

DR. SO HYUN KIM (Orcid ID : 0000-0003-4269-0866)

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Stimulus processing and error monitoring in more-able kindergarteners with Autism Spectrum Disorder (ASD): A short review and a preliminary ERP study

So Hyun Kim<sup>1</sup>, Jennie Grammer<sup>2</sup>, Nurit Benrey<sup>1</sup>, Frederick Morrison<sup>3</sup>, Catherine Lord<sup>1</sup>

<sup>1</sup>Weill Cornell Medicine, Center of Autism and Developing Brain, 21 Bloomingdale Rd, White Plains, NY, USA

<sup>2</sup>University of California Los Angeles, Graduate School of Education and Information Studies, Los Angeles, CA, USA

<sup>3</sup>University of Michigan, Department of Psychology, Ann Arbor, MI, USA

Corresponding Author: So Hyun (Sophy) Kim, Weill Cornell Medicine, Center for Autism and the Developing Brain (CADB), 21 Bloomingdale Rd, White Plains, NY 1060, T: 914-997-5269 F: 914-997-5535, sok2015@med.cornell.edu

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## Abstract

Deficits in executive functions (EF) in individuals with autism spectrum disorder (ASD) have been identified. However, there is limited evidence about patterns of deficits in EF-related skills, especially at the neurobiological level, in young children with ASD and little is known about how these skills are related to other domains of functioning and symptom severity. In this study, we provide a focused review of EF-related Event-Related Potentials (ERP) studies in children with ASD, accompanied by preliminary data for neurophysiological correlates of EF on a child-friendly Go/No-go task. We focus our preliminary investigation on ERPs associated with stimulus processing (N2, P3) and error monitoring (error/correct-related negativity [ERN, CRN], error positivity [Pe]) in 5-year-old kindergarteners with ASD and typical controls matched on age, gender, and task accuracy. Children with ASD showed significantly greater amplitudes of ERN/CRN compared to matched controls, suggesting heightened response monitoring. The ASD group also showed less distinct inhibitory P3 compared to the TD group, potentially suggesting atypical stimulus processing. In children with ASD, higher autism symptom severity was correlated with larger P3. **Better behavioral performance on an EF-related task was correlated with smaller CRN.** Our study is the first investigation to demonstrate the presence of N2, P3, ERN/CRN and Pe in kindergarteners with ASD. The potential links between ERP patterns and behavioral and clinical features in more-able children with ASD highlight the need for further exploration into the functional mechanisms of these atypical neural activities and for more focused behavioral interventions targeting cognitive control and response monitoring.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, characterized by impairments in social communication and the presence of restricted and repetitive interests and behaviors (American Psychiatric Association, 2013). Studies have identified deficits in executive functions in preschoolers, children, and adults with ASD

(Hill, 2004). Executive functions (EF) include skills such as attention control, response inhibition, and working memory, that regulate goal-directed behavior. Studies based on typically developing children have shown evidence for an association between children's EF and other neurobehavioral and clinical features such as academic achievement (Burrage *et al.*, 2008; Brock *et al.*, 2009; Willoughby *et al.*, 2012), externalizing and internalizing problems (Riggs *et al.*, 2004; Hughes & Ensor, 2011), and social emotional development (Riggs *et al.*, 2006). Although there has been increasing interest in the importance of EF for children with ASD, less is known about brain and behavioral correlates of EF skills – including inhibitory control or self-monitoring. Thus, associations between EF and abilities in children with ASD in other important domains of functioning, including academic and cognitive abilities and autism symptoms, have yet to be fully elucidated. The present study aims to review the current literature on EF-related ERPs in children with ASD and to examine the electrophysiological correlates of EF and their associations with other behavioral and clinical features in a preliminary sample of kindergartners with ASD and matched controls.

### Electrophysiological Correlates of EF

In an effort to examine the neural correlates of children's EF skills, studies have focused on changes in ERP components that reflect a network of structures, including the anterior cingulate cortex (ACC) and the lateral prefrontal cortex, involved in detecting response conflict and attention control. The ACC has been implicated in cognitive control functions, which are thought to enable the brain to adapt behavior to changing task demands and environmental circumstances (Botvinick *et al.*, 2004). In addition to functional and structural abnormalities in the ACC (Mundy, 2003; Thakkar *et al.*, 2008; Santesso *et al.*, 2011), abnormal ACC activation has been found during a range of cognitive tasks in ASD. This abnormal activation has been associated with symptoms of ASD including social impairment (Haznedar *et al.*, 2000; Kennedy *et al.*, 2006) and restricted and repetitive behaviors (Shafritz *et al.*, 2008). Thus, it is possible that response monitoring may be impaired in individuals with ASD such that they may show difficulties in evaluating behavior and its consequences to determine whether or

not current strategies should be maintained. This, in turn, contributes to symptoms such as behavioral rigidity (Thakkar *et al.*, 2008). Therefore, it has been hypothesized that individuals with ASD would show abnormal patterns of brain activities related to stimulus processing and response monitoring.

### Stimulus Processing

Researchers interested in children's EF have focused on two stimulus-locked ERPs, the N2 and P3, observed when participants process stimuli that reflect conflicting demands (e.g., Pliszka *et al.*, 2000; Donkers & van Boxtel, 2004; Smith *et al.*, 2004; Cragg *et al.*, 2009; Nieuwenhuis *et al.*, 2003). These stimulus-locked ERPs have been believed to reflect cognitive control, such as strategic monitoring (e.g., "How fast should I be responding?") and control of motor responses (Folstein & Van Petten, 2008). The N2 is a negative deflection seen in the frontal electrodes peaking around 200 ms to 400 ms after a stimulus is presented. The amplitudes of N2 tend to increase in no-go trials, thus the N2 is often seen to reflect the detection of response conflict and inhibition (Pliszka *et al.*, 2000; Donkers & van Boxtel, 2004; Smith *et al.*, 2004; Cragg *et al.*, 2009; Nieuwenhuis *et al.*, 2003).

In contrast, the P3 is a positive waveform that occurs about 300 to 500 ms after a stimulus is presented, and is observed in the frontal and posterior electrodes (Munro *et al.*, 2007; Maguire *et al.*, 2009). P3 amplitudes are larger in response to no-go versus go trials, suggesting that P3 may also be related to the processes engaged in response inhibition (Munro *et al.*, 2007; Maguire *et al.*, 2009). It has been suggested that though P3 is different from N2 because no-go P3 may reflect differences in stimulus frequency or "relative novelty" (Lavric *et al.*, 2004).

