For example, unaffected family members ASD probands display deficits in executive functioning, including deficits in cognitive flexibility (Van Eylen et al. 2016; Wong et al. 2006). Likewise, 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 and Vander Wyk 2013; Belmonte et al. 2010; Kaiser et al. 2010; Peterson et al. 2006). Altered neural activation and specific deficits in executive functions tied to performance monitoring may be manifest by reduced ERN amplitudes in relatives of ASD probands.

Studies among other populations (e.g., OCD, ADHD) reveal similar patterns of ERN amplitude reduction or attenuation among probands with psychopathology and relatives of affected individuals compared to controls, providing compelling evidence that the ERN may serve as an endophenotype for some forms of psychopathology (Riesel et al. 2011; Albrecht et al. 2008; McLoughlin et al. 2009). However, the methodology utilized within these studies is variable, is not directly related to ASD, and does not facilitate comparison among individuals with shared genetics, limiting the interpretability of the role of kinship in ERN generation (i.e., whether the subject is a mother, father, sibling, or proband). For example, one study compared relatives to control participants but did not include affected probands (Euser et al. 2012). Most other studies utilized participants who were related to affected individuals but were not all biologically related to the probands included in the study (McLoughlin et al. 2009; Riesel et al. 2011; Carrasco et al. 2013; Simmonite et al. 2012). Although these studies suggest that the ERN may serve as a marker of susceptibility among unaffected relatives across different disorders, it is necessary to examine ERN amplitudes using a sample in which all relatives are biologically related to probands in order to more accurately understand the role of genetics in ERN activation.

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. First, we hypothesized that ASD probands would display reduced-amplitude ERN and decreased behavioral modification (longer response times [RTs] on error trials, greater error rates) relative to control youth, indicating that the ERN meets the first criteria as a potential endophenotype of ASD. Second, we hypothesized that ERN amplitudes would differ based on family and kinship status; families of ASD probands would display similar electrophysiological and behavioral patterns as seen in ASD probands (i.e., less negative ERN amplitudes, decreased behavioral modification) compared to controls.

Methods

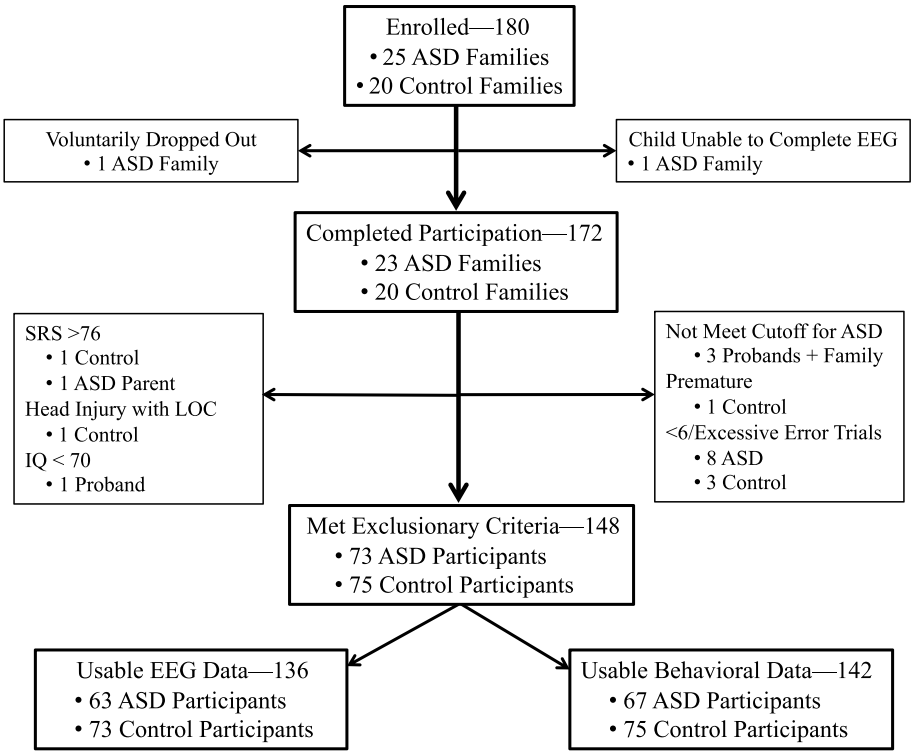
Participants

The Brigham Young University Institutional Review Board approved study procedures. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. After description of the study to participants, informed consent/assent was obtained from all individual participants included in the study. We collected data from males ages 10–17, including youth diagnosed with ASD and control youth. We also collected data from biological family members that included the youths' mother, father, and one male sibling within the same age range (10–17). Participants were excluded if they were non-native English speakers or had a gestation of less than 34 weeks. Family members were excluded if they had psychotic diagnoses but were not excluded due to history of other psychological diagnoses. Initial study enrollment included 180 participants from 42 families. For a full summary of participant dropout and exclusion, see Fig. 1. Ultimately, there were 148 participants who met full inclusion criteria (73 ASD probands/relatives, 75 control youth/relatives). Of those who met full inclusion criteria, 135 participants (62 ASD probands/relatives, 73 control youth/relatives) had full data for both behavioral and ERP measures. One sibling of an ASD proband did not have behavioral data due to computer malfunction and eight participants (six ASD probands/relatives, two controls) did not have ERP data due to six or fewer useable error-related ERP trials (Olvet and Hajcak 2009).