Although N2 and P3 have been consistently detected in typically developing adults (Dimoska *et al.*, 2006; Maguire *et al.*, 2009; Karch *et al.*, 2010; Smith *et al.*, 2010; Gajewski & Falkenstein, 2013), fewer studies have systematically examined these components in young children. However, recent evidence indicates that they can be elicited in typically developing children as young as 4 years as well as older children and adolescents with ASD or attention deficits and hyperactivity disorder (ADHD) (Ciesielski *et al.*, 2004; Groen *et al.*, 2008; Albrecht *et al.*, 2010; Barry & De Blasio,

2015). In addition, links between higher P3 amplitudes and more advanced academic skills in 8-9 year old typically developing children have been reported (Hillman *et al.*, 2012).

Studies focused on N2 and P3 in individuals with ASD are still relatively rare, and results suggest that the differences in the ERP patterns between ASD and typical controls may vary by task paradigm (visual vs. auditory) and developmental level (adults vs. children). P3 amplitudes were smaller in adults with ASD during both visual and auditory tasks (Courchesne *et al.*, 1989) and in children with ASD as young as 8 years during auditory tasks (Dawson *et al.*, 1988; Lincoln *et al.*, 1993) compared to typical controls. However, other studies showed the opposite, suggesting that children with ASD as young as 9 years might have exaggerated P3 compared to typical peers during visual tasks (Kemner *et al.*, 1994; Sokhadze *et al.*, 2012). No significant differences in N2 amplitudes between ASD and TD groups were found in these studies, but a recent study showed that 7 to 11-year-old children with ASD had larger N2 during a flanker task compared to matched controls, suggesting that children with ASD may recruit more neural resources relative to typical peers when inhibiting conflicting information (Faja *et al.*, 2016). These findings suggest that young children with ASD show enhanced N2 and/or P3 amplitudes based on a visual ERP task. However, because all of the past studies were focused on older school-age children and adults with ASD, it was not clear whether similar patterns of differences in N2 and P3 could emerge for kindergartners with ASD.

### Response Monitoring

The ERN is a response-locked medial-frontal negativity that occurs about 50 to 100 ms after the commission of an error (Grammer *et al.*, 2014). Researchers have also identified a smaller negativity, the Correct-Response Negativity (CRN), a response-locked component observed on correct trials at the same latency as the ERN (Gehring *et al.*, 2012). Although debate exists regarding the functional significance of the ERN, studies have shown that the ERN is involved in signaling and implementing cognitive control by indicating situations in which conflict arises (Frank *et al.*, 2005; Luck & Kappenman, 2011; Larson *et al.*, 2014). Although the cognitive process linked to CRN

is less clear, recent findings indicate that CRN may reflect an evaluation of adaptive versus maladaptive response strategies on correct trials (Bartholow *et al.*, 2005). **Some research also indicates that the CRN is larger for correct trials that are perceived as incorrect, and thus are linked to overactive performance monitoring in clinical populations with anxiety disorders (Hajcak & Simons, 2002).**

The Pe is a posterior positivity that follows the ERN and typically occurs about 200 to 500 ms after a mistake has been made. Although the functional significance of the Pe is still under investigation, unlike the ERN, the Pe is thought to be related to an individual's awareness of mistakes (Hajcak *et al.*, 2003; Schneider, 2010; Gehring *et al.*, 2012). Moreover, the Pe has been linked to motivational processes (Kim *et al.*, 2017) and academic skills in early childhood (Kim *et al.*, 2016a).

In contrast to the extensive literature in adult populations (for a review, see Gehring *et al.*, 2012), much less is known about the ERN, CRN, and Pe in children. However, using child-friendly tasks, ERN, CRN, and/or Pe have been detected in typically developing children as young as 3 years and older children with ASD and other disorders in a few studies (Henderson *et al.*, 2006; Groen *et al.*, 2008; Grammer *et al.*, 2014).

Variable patterns of abnormal response monitoring evidenced in electrophysiological data have been documented in individuals with ASD, exclusively during school-age or adulthood. Similar to the findings on N2 and P3, the effect of ASD diagnosis on the variability of these response monitoring ERP patterns may be mediated by the task (auditory vs. visual, flanker vs. decision task) and the participant's developmental (adult vs. child) as well as cognitive levels (average vs. below average IQ). For instance, some studies based on children and adults with ASD who had a wide range of cognitive abilities have shown decreased ERN and/or Pe amplitudes compared to typical controls based on auditory and visual flanker and discrimination tasks (Vlamings *et al.*, 2008; South *et al.*, 2010; Santesso *et al.*, 2011). However, another study based on more-able children with ASD with a verbal IQ >103 showed larger ERN elicited in response to errors on a Flanker task compared to controls (Henderson *et al.*, 2006). Based on this, it can be expected that for more-able children with ASD, ERN amplitudes may be enhanced compared to matched controls based on a visual ERP

task. Furthermore, larger ERNs in more-able school-age children with ASD were associated with fewer symptoms of social impairment and lower anxiety levels (Henderson *et al.*, 2006); surprisingly, associations with behavioral and clinical features are not yet known in young children with ASD under 8-10 years.

### The Preliminary Study

Given the limited and inconsistent findings in previous research, we focused our efforts on three aims in this preliminary study: 1) to examine whether a recently developed and validated Go/No-go task (Grammer *et al.*, 2014) can elicit N2, P3, ERN/CRN and Pe in kindergartens with ASD and typically developing (TD) children matched on age, gender, and task accuracy, 2) to compare the ERP patterns between the ASD and TD groups, and 3) to examine the relations between the neurocognitive correlates of cognitive control and error processing and patterns of behavioral functioning in the ASD group.

Based on recent literature, we expected that the use of a child-friendly Go/No-go task would enable us to successfully elicit our target ERP components in kindergarteners with ASD and matched controls as they were effectively elicited by the same task in typically developing kindergarteners and preschoolers (Grammer *et al.*, 2014). We also hypothesized that N2, P3 and ERN/CRN amplitudes would be larger in the ASD compared to the TD group, given the findings that showed enhanced N2 (Faja *et al.*, 2016), P3 (Kemner *et al.*, 1994; Sokhadze *et al.*, 2012b) and ERN (Henderson *et al.*, 2006) in more able children with ASD using visual ERP tasks. Along this line, we expected larger amplitudes in these components to be associated with higher autism symptom severity. Finally, we hypothesized that larger Pe and ERN amplitudes would be associated with more advanced academic skills, consistent with findings based on TD children (Grammer *et al.*, 2014; Kim *et al.*, 2016).

## Methods

### Participants

Eligible participants included 9 kindergartners with ASD and 95 typically developing (TD) children. Based on a propensity score matching analysis (see Statistical Analyses for more details), 18 typically developing children (with 2 TD cases for each ASD case on age, gender, and error rates on the go/no-go task; 17 boys) were selected to be matched with 9 ASD cases (8 boys). Participants were recruited from urban and suburban areas in New York and Michigan, with 50% and 77% of the families describing their race as Caucasian for the ASD and TD groups respectively. Both groups showed comparable age ( $M=5$  years,  $SD=0.3$ ) and gender ratio (See Table 1). Although children were not statistically matched on achievement scores, we compared scores on the Woodcock-Johnson (Woodcock, McGrew, Mather, & Schrank, 2001) for the ASD and TD groups. Children with ASD performed significantly higher on the Letter-Word Identification test ( $t(27)=2.255$ ,  $p=0.047$ ), but the two groups obtained comparable scores on Applied Problems.

All of the children with ASD were from a public school integrated program (general education classrooms) for more-able children with ASD. Criteria for this program included average to above average IQ scores based on Stanford Binet Intelligence Scale (Thorndike, Hagan, & Sattler, 1986; with full-scale IQ scores of at least 85) and a community diagnosis of ASD as well as a confirmed classification on the gold-standard diagnostic measure, the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) although the scores and the protocols were not available to the research team. Parents and teachers of these children did not report any current concerns for language or cognitive delays. All families consented to participate in the study approved by the Institutional Review Boards (IRB) at Weill Cornell Medicine, the University of Michigan, or Albert Einstein Medical School in compliance with the World Medical Association Declaration of Helsinki.

#### ERP Task

A child-friendly Go/No-go task (Grammer et al., 2014; McDermott et al., under review) was used for all children. In this task, called the Zoo Game, children are told that they are playing a game to help a zookeeper. The children are asked to help the zookeeper catch all the animals loose in the zoo except for three friendly orangutans



who are helping the zookeeper. Therefore, children are asked to press a button as quickly **as possible** when they see an animal (go trials) but inhibit their responses when they see an orangutan (no-go trials).

A child starts the game with a practice block of 12 trials (9 animals and 3 orangutans) followed by 8 blocks of the task, each with 40 trials, with a total of 320 trials (240 Go and 80 No-go trials). Each image was preceded by a fixation cross displayed for a randomized interval ranging from 200 to 300 ms. The stimuli were presented for 750 ms, followed by a blank screen for 500 ms. Responses could be made while the stimulus was on the screen or at any point during the following 500 ms. Each block consisted of novel sets of animal photographs, and each set was balanced with respect to color, animal type and size. Children were given performance feedback of either “Try to catch them even faster next time!” or “Watch out for the orangutan friends!” after each block of the task. These prompts were given to the children based on the calculation of the error rates at approximately 10% to ensure an adequate number of trials for stable error-related waveforms. Children were allowed to have “Wiggle Time” between blocks. The values reflecting percent error and percent correct on the ERP task were calculated as a function of the number of accurate or inaccurate responses for each of the go and no-go trials separately. Because we were only able to examine ERPs linked to responses of commission, we calculated performance on error trials of commission and accurate responses separately out of the total possible given the number of trials within the task.

#### Electrophysiological recording, data reduction, and data processing

The EEG was recorded using a BioSemi ActiveTwo system from DC-104Hz with 32Ag/AgCl scalp electrodes, two mastoid electrodes, and two vertical and two horizontal electro-oculogram electrodes. Data recording was referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode. Data were digitized at 512 Hz and resampled offline at 256 Hz. EEG data were screened based on automated algorithms that rejected individual sweeps in which 1) the absolute voltage range for any individual electrode exceeded 500  $\mu\text{V}$  (to keep the trials with EOG blinks and eye movements that could be corrected by subsequent

ocular movement correction), 2) a change greater than 50  $\mu\text{V}$  was measured from one datapoint to the next, or 3) the data deviated by more than +25 or -100 dB in the 20-40 Hz frequency window (for muscle artifacts). After screening data with visual inspection, ocular movement artifacts were corrected using the standard algorithm (Gratton *et al.*, 1983). Waveforms were filtered with a nine-point Chebyshev II low-pass, zero-phase-shift digital filter (MATLAB, 2010), with a half-amplitude cutoff at approximately 24 Hz.

#### ERP measures

Based on visual inspection of the grand ERPs and previous studies with young children, stimulus-locked N2, P3 and response-locked ERN, CRN, and Pe were quantified using mean amplitude measures relative to a pre-stimulus/response baseline of -200 to -100 ms along the midline (FCz, Cz, and Pz). The mean N2 amplitude was computed on go and no-go trials in a window from 100 to 200 ms from the onset of the stimulus. The mean P3 amplitude was computed on the same trials in a window from 250-350 ms. The difference between amplitudes on go relative to no-go trials ( $\Delta\text{N2}$  and P3) was also calculated by subtracting the go waveforms from the no-go waveforms (No-go – Go). The mean ERN amplitude was computed on incorrect-response trials in a window from 0 to 50 ms following the response. The CRN consisted of the same measure computed on correct response trials. The difference between ERN and CRN ( $\Delta\text{ERN}$ ) was also calculated by subtracting the CRN from the ERN waveforms (ERN - CRN). The Pe was computed on incorrect and correct response trials in a window from 200 to 500 ms. A difference score on Pe ( $\Delta\text{Pe}$ ) was also calculated similarly (Pe error trials – Pe correct trials).

#### Behavioral and clinical measures

For children with ASD, because we were interested in the associations between ERP components and other behaviors (EF, autism symptom severity, achievement), several behavioral measures were used.

#### Executive functions

In addition to the ERP task targeting inhibitory control, EF was assessed using 3 subsets from a computerized battery that measured different components of executive functions: response inhibition, working memory, and attention shifting (Willoughby *et al.*, 2012). The Spatial Conflict Arrows (SCA) task was used to measure inhibitory control. In this task, arrows appear above two side-by-side circles on either side of the screen. The arrows that appear can point to any side, and the participants have to press the button based on the direction in which the arrow is pointing. The Pick the Picture (PTP) task was used to measure working memory. In this task, the participant begins by selecting a picture from the two pictures that appeared on the screen. Then the same pictures appear on the screen, in a different order, and the participant must choose the same picture they had previously selected. The Something's the Same (STS) task is used to measure attention shifting. For this task, the experiment begins by highlighting the different qualities each picture has: color, size, and shape. The participants are asked to select pictures that share different qualities. We report the proportions of correct responses for these tasks. The psychometric properties on the EF tasks based on a large sample of preschool children ( $n=1,292$ ) were strong with moderate to high reliability and criterion validity (Willoughby *et al.*, 2012).

#### Academic achievement

The Woodcock Johnson (WJ; Woodcock *et al.*, 2001) achievement test was administered to all children with ASD as well as typical controls. We utilized two subtests to measure different levels of academic achievement. The Letter-Word Identification task measures the participants' reading and writing ability by requiring them to identify different letters. The Applied Problems task measures the participants' quantitative ability by requiring them to solve written mathematical problems.