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) × 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. Medications included: stimulants (dexmethylphenidate, methylphenidate,

Fig. 1 Participant flowchart



Vyvanse), non-stimulant ADHD medications (clonidine, Straterra), antipsychotics (ziprasidone, risperidone, aripiprazole), antidepressants (sertraline, vilazodone, venlafaxine, trazodone, Wellbutrin, Cymbalta), glucocorticoid (Florinef), thyroid medication (synthroid, armour thyroid, westhroid), hormone medications (Sprintec, progesterone), and medication for treatment of multiple sclerosis (naltrexone).

Clinical Diagnosis and Assessment

Intellectual functioning was determined using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999). Social functioning was evaluated using the parent-report or spouse-report version of the Social Responsiveness Scale, Second Edition (SRS-II), with raw scores of 76 or above indicative of clinical levels of social impairment (Constantino and Gruber 2012). To assess the broader autism phenotype, participants completed the parent-report youth version of the Autism Spectrum Quotient (AQ; Baron-Cohen et al. 2006) or adult self-report AQ (Baron-Cohen et al. 2001). 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.

Autism Diagnosis

Autism diagnostic status was assessed in all youth participants to either confirm or rule-out ASD. Community mental health providers, psychiatrists, or physicians previously diagnosed all probands with ASD. Diagnosis was confirmed using the Diagnostic and Statistical Manual of Developmental Disorders-IV criteria based on information from the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al. 2000). The ADOS-G was administered by the first or second author who are both ADOS certified. Inclusion as an ASD proband required meeting ADOS total cut-off score of 7. Siblings and control youth scored below raw scores of 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).[1]

Experimental Task

Participants completed a modified Eriksen flanker task (Eriksen and Eriksen 1974) with a five-letter array with the letters 'H' or 'S' and were instructed to respond to the middle (target) letter as quickly and accurately as possible with a right-hand middle or index finger button press. There were three blocks of 200 trials for 600 total trials; 50%

[1] One youth with ASD and three siblings were missing SRS-II scores. ADOS-G scores were obtained from the ASD proband (total score of 21), indicating that he displayed symptoms above the diagnostic threshold. All participants were retained in analyses to maintain statistical power. All analyses were replicated excluding these participants, and the pattern of significance remained consistent.

were incongruent (e.g., HHSHH, SSHSS) and 50% were congruent (e.g., SSSSS, HHHHH). Response types were counterbalanced across participants. Flanker stimuli were presented 100 ms before target stimuli, which remained on the screen for 600 ms with random 800-to-1200 ms inter-trial interval. Participants completed 24 practice trials to ensure understanding; practice trials were repeated until participants achieved 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 (20 K nominal gain, band-pass = 0.10–100 Hz) referenced to the vertex electrode and digitized continuously at 250 Hz with a 24-bit analog-to-digital converter. Impedances were maintained below 50kΩ. Data were average-re-referenced off-line and digitally low-pass filtered at 30 Hz. Bad channels were identified as channels with less than a 0.4 absolute correlation with neighboring channels and on a trial-by-trial basis if they had a difference of 100 μv from the minimum/maximum values for that trial or differed 30 μv or more from neighboring channels. Eye blinks were removed using independent component analysis and saccades were removed using principal components analysis with promax rotation on EEGLAB (Delorme and Makeig 2004) and the ERP PCA Toolkit (Dien 2010).

Individual-subject ERP data were segmented separately for correct and error trials excluding errors of omission. Epochs spanned from 400 ms pre-response to 800 ms post-response and were baseline adjusted from −400 to −200 ms. ERN (and correct-trial analogue CRN) amplitudes were calculated as the average negative amplitude from 15 ms pre- and 15 ms post-peak using a window between 0–150 ms at electrodes FCz, 7, 106, and Cz. Window and electrode locations were chosen based on examination of the current data and previous research (South et al. 2010). We utilized an ROI-based approach for electrode selection to improve reliability of ERP measurement (Baldwin et al. 2015).

Power Analyses

Prior to beginning the study, we conducted power analyses to ensure inclusion of a sufficient number of youth to achieve adequate statistical power to detect the primary effects of interest. All power estimates were calculated using G*Power analysis software. Power estimates were first calculated to determine the sample size necessary for a comparison of the ERN between ASD and control youth using a η^2_p effect size of 0.09, as observed in a significant group × accuracy ERN interaction taken from our previous publication (South et al. 2010), a significance level of 0.05, an estimated correlation among repeated measures of 0.5, and a power level of 0.9. These analyses revealed that a sample size of 15 per group is necessary to detect meaningful differences in a within-/between-subjects interaction between these groups utilizing a group × accuracy repeated measures ANOVA. In addition, to corroborate this sample size, we used preliminary study data to calculate sample sizes needed for analyses of ASD probands, ASD siblings, and control youth. Using a η^2_p effect size of 0.14 from the group × accuracy ERN interaction, significance level of 0.05, correlation among repeated measures estimated at 0.5, and power level of 0.9, we estimated a necessary sample size of 10 per group. Thus, our group membership was sufficiently powered based on our a priori power calculations.

Statistical Analysis

Statistical analyses were completed with both SPSS 22 (IBMCorp 2013) and STATA 13.1 (StataCorp 2013) analysis software. Symptom measures (e.g., AQ, SRS, BAPQ), behavioral data (i.e., response time and error rate), and ERP data were examined for outliers by group (ASD, control). Possible outliers were winsorized to 2.5 interquartile ranges from the median (Ratcliff 1993). RT data were log transformed due to negative skew and non-normal distribution as indicated by the Shapiro–Wilk test of normality. We calculated post-error slowing using a pairwise comparison of the trials before and after an error (average $RT_{post\text{-}error} - RT_{pre\text{-}error}$). We only included error trials in analyses that were preceded or followed by at least one correct response. We utilized this method in order to reduce confounding effects of fluctuations in performance due to changes in motivation or ability (van den Brink et al. 2014; Dutilh et al. 2012). There were no significant between-group differences on background noise estimates, number of trials retained for analysis, or number of trials corrected for ocular artifact (youth: $Fs < 0.77$, $p > .52$, adults: $Fs < 0.87$, $p > .36$; see Tables 1 and 2 for values).