#### Autism symptom severity

Three parent questionnaires were used to measure autism symptom severity for the children with ASD. The Social Communication Questionnaire (SCQ; Rutter *et al.*, 2003) was used to examine levels of social communication impairments and restricted and repetitive interests and behaviors. The Repetitive Behavior Scale- Revised (RBS-R;

Lam & Aman, 2007) was used to measure the frequency and intensity of repetitive behaviors. The Pervasive Problems domain from the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) was also used to determine the level of social communication impairments and other ASD-related behaviors.

### Statistical Analysis

Propensity score matching based on a randomized nearest neighbor approach was used to match ASD to TD cases at a 1:2 ratio based on gender and error rates on Go/No-go task based on 9 ASD cases and 95 TD cases. Out of 95 TD children, 63 children were within the age range comparable to the ASD cases (5-6 years) who were included in the propensity matching analysis. The 1:2 ratio was used instead of 1:1 ratio to maximize the utility of the dataset of TD children. The fit of the model significantly declined for 1:3+ ratio. All ERP components were examined using three-way (trial [go vs. no-go] for N2 and P3 and accuracy [error vs. correct] for ERN and Pe, site [FCz, Cz, vs. Pz] and diagnosis [ASD vs. TD]). ERP amplitudes were further compared through the use of t-tests. The relations between behavioral performance on the task as well as other behavioral and symptom measures and ERP amplitudes were explored through both parametric (Pearson [ $r$ ]) and non-parametric (Spearman [ $r_s$ ]) correlations. Given the small sample size, we present results based on both correlation analyses and point out the data that are significant by both analyses. All analyses were conducted on SPSS.

### Results

Even after the ASD and TD groups were matched on age, gender and the error rates, the ASD group showed higher error rates (23%) compared to the TD group (15%) although the difference was not statistically significant given the large variance in the error rates in the ASD group ( $SD=13$ ). Mean reaction times were not significantly different between the two groups. Both groups had a sufficient number of usable error trials post processing (range 5-59) of the ERP data.

The presence of N2, P3, ERN/CRN and Pe in ASD and matched controls

## N2

The response-locked waveforms at electrode sites along the midline at FCz, Cz, and Pz can be seen in Figure 1. Average amplitudes for the go and no-go trials, as well as the difference between them, can be seen in Table 2. Visual inspection of the waveforms revealed a negative deflection around 100 to 200 ms (N2) after the stimulus for the no-go trials for both ASD and TD groups. A three-way Repeated Measures (RM) ANOVA showed main effects of greater negativity on no-go trials ( $F(1,25)=5.519$ ,  $p=0.027$ ) and fronto-central sites (FCz) ( $F(2,24)=4.704$ ,  $p=0.039$ ) across ASD and TD groups. Examining the amplitudes of the ASD group, paired sample t-tests revealed significantly more negative amplitudes at FCz and Cz than at Pz for no-go trials ( $t(9)=2.167$ ,  $p=.024$  for FCz,  $t(9)=2.299$ ,  $p=.027$  for Cz). Similarly, for the TD group only, the mean amplitudes at FCz were significantly more negative than the amplitude at Pz for no-go trials ( $t(18)=1.769$   $p=0.048$ ). These results indicate that N2 was successfully elicited by the Go/No-Go task; more strongly for no-go versus go trials, at the fronto-central compared to the posterior sites, for both ASD and TD groups.

## P3

Examination of Figure 1 also revealed the presence of P3 at Pz for both ASD and TD groups to be relatively more pronounced on no-go trials compared to go trials. The RM ANOVA showed main effects of greater positivity on no-go trials ( $F(1,25)=29.368$ ,  $p=0.001$ ) and the posterior sites ( $F(2,24)=16.881$ ,  $p=0.001$ ) across ASD and TD groups. When the amplitudes among the three different sites were examined separately for the ASD group only, paired sample t-tests revealed that the mean amplitude at Pz was significantly more positive than the amplitude at FCz and Cz for no-go trials ( $t(9)=4.598$ ,  $p=0.001$  for FCz,  $t(9)=3.709$ ,  $p=0.002$  for Cz). Similarly, the mean amplitude at Pz for the TD group was significantly more positive than the amplitude at FCz and Cz for no-go trials ( $t(9)=2.868$ ,  $p=.006$  for FCz,  $t(9)=2.258$ ,  $p=0.018$  for Cz). These results indicate that P3 can be observed validly in kindergarteners with ASD and typical

controls, stronger for no-go versus go trials at the posterior compared to fronto-central sites.

#### ERN/CRN

As shown in Figure 2, a negative deflection around the time of error commission relative to correct responses was observed both for ASD and TD children for the frontal sites, Cz and FCz. Average amplitudes for the error and correct trials, as well as the difference between them, can be seen in Table 2. A three-way RM ANOVA revealed a significant main effect of greater negativity on error trials ( $F(1,25)=6.180$ ,  $p=0.020$ ) and a marginal effect of greater negativity at the fronto-central sites (FCz) ( $F(2,24)=3.755$ ,  $p=0.050$ ) across ASD and TD groups. An interaction of site and trial accuracy also emerged; the difference between the correct and error trials was significantly larger for Cz than the other two sites ( $F(2,24)=10.680$ ,  $p=0.001$ ) across ASD and TD groups. For ASD group only, mean amplitude for error trials at Cz was significantly more negative than for correct trials ( $t(9)=2.352$ ,  $p=0.021$ ). For TD group only, mean amplitude for error trials at Cz was also significantly more negative than for correct trials ( $t(18)=-1.96$ ,  $p=0.029$ ). The same pattern of findings emerged for the analyses of FCz. These results indicate the presence of the ERN and CRN, with the ERN amplitudes stronger than CRN at the fronto-central compared to posterior sites for both ASD and TD groups combined.

#### Pe

Examination of Figure 2 also revealed the presence of the Pe at Pz for both ASD and TD groups in contrast to frontal sites, located posteriorly along the midline. The results from the RM ANOVA showed a significant main effect of site, suggesting that there was greater positivity at posterior sites across both error and correct trials ( $F(2,24)=6.081$ ,  $p=0.009$ ). A main effect of trial accuracy also emerged with greater positivity observed on error trials relative to correct trials ( $F(1,25)=18.512$ ,  $p=0.001$ ). A significant interaction of site and trial was also found, suggesting that the differences between the correct and error trials was significantly greater at posterior (Pe) relative to frontal sites (Cz and FCz) on error trials ( $F(2,24)=17.311$ ,  $p=0.001$ ). No significant

difference in amplitudes emerged among sites when they were compared for the ASD group only, but paired sample t-tests revealed that Pz amplitudes for error trials were significantly more positive than correct trials ( $t(9) = 2.697$ ,  $p = 0.024$ ). Similarly, for TD group only, Pz amplitudes for error trials were significantly more positive than correct trials ( $t(18) = 3.305$ ,  $p = 0.029$ ). These results indicate that Pe can be observed during the Go/No-Go task for both the ASD and TD groups, stronger for error versus correct trials at the posterior compared to fronto-central sites.

#### Comparison of ASD vs. TD groups on the ERP amplitudes

No diagnostic difference emerged for the N2 amplitudes. For P3, an interaction effect from the RM ANOVA model emerged between trial and diagnosis ( $F(1,25) = 16.881$ ,  $p = 0.017$ ); TD children showed larger differences in amplitudes between go vs. no-go trials compared to the ASD group (e.g., Pz  $\Delta P3$  M=4.2, SD=3.9 for TD; M=2.7, SD=3.2 for ASD). **For ERN/CRN, the RM ANOVA showed a significant interaction effect of site and diagnosis ( $F(1,25) = 16.881$ ,  $p = 0.036$ ). For instance, the difference between ASD and TD in ERN/CRN amplitudes (ASD > TD) were larger for Cz and/or FCz than for Pz (see Table 2). In addition, children with ASD showed significantly larger ERN and CRN across all sites compared to TD children ( $t(25) = 2.652$ ,  $p = 0.009$  for ERN,  $t(25) = 8.527$ ,  $p = 0.001$  for CRN).**

#### Associations between ERP components and other behaviors for children with ASD

Table 2 and 3 show the mean scores on the instruments used to examine the levels of functioning in a variety of domains of cognitive and achievement skills and symptoms of ASD. The results from the computerized tasks showed that the mean proportions of correct responses ranged from 78 to 90% depending on the domain. The mean levels of autism symptom severity on three different measures, SCQ, RBS-R, and CBCL Pervasive Problems domain were clinically elevated based on the cutoffs suggested by the authors.

### Executive functions

Both parametric and non-parametric correlations were significant for the association between lower accuracy (higher error rates) on the zoo task and larger Cz CRN ( $r=.73$ ,  $p=0.027$ ;  $r_s=.77$ ,  $p=0.016$ ) in children with ASD. The other correlations were only significant for one of the methods. Higher accuracy (a lower error rate) on the zoo task was correlated with a larger difference between error and correct trials for posterior Pe amplitudes ( $r_s=-.77$ ,  $p=0.016$ ) and a larger difference in P3 between go and no-go trials ( $r_s=-.73$ ,  $p=0.025$ ). Higher accuracy rates on one of the computerized EF tasks, Spatial Conflict Arrows, were also correlated with larger posterior P3 amplitudes during go trials ( $r=.68$ ,  $p=0.048$ ), smaller N2 for the go trials ( $r_s=-.78$ ,  $p=0.013$ ) and a larger difference between go and no-go trials for N2 ( $r_s=.71$ ,  $p=0.031$ ). All p's were less than 0.05.

### Academic achievement

ERP amplitudes were not correlated with academic achievement.

### Autism symptom severity

Both parametric and non-parametric correlations were significant for the association between higher symptom severity and higher P3 for no-go ( $r=.73$ ,  $p=0.040$ ;  $r_s=.71$ ,  $p=0.047$  for SCQ,  $r=.77$ ,  $p=0.042$ ;  $r_s=.76$ ,  $p=0.049$  for CBCL Pervasive problems) and go trials ( $r=.82$ ,  $p=0.023$ ;  $r_s=.76$ ,  $p=0.049$  for CBCL Pervasive problems). These confirm our prediction that higher P3 is associated with higher autism symptom severity. Larger differences in N2 amplitudes between go and no-go trials were also associated with lower levels of repetitive behaviors ( $r=-.68$ ,  $p=0.042$  for RBS-R), but not for the non-parametric correlation.

### Discussion

The purpose of the present study was to provide a short review focused on EF-related ERPs in children with ASD and to present initial evidence for the neurophysiological correlates of cognitive control based on a preliminary sample of 5-



year-old kindergarteners with ASD and matched controls based on age, gender, and error rates using a child friendly visual Go/No-go task. To our knowledge, our preliminary study is the first investigation to identify EF-related components in children with ASD who are younger than 8-10 years and to examine the associations between ERP patterns with other behavioral and clinical domains. Our findings showed that a developmentally appropriate Go/No-Go task can successfully elicit N2 and ERN/CRN at the fronto-central and P3 and Pe at the posterior sites in the combined sample of kindergarteners with ASD and matched controls, consistent with past studies based on typically developing children (Ciesielski *et al.*, 2004; Abundis-Gutiérrez *et al.*, 2014; Grammer *et al.*, 2014; Barry & De Blasio, 2015) as well as in older school-aged children with ASD (Kemner *et al.*, 1994; Henderson *et al.*, 2006; Vlamings *et al.*, 2008; South *et al.*, 2010; Santesso *et al.*, 2011; Sokhadze *et al.*, 2012). Due to small sample sizes, especially for the ASD group, the statistical significance for the site and trial effects on the waveforms varied more when the analyses were performed separately for each group, with stronger signals for N2 and P3 compared to ERN/CRN and Pe. As hypothesized, ERN and CRN amplitudes were larger in the ASD compared to the TD group, consistent with past findings (e.g., Henderson *et al.*, 2006). Children with ASD also showed less distinct inhibitory P3 compared to matched controls, suggesting abnormal neural activities related to response inhibition and error monitoring in ASD.

#### Assessing cognitive control in young children and children with ASD

One of the key considerations in assessing neurophysiological data in young children and those with special needs is to ensure that children are engaged and motivated throughout the ERP testing. Therefore, we used a child-friendly Go/No-go task that was adapted from a well-validated task developed by McDermott and colleagues (under review) in order to maximize the child's ability to be engaged during the ERP session. The feasibility of the task has been validated for typically developing children as young as 3-4 years (Grammer *et al.*, 2014), and allowed us to examine our target ERPs in typically developing kindergarteners as well as those with ASD. The ERP testing occurred during an interesting story with engaging animal images that

included clear and easy to understand distinctions between go and no-go trials. The testing was fast-paced to reduce fatigue, but when needed, movement breaks were allowed to minimize artifacts in the data. Attrition is often an issue when conducting ERP experiments with young children especially for clinical populations, but all children with ASD were able to complete the task. We believe that our efforts to create the comfortable and friendly testing environment and task contributed to successfully identifying target ERP components even for the small number of children with ASD. These results also point to the need for more developmentally appropriate measures to assess EF related neurophysiological correlates in young children and children with ASD whose developmental skills may vary more widely than typically developing children.

### Stimulus processing

As consistent with past studies with typically developing adults and children (Pliszka *et al.*, 2000; Nieuwenhuis *et al.*, 2003; Donkers & van Boxtel, 2004; Smith *et al.*, 2004; Cragg *et al.*, 2009), in our sample there was evidence for the presence of N2 and P3 in response to stimuli in both kindergartners with ASD and matched group of typically developing children. Building on previous research, we see enhanced N2 and P3 amplitudes during inhibition (No-go trials) versus execution (Go-trials) in both kindergartners with ASD and matched controls, reflecting response inhibition and decision making processes (Pliszka *et al.*, 2000; Donkers & van Boxtel, 2004; Munro *et al.*, 2007; Cragg *et al.*, 2009; Maguire *et al.*, 2009).