Demographic Data

One-way ANOVAs were conducted separately for parents and youth to examine group differences in demographics. Significant ANOVAs were decomposed using the Tukey Honestly Significance test in order to maintain alpha levels while completing multiple comparisons.

ASD and Control Youth Group Comparisons

To initially examine differences between ASD probands and control youth (analyses did not include ASD siblings),

Table 1 ERP and behavioral summary data for adults

Measure	ASD fathers			ASD mothers			Control fathers			Control mothers		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
Age	42.50	4.73	37 to 51	40.00	4.12	34 to 49	44.37	6.56	36 to 56	41.83	5.46	33 to 51
Education	15.81	3.15	12 to 22	15.65	2.29	12 to 20	17.90	2.83	12 to 25	15.11	1.71	11 to 18
FSIQ	117.13	9.20	100 to 130	112.67	8.89	98 to 126	120.58	8.93	101 to 133	114.72	8.07	100 to 133
VIQ	110.67	8.65	95 to 125	108.22	10.81	92 to 127	116.79	10.53	93 to 131	111.67	8.12	98 to 133
PIQ	120.40	11.87	99 to 136	114.22	8.09	100 to 127	120.05	9.20	99 to 136	114.33	8.18	101 to 131
SRS-II	48.00	7.05	37 to 61	44.27	5.70	36 to 55	41.61	6.23	36 to 65	44.12	5.67	38 to 54
AQ	16.25	6.63	9 to 32	12.41	6.97	6 to 33	44.37	6.56	9 to 26	13.94	5.47	5 to 25
ERN	−2.24	3.40	−9.90 to 2.20	−2.32	2.93	−9.03 to 1.83	−1.99	2.32	−6.89 to 1.59	−1.55	2.25	−7.56 to 1.56
CRN	1.42	0.92	0.11 to 2.93	0.52	1.87	−4.65 to 3.85	1.42	1.50	−2.45 to 4.18	0.62	1.86	−2.27 to 4.48
Incongruent RT	483.02	45.06	409 to 585	467.58	39.22	393 to 562	480.62	29.61	423 to 527	476.09	33.34	412 to 540
Congruent RT	432.67	47.01	347 to 520	415.26	38.27	350 to 496	422.92	29.06	372 to 477	424.85	36.28	331 to 488
Incongruent error	0.25	0.14	0.05 to 0.57	0.20	0.12	0.50 to 0.39	0.20	0.11	0.08 to 0.51	0.19	0.10	0.04 to 0.33
Congruent error	0.08	0.07	0.00 to 0.23	0.06	0.04	0.01 to 0.16	0.06	0.05	0.01 to 0.25	0.06	0.05	0.00 to 0.22
Correct trials	388.00	89.79	214 to 524	452.06	51.17	342 to 542	441.21	69.91	287 to 541	428.11	69.91	287 to 541
Error trials	45.93	27.51	7 to 117	45.41	35.43	10 to 146	37.21	16.57	10 to 64	40.28	23.76	7 to 77
Post-error slowing	10.98	24.17	−23 to 71	16.68	13.06	−2 to 45	8.74	19.34	−26 to 43	15.38	22.95	−16 to 76

ERN error-related negativity, *CRN* correct-related negativity, *RT* response time

Table 2 ERP and behavioral summary data for youth

Measure	ASD probands			ASD siblings			Control youth		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
Age	13.50	1.38	11 to 16	12.13	1.93	10 to 16	12.66	2.16	10 to 17
FSIQ	105.72	15.79	76 to 140	113.19	11.68	79 to 128	111.84	9.06	86 to 132
VIQ	102.11	17.01	72 to 137	110.13	9.65	88 to 128	110.58	10.80	85 to 135
PIQ	108.61	13.53	86 to 133	114.19	14.81	76 to 136	110.87	9.63	91 to 129
ADOS-G	12.89	3.79	7 to 21	–	–	–	–	–	–
SCQ	18.67	6.62	7 to 34	2.77	2.28	0 to 7	3.34	2.32	0 to 8
SRS	77.56	8.52	63 to 98	48.33	11.36	38 to 72	45.24	6.33	37 to 64
AQ	–	–	–	10.08	6.91	0 to 25	11.97	5.13	3 to 30
ERN	−1.07	1.90	−3.46 to 2.24	−0.81	1.73	−3.42 to 2.02	−1.09	2.52	−6.80 to 3.65
CRN	0.58	1.89	−2.04 to 5.27	1.35	1.79	−1.73 to 3.97	0.89	2.00	−2.90 to 6.24
RT incongruent	445.16	33.65	372 to 509	454.70	32.78	396 to 520	460.06	41.06	357 to 524
RT congruent	419.28	32.22	357 to 464	427.90	34.22	383 to 493	422.07	40.84	301 to 493
Error incongruent	0.36	0.15	0.15 to 0.73	0.34	0.11	0.15 to 0.56	0.31	0.14	0.06 to 0.61
Error congruent	0.19	0.11	0.07 to 0.41	0.20	0.11	0.03 to 0.46	0.15	0.11	0.02 to 0.36
Correct trials	291.75	101.12	165 to 463	306.07	94.85	177 to 511	315.39	177.66	95 to 522
Error trials	70.69	46.43	18 to 162	65.00	24.41	24 to 116	56.78	31.07	11 to 135
Post-error slowing	3.17	18.06	−42 to 37	8.69	17.34	−24 to 49	12.18	18.31	−23 to 45

ERN error-related negativity, *CRN* correct-related negativity, *RT* response time

behavioral and electrophysiological data were examined using 2 group (ASD proband, control youth) × 2 accuracy (error, correct) or congruency (congruent, incongruent) robust ANOVAs, respectively. Robust ANOVAs calculated using the ERP PCA Toolkit included winsorized covariances, bootstrapping, and Welch–James approximate degrees of freedom to correct for outliers, non-normality, and heterogeneous error variance. For bootstrapping, the number of iterations was 50,000 and the seed for number generation was 1000. Post-error slowing and ΔERN were examined by group using independent samples t tests.