Unlike a previous study with older children with ASD based on a flanker task (Faja *et al.*, 2016), we did not find any significant difference in N2 amplitudes between the ASD and TD groups. This is consistent with another finding based on school-age children with ASD using an illusory figure categorization task (Sokhadze *et al.*, 2012), and may reflect the impact of task design and developmental changes on the results of the ERP patterns. However, we found that children with ASD showed significantly smaller differences in P3 amplitudes between go vs. no-go trials at the posterior sites compared to matched typically developing children. The less distinct P3 found in

children with ASD compared to the TD group suggests that children with ASD may engage in atypical, potentially less efficient, strategic monitoring for stimuli with “relative novelty” (Lavric *et al.*, 2004).

## Response Monitoring

Consistent with findings from the studies based on typically developing children (Grammer *et al.*, 2014; Kim *et al.*, 2016a), our data demonstrate the presence of ERN and Pe in kindergarteners with ASD and matched controls. Consistent with the literature suggesting that ERN and Pe reflect neural networks signaling the need for further improvement in performance due to cognitive conflicts arising from errors (Larson *et al.*, 2014), we found that both ERN and Pe were significantly larger during error relative to correct trials.

Unlike adults (Santesso *et al.*, 2011; South *et al.*, 2010) or children with ASD with a wide range of cognitive functioning (Vlamings *et al.*, 2008) who showed reduced ERN and/or Pe amplitudes, ERN amplitudes were significantly larger for our focused sample of more-able children with ASD compared to controls, as hypothesized based on the previous study of children with IQ scores > 103 (Henderson, 2006). CRN amplitudes were also enhanced in the ASD relative to the TD group. The enhanced amplitudes in these response-locked ERP indicate that children with ASD may show heightened response monitoring (CRN/ERN) and increased awareness to errors (ERN) during the ERP task (Hajcak *et al.*, 2003).

## Associations between ERP and other behavioral and clinical characteristics In ASD

**Larger CRN reflective of heightened response monitoring in children with ASD were associated with lower levels of performance on a Go/No-Go task tapping into EF, specifically inhibitory control. A few studies have also suggested that larger CRN may reflect increased reactivity of the response monitoring system, often related to anxiety (Hajcak & Simons, 2002; Gehring *et al.*, 2012). Therefore, even though our study is the first to find the potential link between**

**higher CRN amplitudes and more impairments in inhibitory control in young children with ASD, enhanced CRN found in our sample suggests that their tendency to be hyper-sensitive to cognitive performance may negatively affect their performance on EF-related tasks.**

In contrast, ERP amplitudes that were targeted by our task were not correlated with achievement. A recent paper based on typically developing children examining associations between Pe and achievement in math and reading revealed that the links between Pe and achievement may be rather specific for children having academic difficulty because these associations were not observed in children performing above grade level (Kim *et al.*, 2016b). This may be why we did not find any significant association between achievement and Pe in our more-able ASD group. However, because our study is preliminary, replications are needed before further inferences are made.

As hypothesized, enhanced P3 amplitudes for both go and no-go trials were correlated with higher overall autism symptom severity (on SCQ and CBCL), although ERN was not. These results suggest a potential link between response inhibition and autism symptom severity in kindergartners with ASD; for children with more severe symptoms of social communication deficits and repetitive behaviors, more effort may be required to sustain the performance on a cognitive task compared to those with milder symptom presentations. Another, not mutually exclusive hypothesis, would be that less efficient inhibitory control processes in children with ASD may further exacerbate their ability to engage in social interactions as well as their behavioral rigidity.

#### Clinical and theoretical implications

It has been proposed that the anterior cingulate cortex (ACC) is engaged in various aspects of cognitive task performance including attentional control (Posner & Raichle, 1994). Given the link between the ACC and some of the EF related components observed in our study, it is possible that the abnormal ERP patterns we observe in kindergartners with ASD may be partly accounted for by functional and structural abnormalities in the ACC (Mundy, 2003; Thakkar *et al.*, 2008; Santesso *et al.*,

2011). Furthermore, our preliminary findings indicate that atypical brain activity reflected by the larger amplitudes in these EF-related ERP components may interfere with other cognitive and other behavioral functioning. For instance, heightened CRN, reflective of over-reactive response monitoring, was related to less effective inhibitory control. Moreover, children with higher autism symptom severity showed higher P3 amplitudes, which may suggest that these children need more effort to sustain performance on a cognitive task compared to those with milder symptom presentations. These underlying mechanisms of the atypical brain activities in young children with ASD warrant further exploration. Furthermore, these results highlight the need for more focused behavioral interventions targeting inhibitory control and response monitoring for children with ASD.

#### Limitations and future directions

Our preliminary data is based on a small sample size, especially for children with ASD. Therefore, given the heterogeneous behavioral presentations of the population under investigation, the results cannot be generalized into other children without further replications in larger, independent samples. Although the children were confirmed to exceed the ASD cutoff scores on the ADOS and to have average to above average scores on the Stanford Binet Intelligence Scale, we did not have an access to the protocols and scores for this study. **Given the significant associations between IQ and the EF-related ERP patterns in ASD observed in previous studies (e.g., Salmond et al., 2007), future studies should use the quantitative measures of IQ to stratify samples and examine or control for the effects of IQ on the ERP patterns.** TD controls were a part of a larger dataset, but the number of typical participants was intentionally limited to a smaller subset of children matched with ASD cases based on age, gender, and error rates. Despite of these limitations, with a focused set of research questions and hypotheses, and a sample of children with ASD within a narrow range of cognitive functioning and age, we observed significant effects. When Bonferroni or FDR corrections were implemented to correct for multiple correlational analyses, results were not all maintained. Nevertheless, considering the

lack of studies examining the EF related ERP components in children with ASD, especially during early childhood, we believe that our results show preliminary evidence for atypical brain activities related to stimulus processing and response monitoring in more-able children with ASD as young as 5 years old. As developmental changes are known to impact ERP patterns observed in this study (Grammer *et al.*, 2014), longitudinal studies based on developmentally appropriate measures can also help us explore changes in neurophysiological processes and their associations with other behavioral functioning.

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## Competing Interests

Dr. Lord receives royalties from the publication of the Autism Diagnostic Observation Schedule. All other authors report no potential conflicts of interest.

## Author Contributions

Dr. Kim has contributed to the design of the work, data analysis and interpretation, drafting and revising the article.

Dr. Grammer has contributed to the design of the work, data collection, data analysis and interpretation, drafting and revising the article.

Ms. Benrey has contributed to the data analysis and drafting and revising the article.