Family Comparisons

To examine differences between families of ASD probands and control families, separate linear regressions were conducted for the following dependent variables: SRS-II, AQ, incongruent error rates, incongruent RTs, and ΔERN. To capture the difference between error and correct trials and further isolate error-related activity, we calculated ΔERN scores by subtracting correct trial ERN from error trial ERN. To examine differences by group and determine the familial aggregation of a trait, we included group (ASD/ASD relative, control youth/relatives) and kinship (four factors: mother, father, sibling, proband), and a group × kinship interaction as independent variables in regressions (Lee et al. 2013). One control youth from each family was randomly selected as the "proband" and one as the "sibling" for regressions. Participants were dummy coded by group, with ASD participants/relatives as the reference, and kinship, with probands or mothers as the reference. Because participants were nested within families, we used robust standard errors (i.e., Huber–White sandwich estimator) to account for non-independence of residuals due to shared genetic and environmental effects (Lee et al. 2013; Ari and Güvenir 2002; Williams 2000). We also conducted zero-order correlations to examine relationships between incongruent error rates, incongruent RTs, post-error slowing, ΔERN, SRS-II total scores, SRS-II Social Communication and Interaction scores, SRS-II Restricted Interests and Repetitive Behavior scores, and AQ.

Results

Demographic Data

Demographic, IQ, and symptom measures are displayed in Tables 1 and 2. ASD probands and siblings and control probands and siblings did not significantly differ on age, $F(3,68) = 1.46$, $p = .23$, years of education, $F(3,62) = 0.56$, $p = .64$, FSIQ, VIQ, or PIQ, ($Fs < 2.13$, $ps > 0.11$).

Control and ASD parents did not significantly differ in age ($Fs < 2.11$, $ps > 0.11$) but did significantly differ in years of education, $F(3,66) = 4.31$, $p = .001$, with higher levels of education among control fathers relative to control mothers (mean difference = 2.78, Tukey HSD $p = .85$) and ASD mothers (mean difference = 2.25, Tukey HSD