Dr. Morrison has contributed to the conception and design of the work, and drafting and revising the article.

Dr. Lord has contributed to the conception and design of the work, and drafting and revising the article.

All authors have approved this final version of the manuscript to be published.

## Data accessibility

The data used in this study are not accessible because many families did not consent for the data to be available publicly beyond this study.

## Abbreviations

EF Executive Function

ASD Autism Spectrum Disorder

ADHD Attention Deficit and Hyperactivity Disorder

TD Typically Developing

ERP Event Related Potentials

ACC Anterior Cingulate Cortex

ERN Error Related Negativity

CRN Correct- Response Related Negativity

Pe Error Positivity

N2 (N200)

P3 (P300)

Hz Hertz

SCA Spatial Conflict Task

PTP Pick the Picture

STS Something's the Same

SCQ Social Communication Questionnaire

RBS-R Repetitive Behavior Scale- Revised

CBCL Child Behavior Checklist

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Table 1. Demographics

	ASD	Matched TD controls
N (n boys)	9 (8 boys)	18 (17 boys)
Age (average)	5.66 (.35)	5.69 (.28)
Race (% of Caucasian)*	50%	76.92%
Zoo task		
% error	23.19% (12.7)	14.84% (5.09)
% correct	95.14% (4.29)	88.10% (14.07)
Reaction time (error)	452.60 (78.09)	458.95 (67.28)
Reaction time (correct)	572.21 (62.69)	536.77 (63.09)
Achievement (standard score mean=100, SD=15)*		
Letter-word identification <sup>a</sup>	127.89 (24.20)	104.60 (27.37)
Applied problems	113.33 (13.03)	108.40 (10.25)

\*1 case from the ASD and 5 cases from the TD group did not provide information on race. 3 cases from the TD group did not complete the achievement testing. <sup>a</sup>Significant difference between two groups emerged ( $p < 0.05$ ).

Table 2. Mean (SD) N2, P3, ERN/CRN and Pe at FCz, Cz, and Pz.

	ASD			TD		
	FCz	Cz	Pz	FCz	Cz	Pz
N2 NoGo	-4.67 (3.10)	-4.30 (3.68)	1.54 (10.33)	-6.18 (3.88)	-4.52 (5.33)	2.33 (20.04)
N2 Go	-4.50 (2.77)	-4.08 (3.53)	2.93 (10.04)	-5.89 (2.91)	-4.69 (4.51)	2.49 (19.16)
$\Delta$ N2	-.17 (1.65)	-2.2 (1.48)	-1.39 (2.16)	-.30 (1.67)	-1.49 (2.67)	4.21 (3.90)
P3 NoGo	-8.62 (3.73)	-5.36 (5.01)	11.00 (12.25)	-5.03 (5.08)	-1.83 (7.53)	11.59 (24.05)
P3 Go	-9.11 (1.94)	-6.72 (5.10)	8.32 (11.36)	-8.79 (4.90)	-6.52 (7.66)	7.38 (21.85)
$\Delta$ P3	.49 (3.63)	1.36 (3.40)	2.68 (3.15)	3.77 (2.70)	4.70 (3.07)	4.21 (3.90)
ERN	-5.71 (5.73)	-4.42(8.71)	4.00 (9.73)	-1.84 (5.45)	-0.62 (4.78)	-.31 (5.01)
CRN	-1.12 (2.82)	2.59 (2.02)	.98(3.25)	.35 (3.08)	1.97(2.89)	-.74 (3.77)
$\Delta$ ERN	-4.59 (5.34)	-7.01(8.53)	3.01 (9.49)	-2.19 (3.93)	-2.59 (4.49)	.44 (5.64)



Pe	.58(9.48)	10.79 (6.74)	9.3 (18.74)	3.23(9.18)	8.24 (9.64)	5.09 (12.20)
Pe correct	6.45(5.27)	5.69(5.89)	-8.06 (7.32)	3.87(6.24)	5.86(6.21)	-7.14 (9.86)
$\Delta$ Pe	-5.87(11.50)	5.10 (5.29)	17.36 (19.04)	-.54 (10.05)	2.38 (5.96)	12.23 (10.13)

Table 3. Behavioral measures for children with ASD

	Mean	SD	range
<i>Executive Function based on Computerized EF Task</i>			
SCA %s of correct responses	.90	.14	.64-1.00
PTP %s of correct responses	.77	.09	.63-.91
STS %s of correct responses	.83	.08	.63-.93
<i>Autism Severity</i>			
SCQ Total (ASD cutoff = 15)*	18.25	4.33	10.0-13.0
RBS-R Total (range = 0-129)	38.11	14.14	14.0-60.0
CBCL Pervasive Problem (Clinical range cutoff = 69)*	73.00	7.44	63.0- 84.0

SCA Spatial conflict arrows, *PTP* Pick the picture, *STS* Something's the same

SCQ Social communication scale, *RBS-R* Repetitive behavior scale-revised, *CBCL* Child Behavior checklist

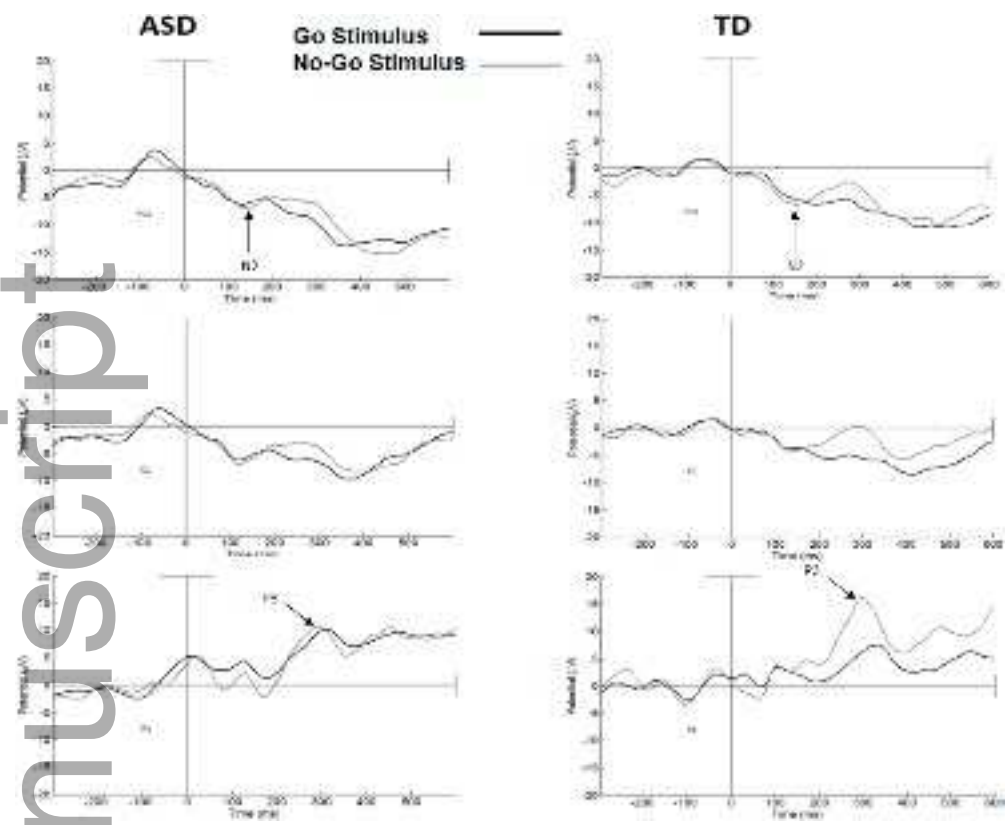
\*One case and two cases did not complete SCQ and CBCL respectively.