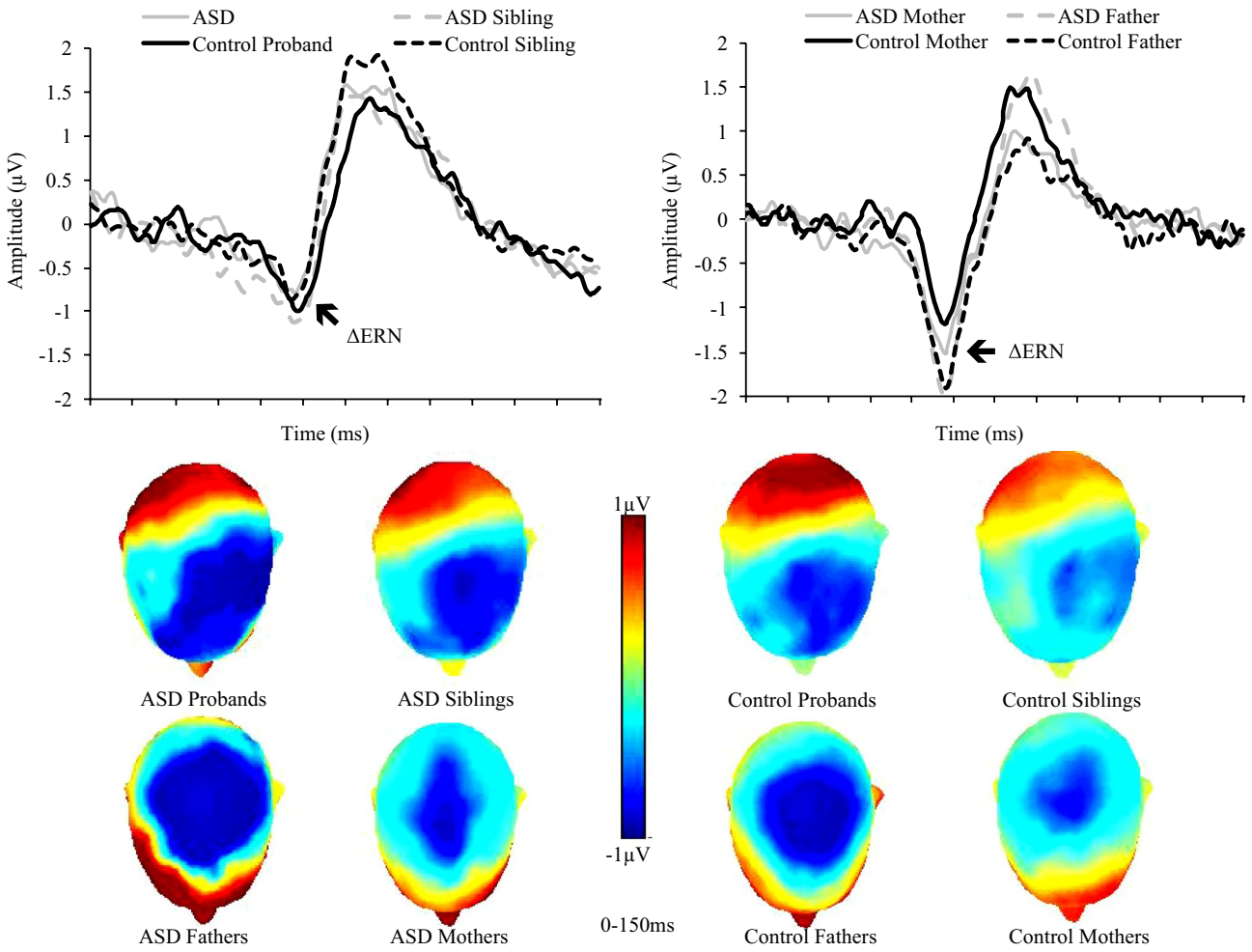


Fig. 2 ΔERN amplitudes and topographical maps by youth and adult groups. ΔERN amplitudes were averaged over electrodes FCz, 7, 106, Cz. Scalp maps represent the average from 0 to 150 ms

$p = .06$). There were no differences between ASD fathers and control fathers, control mothers, or ASD mothers or between ASD mothers and control mothers (mean difference > 0.17, Tukey HSD $p < 1.0$). Groups differed on FSIQ, $F(3,66) = 2.78$, $p = .05$, 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 (mean difference = 7.91, Tukey HSD $p = .04$) and VIQ scores (mean difference = 8.57, Tukey HSD $p = .04$) than ASD mothers. No other mean differences were significant for FSIQ or VIQ (mean difference > 0.17, Tukey HSD $ps < 1.0$).

ASD and Control Group Comparisons

ERN

See Fig. 2 for ERN difference waveforms and topographical maps. The group × accuracy robust ANOVA examining ERN amplitudes among ASD probands and control youth revealed a significant main effect of accuracy, with significantly more negative amplitudes on error trials relative to correct trials, $T_{WJt}/c(1.0, 29.4) = 59.86$, $p < .001$. The main effect of group was not significant, $T_{WJt}/c(1.0, 27.5) = 0.24$, $p = .63$. Importantly, the accuracy × group interaction was not significant, $T_{WJt}/c(1.0, 29.2) = 0.90$, $p = .35$, suggesting ASD probands and control youth did not demonstrate significant differences for the ERN. Similarly, there were no between-group differences for ΔERN amplitude, $t(50) = -0.71$, $p = .48$.

Behavioral Data

Analyses of behavioral performance among ASD probands relative to control youth similarly revealed no significant differences. 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

Table 3 Regression model for symptom measures

Variables	R^2	*p* value	*B*	Robust *SE*	*t* value	*p* value	VIF
DV: SRS-II	0.74	<0.01					
Group			−34.6	2.33	−14.86	<0.01	3.76
Kinship[a]: mothers			−33.3	2.37	−14.05	<0.01	3.04
Fathers			−29.56	2.59	−11.41	<0.01	3.22
Siblings			−29.23	4.74	−6.17	<0.01	3.51
Group × kinship[b]							
Control mothers			34.42	2.84	12.14	<0.01	3.46
Control fathers			27.87	2.91	9.56	<0.01	3.80
Control siblings			33.03	4.93	6.71	<0.01	4.25
DV: AQ	0.15	0.05					
Group			1.65	2.08	0.80	0.43	2.91
Kinship[c]: fathers			3.89	2.84	2.73	0.16	2.80
Siblings			−2.22	2.44	−0.91	0.37	3.04
Group × kinship[d]							
Control fathers			−0.26	3.33	−0.08	0.94	3.56
Control siblings			0.22	2.87	0.08	0.94	3.89

SE standard error, *VIF* variance inflation factor, *SRS* social responsiveness scale, *AQ* autism spectrum quotient

[a]Kinship includes comparisons to probands, siblings, mothers, and fathers

[b]Group × kinship includes comparisons to ASD probands, ASD siblings, ASD mothers, and ASD fathers

[c]Kinship includes comparisons to siblings, mothers, fathers

[d]Group × kinship includes comparisons to ASD siblings, mothers, and fathers

group × 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 × 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. There were no significant between-group differences in post-error slowing $t(54) = 1.73$, $p = .09$.

Family Comparisons

Symptom Measures

We utilized linear regressions with group (ASD/ASD relative, control) and kinship (mother, father, sibling, proband) to examine whether subthreshold symptoms of ASD, as measured by the SRS-II and AQ, differed based on kinship status among ASD probands and families compared to control families. The model examining differences based on SRS-II scores was significant (see Table 3). Group status 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 ASD probands. group × kinship interactions were significant (see Table 3 for statistical results). 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 control siblings. The model examining group and kinship differences in AQ scores was significant. However, no individual predictors or the interaction between kinship and group were significant for the AQ scores.

ΔERN

We next utilized linear regressions to examine group and kinship differences in ΔERN amplitudes. See Table 4 for regression findings and Fig. 2 for scalp maps and waveforms. The ΔERN model was not significant, $F(7,37) = 1.21$, $p = .32$. Group and kinship were not significant predictors and no interactions between kinship and group were significant.

Behavioral Data

See Fig. 3 for graphs depicting error rates and RTs and Table 5 for regression findings. Regression models examining differences between group and kinship for error rates and RTs were significant. Group was not a significant predictor and the group × kinship interaction was not significant for RTs or error rates. However, Kinship was

Table 4 Regression model for ERP measures

Variables	R^2	*p* value	*B*	Robust *SE*	*t* value	*p* value	VIF
DV: ΔERN	0.07	0.32					
Group			−0.31	0.31	−0.98	0.33	4.10
Kinship[a]: mothers			−0.32	0.28	−1.13	0.26	3.15
Fathers			−0.71	0.41	−1.72	0.09	3.29
Siblings			−0.17	0.22	−0.75	0.46	3.29
Group × Kinship[b]							
Control mothers			0.55	0.50	1.10	0.28	3.68
Control fathers			0.24	0.51	0.47	0.64	3.93
Control siblings			0.38	0.36	1.06	0.30	3.93
DV: ΔERN[c]	0.07	0.12					
SRS-II			0.004	0.008	0.65	0.52	1.32
Kinship[a]							
Mothers			0.03	0.32	0.08	0.94	1.83
Fathers			−0.56	0.29	−1.93	0.06	1.85
Siblings			0.09	0.22	0.04	0.69	1.69

SE standard error, *RT* response time, *ERN* error-related negativity, *VIF* variance inflation factor

[a]Kinship includes comparisons to probands, siblings, mothers, and fathers

[b]Group × Kinship includes comparisons to ASD probands, ASD siblings, ASD mothers, and ASD fathers

[c]Regression model for ERN analyses without group as a predictor

significant for error rates and RTs among mothers and fathers but not siblings. For post-error slowing, the overall regression model was not significant (see Table 5). However, Group and Kinship were significant predictors due to greater post-error slowing in control mothers. The group × kinship interaction was not significant.

Correlations

Zero-order correlations were conducted to examine relationships between electrophysiological and behavioral data. Incongruent RTs, incongruent error rates, and post-error slowing were significantly correlated with SRS-II scores. Higher SRS-II total scores, $r(127) = -0.20$, $p = .03$, and higher SRS-II Restricted Interests and Repetitive Behavior scores, $r(127) = -0.20$, $p = .02$, predicted lower RTs. Higher error rates were associated with higher SRS-II total scores, $r(127) = 0.29$, $p = .001$, higher SRS-II Social Communication and Interaction scores, $r(127) = 0.25$, $p = .005$, and higher SRS-II Restricted Interests and Repetitive Behavior scores, $r(127) = 0.21$, $p = .02$. For post-error slowing, reduced post-error slowing was significantly associated with higher SRS-II total scores, $r(127) = -0.23$, $p = .01$, higher SRS-II Social Communication and Interaction scores, $r(127) = -0.19$, $p = .03$, and approached significance for higher SRS-II Restricted Interests and Repetitive Behavior scores, $r(127) = -0.16$, $p = .06$. SRS-II total scores and all SRS-II subscale scores were not significantly related to ΔERN amplitudes ($ps > 0.26$).

Secondary Analyses

It is possible that including group as a predictor in regressions limited our ability to understand the relationship between ASD symptomology and ERN amplitude, as limiting analyses to current diagnostic definitions may reduce our ability to identify the influence of dimensional ASD symptoms on ERN amplitudes (Miller and Rockstroh 2013). Thus, we conducted regressions on ΔERN amplitudes as dependent variables without group as a predictor. Independent 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 4 for regression results. The model for ΔERN amplitudes was not significant, $F(4, 36) = 1.97$, $p = .12$, and explained 7% of the variance. Kinship and SRS-II were not significant predictors, $t(36) = -1.93$, $p = .06$. Thus, analyses without group as a predictor remained consistent with ΔERN analyses.

Discussion

We sought to identify whether the ERN qualifies as an endophenotype of ASD by comparing ERP and behavioral data among ASD probands and their families relative to control families. In contrast to our predictions and previous research (Sokhadze et al. 2010, 2012; South et al. 2010; Vlamings et al. 2008), we did not observe significant group differences in ERN amplitude when