### Figure Captions

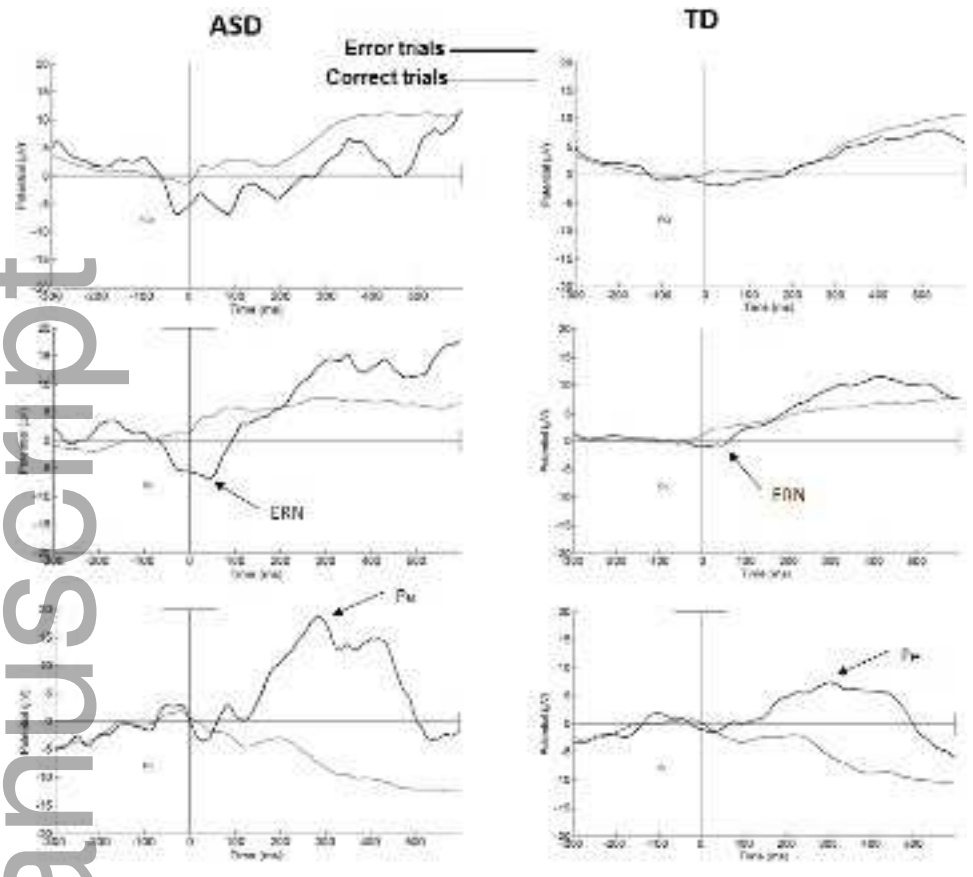
Figure 1. Stimulus-locked waveforms at Fcz, Cz, and Pz for the ASD and TD groups

Figure 2. Response-locked waveforms at Fcz, Cz, and Pz for the ASD and TD groups

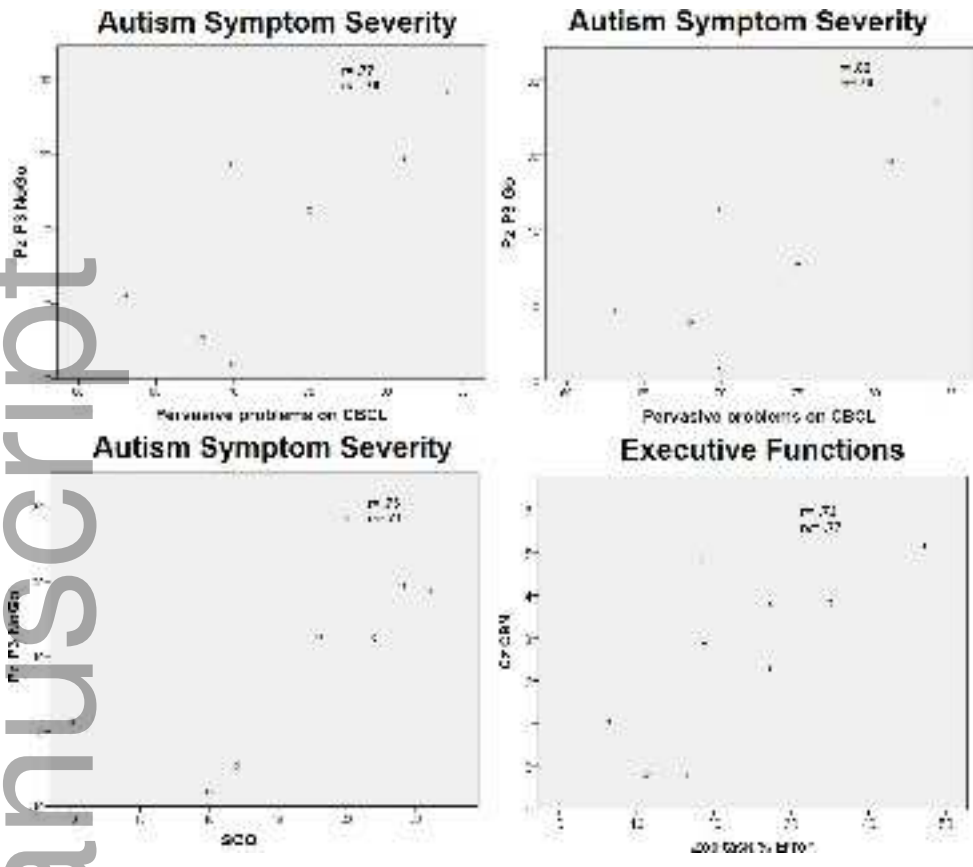
Figure 3. Parametric and non-parametric correlations between ERP amplitudes and behavioral data for children with ASD



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ejn\_13580\_f2.tif



ejn\_13580\_f3.tif