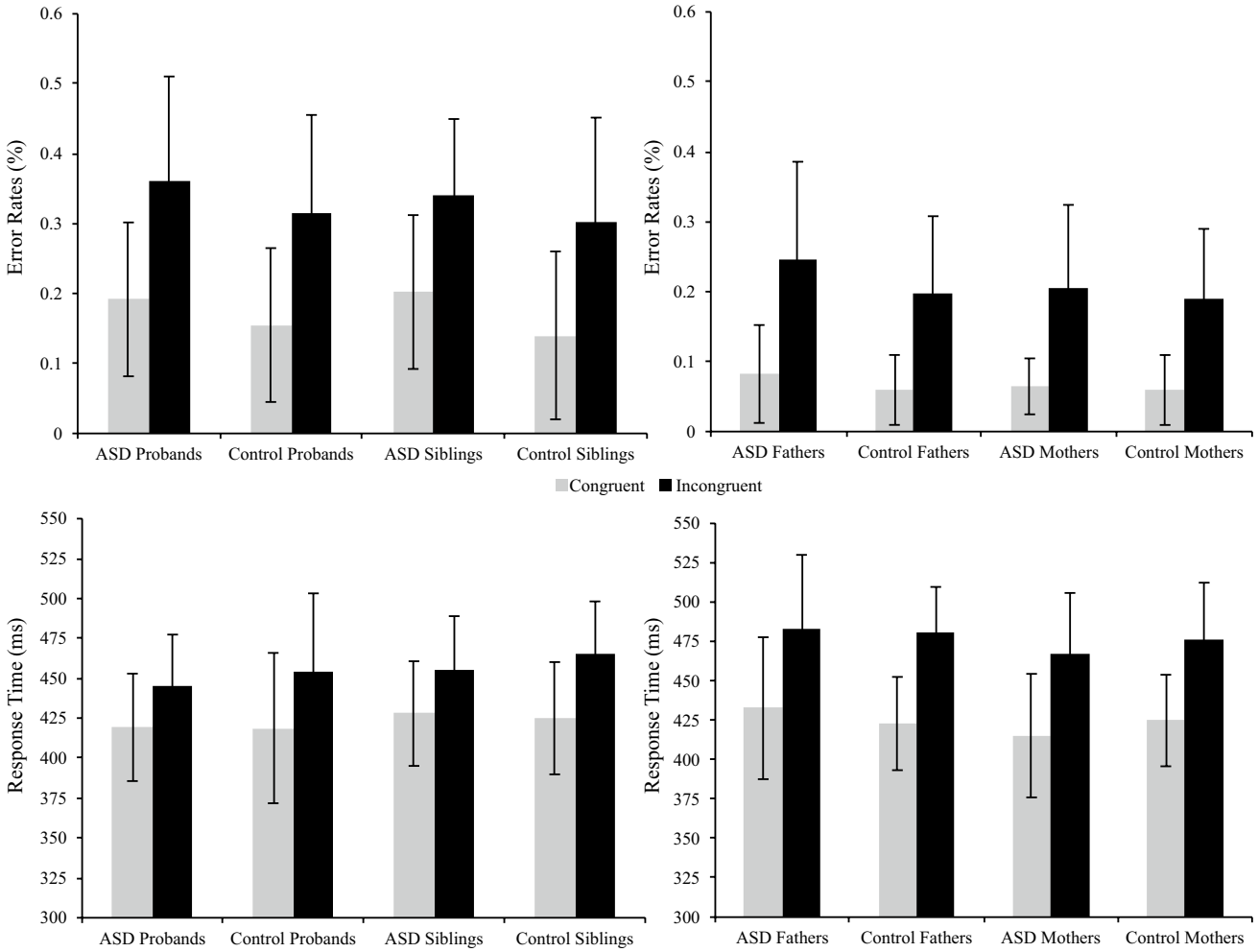


Fig. 3 Behavioral data as a function of group and trial type. Error bars represent the standard deviation

comparing ASD probands to control youth. These findings do not provide evidence that the ERN meets the first criteria as an endophenotype of ASD, as ERN amplitude differences were not associated with ASD and may not reflect underlying deficits in cognitive and neural development.

The current finding of no group differences in ERN amplitude adds to a mixed literature on ERN amplitudes and error processing in ASD. Whereas several studies reveal attenuated ERN amplitudes in ASD youth (Sokhadze et al. 2010, 2012; South et al. 2010; Vlamings et al. 2008) and adults (Santesso et al. 2011) relative to controls, two studies among youth with ASD reveal a lack of group differences in ERN amplitudes relative to control 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 controls (Henderson et al. 2006). While several studies point to ERN amplitude differences in ASD relative to controls, this pattern has not been replicated in all samples, including current data.

In order to test whether similar patterns of reduced neural differentiation between error and correct trials were also 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 effects of Kinship and shared genetics, group and Kinship did not significantly predict ΔERN amplitude. 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

Table 5 Regression model for behavioral measures

Variables	R^2	*p* value	*B*	Robust *SE*	*t* value	*p* value	VIF
DV: incongruent errors	0.21	<0.01					
Group			−0.045	0.05	−0.91	0.37	3.93
Kinship[a]: mothers			−0.156	0.03	−5.28	<0.01	2.99
Fathers			−0.115	0.04	−2.76	0.01	3.11
Siblings			−0.021	0.04	−0.52	0.61	3.22
Group × Kinship[b]							
Control mothers			0.031	0.05	0.61	0.54	3.49
Control fathers			−0.002	0.05	−0.06	0.96	3.72
Control siblings			0.007	0.06	0.11	0.91	3.91
DV: incongruent RTs	0.11	0.02					
Group			0.008	0.01	0.55	0.58	3.93
Kinship[a]: mothers			0.211	0.01	1.99	0.05	2.99
Fathers			0.035	0.01	2.62	0.01	3.11
Siblings			0.009	0.01	0.84	0.41	3.22
Group × Kinship[b]							
Control mothers			0.001	0.02	0.05	0.96	3.49
Control fathers			−0.009	0.02	−0.50	0.62	3.72
Control siblings			0.002	0.02	0.14	0.89	3.91
DV: post-error slowing	0.05	0.13					
Group			12.395	5.56	2.23	0.03	3.93
Kinship[a]: mothers			13.512	5.43	2.49	0.02	2.99
Fathers			7.808	8.23	0.94	0.35	3.11
Siblings			5.522	6.77	0.82	0.42	3.22
Group × Kinship[b]							
Control mothers			−13.695	8.28	−1.65	0.11	3.49
Control fathers			−14.629	10.42	−1.40	0.17	3.72
Control siblings			−11.942	8.72	−1.37	0.18	3.91

SE standard error, *RT* response time, *ERN* error-related negativity, *VIF* variance inflation factor

[a]Kinship includes comparisons to probands, siblings, mothers, and fathers

[b]Group × Kinship includes comparisons to ASD probands, ASD siblings, ASD mothers, and ASD fathers

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). It may be that overall symptom levels are less influential on ERN amplitudes than the specific nature of symptoms (e.g., social, communication, restricted/repetitive behavior) or pattern of symptom presentation (e.g., degree of social deficits relative to deficits in stereotyped behaviors).

Our findings do not provide evidence for the ERN as an endophenotype of ASD. The ERN was not significantly different between ASD probands and control youth, suggesting it may not meet the first criteria as an endophenotype. Also, the lack of differences in ASD probands relative to controls suggest that the ERN may 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 and Gottesman 2009). 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 and 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.

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 and Rockstroh 2013; Volkmar and 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 (Gould and Gottesman 2006). 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). 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 (Miller and Rockstroh 2013; Leung et al. 2015). 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.

Behavioral Performance

In contrast to our hypotheses, we did not observe significant differences in RTs or error rates when comparing ASD probands to controls. The lack of group differences in behavior is not surprising given the lack of group differences in ERP amplitudes, adding further support for overall intact performance monitoring processes in our sample of ASD youth relative to control youth.

In behavioral analyses accounting for family and kinship, we did not observe differences by group or in group × kinship interactions for RTs or error rates. For error rates and RTs, kinship was significant among parents, indicating that parents had significantly faster RTs and significantly reduced error rates, possibly due to greater neural maturity in adults resulting in more efficient information processing (e.g., Santesso et al. 2006). However, for post-error slowing, we observed differences due to significantly greater post-error slowing among control mothers relative to ASD mothers.

Although there were no overall group differences in behavioral performance, incongruent error rates and RTs and post-error slowing were significantly correlated with symptoms of ASD. Participants with more restricted and repetitive behaviors were less accurate, responded faster following errors, and trended toward reduced post-error slowing. Higher error rates and post-error slowing were also significantly correlated with higher symptoms of social communication and interaction. Although many studies have not observed group differences in accuracy or response time, several studies point to differences in post-error slowing among between ASD and controls (Sokhadze et al. 2010; South et al. 2010; Vlamings et al. 2008). It is possible that overall higher levels of rigidity may contribute to reduced flexibility and failure to appropriately modify behavior to meet task demands, representing poor executive and behavioral control (Sokhadze et al. 2010; Vlamings et al. 2008).

Future Directions

These findings have implications for a larger discussion of the ERN as an endophenotype (Olvet and Hajcak 2008). Most research on the ERN has explored the first criteria as an endophenotype, or whether the ERN is associated with particular diagnoses. Despite extensive research on the relationship between the ERN and state- and trait-related conditions (Olvet and Hajcak 2012; Clayson et al. 2012), there is considerable within-subject/between-subject variability, bringing into question the relationship between the ERN and psychopathology. Important questions must be addressed 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 how environmental factors mediate the relationship between ERN amplitude and symptoms.

Additional family studies are needed to reestablish the heritability of the ERN and determine whether altered ERN amplitudes co-occur with disorders in families or are present in the same form within families of affected individuals. Family studies are 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 and Gottesman 2009). This study is an important first step but additional research is necessary to understand the heritable nature of the ERN and determine the ways in

which ERN amplitudes signify links between genetics and symptoms.

Limitations

Several limitations should be considered. First, our study included relatively small groups for each cell during analyses, reducing our statistical power and suggesting that our small sample size may have contributed to our null findings. It is possible that statistical power is an issue with any null finding; however, our sample sizes for each group were at or above that estimated by a priori power analyses based on previous research examining the ERN in ASD. Further, results were also non-significant in secondary analyses in which group sizes were relatively larger ($n \geq 33$) due to examining data by kinship alone rather than group and kinship. Thus, although several indicators suggest our sample size was adequate, replication of this study in a larger sample is warranted.

Second, group differences were observed in education and IQ levels among parents. Group differences were primarily driven by higher levels of education among control fathers relative to control mothers and ASD mothers; no differences were observed among control fathers and ASD fathers. A large proportion of our control father sample included academic professors, likely inflating the education level of participants and suggesting that our population may not be representative of a community-based sample. Third, a large proportion of participants had comorbid psychological diagnoses and were taking psychotropic medications. Mental health concerns are common among ASD probands and relatives of individuals with ASD (Bolton et al. 1998; Howlin et al. 2015; Simonoff et al. 2008; Yirmiya and Shaked 2005), but it is possible that comorbid psychological diagnoses influenced group differences. There is also some evidence that medications may influence ERN amplitudes (Groen et al. 2008). 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.

Fourth, our sample of ASD probands had IQs in the average to above-average ranges and may not be representative of the overall ASD population. Regression analyses examining group and kinship differences on the AQ were not significant, also suggesting that relatives of ASD probands included in the current study may not have displayed heightened levels of the broader autism phenotype. However, in regressions examining SRS-II scores we observed significantly higher levels of ASD symptoms among ASD probands/relatives compared to controls. Lower levels of ASD symptoms in relatives may reflect measurement error, as the AQ involved self-report ratings, while SRS-II involved spouse-report ratings. Also, the SRS may be more sensitive to general psychopathology than the AQ (Ingersoll et al. 2011). The discrepancy between SRS-II and AQ scores may reflect greater levels of pathology in ASD relatives rather than greater ASD symptom severity.

Finally, our sample only included male youth, limiting the generalizability of our findings to the entire ASD population that includes females. Current research points to potential sex differences in ASD symptom presentation and cognitive functioning, suggesting that the current findings may differ among females with ASD. 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 et al. 2011; Larson et al. 2011; Moser et al. 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 et al. 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 and Jones 1998), pointing to possible differences based on the sibling sex that we were not able to evaluate in the current study. In the future, it will be important to examine the ERN among family members of female probands or among female siblings in order to determine whether sex differences influence ERN amplitudes or the relationship between ERN amplitude and symptom severity.

Conclusion

We examined the ERN in biological families of individuals with ASD, permitting an examination of the role of heritability and kinship. Error-related negativity amplitudes among youth with ASD were not significantly different from control youth, and group and kinship did not predict ΔERN amplitudes. We did not find support for the ERN as an endophenotype or biomarker of ASD. 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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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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