Comparative Event-related Potential Study of Performance in Visual Oddball Task in Children with Autism Spectrum Disorder, ADHD, Comorbid Autism and ADHD, and Neurotypical Children

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Abstract

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are the most commonly diagnosed neurodevelopmental disorders. Although the comorbidity was excluded in DSM-IV (APA, 2000), DSM-5 (APA, 2013) does not preclude the concurrent diagnosis of ASD and ADHD (ASD+ADHD). This study aimed to understand distinctions in executive deficits among these conditions. We used analysis of reaction time (RT) and event-related potentials (ERP) during performance on oddball task with illusory figures. Participants were children (*N* = 18 per group) with ASD, ADHD, ASD+ADHD, and neurotypical controls (CNT). Analysis revealed that ASD and ASD+ADHD groups committed more errors and had higher omission error rates. Post-error RT in ASD and ASD+ADHD manifested as a post-error response speeding rather than normative RT slowing. The ASD and ASD+ADHD demonstrated an attenuated error-related negativity (ERN) as compared to ADHD and controls. The frontal N100 was enhanced to both target and nontarget figures in ASD and ASD+ADHD groups. Frontal ERPs had prolonged latencies in the ADHD as compared to other groups. The study confirmed the utility of using ERP to elucidate differences between ASD and ADHD and their impact in dual diagnosis. This information helps define the extent of overlap among these conditions both in terms of symptom expression and underlying neuropathology.

Keywords: autism spectrum disorder (ASD); ADHD; event-related potential; attention; oddball task; comorbid ASD+ADHD; executive functions

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Introduction

In DSM-5 (APA, 2013), the autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) diagnoses have almost no core clinical symptom overlap; nevertheless, their similarities in associated features are significant. In DSM-5 and ICD-10 (WHO, 2008) manuals, ASD is defined by significant impairments in reciprocal social interaction and communicative function and restricted, repetitive behaviors and interests, while ADHD is defined by developmentally inappropriate

and functionally impaired levels of hyperactivity, impulsivity, and inattention. However, before the DSM-5 release in 2013, according to diagnostic criteria enunciated in the DSM-IV-TR (APA, 2000), both pervasive disorders of development (PDD; i.e., autistic disorder, Asperger syndrome, PPD-Not Otherwise Specified [PDD-NOS]) and ADHD were classified as mutually exclusionary diagnoses. There was a growing consensus from clinicians and researchers that behavioral characteristics of ADHD are observed in 14–78% of ASD patients (Holtman, Bolte, & Poustka, 2007; Keen & Ward, 2004; Lee & Ousley, 2006; Leyfer et al., 2006; Reiersen, Constantino, Volk, & Todd, 2007; Ruggieri, 2006; Sinzig, Walter, & Doepfner, 2009; Yoshida & Uchiyama, 2004). Furthermore, among patients diagnosed with ADHD, up to two-thirds of individuals exhibited autism-like symptoms, especially in the social communication domain (Cooper, Martin, Langley, Hamshere, & Thapar, 2014; Davis & Kollins, 2012; Leitner, 2014). These studies questioned the validity of comorbidity as an exclusionary criterion within DSM-IV-TR guidelines, and argued in favor of changes (Ruggieri, 2006) that eventually resulted in the revision of this clause in the DSM-5. Although behavioral characteristics of autism and ADHD may coexist, the more relevant question remains whether these neurodevelopmental conditions share the same underlying neuropathology. Some of the shared symptoms between ASD and ADHD suggest that these conditions may well share some aspects of neurodevelopmental pathologies affecting their behavior and performance during neurocognitive tests. However, it should be noted that these neurodevelopmental disorders have been investigated in divergent fields in the past. Rommelse, Geurts, Franke, Buitelaar, and Hartman (2011) reviewed ASD and ADHD phenotypes related literature and emphasized that on most occasions in the past decades ASD and ADHD have been studied in isolation from each other, without networks of collaborating experts and common theoretical frameworks. He strongly argued for the concomitant, rather than individual, investigation of ASD and ADHD.

There is a need to investigate specifics of the overlap and distinction in behavioral and neurophysiological impairments typical for ASD and ADHD and to determine how symptoms combine in ASD+ADHD cases (Lau-Zhu, Fritz, & McLoughlin, 2019). Reports have shown that children with ASD+ADHD present more behavioral difficulties of adaptation to daily life hassles as compared to those with ASD or ADHD alone. Furthermore, compared

with ASD alone, ASD+ADHD are associated with generally poorer quality of life. It was reported (Frazier et al., 2011) that children diagnosed with ASD+ADHD are more likely to be taking psychiatric medication (58%) than those with ADHD (49%) or ASD (34%) alone. It is therefore unsurprising that children with ASD+ADHD could be less responsive to treatments specific to ADHD or ASD alone and therefore require more attention in order to achieve desired outcomes. In addition, it is still not clear whether comorbid ASD+ADHD presents as an additive condition with a similar contribution by both disorders or whether one of these diagnoses contributes more to symptom expression (Tye et al., 2014). Although there are important differences in core symptom definition in the DSM-5, the co-occurrence between ASD and ADHD is supported by numerous clinical, behavioral, neurophysiological, and neuroimaging studies (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Hovik et al., 2014; Johnston, Madden, Bramham, & Russell, 2011; Sinzig, Bruning, Morsch, & Lehmkuhl, 2008; Tye et al., 2014). In previous years most clinical and research studies have reported executive function impairments in ADHD and ASD (see Rommelse et al., 2011) separately; however, in recent years, a considerable amount of studies focused specifically on investigation of the executive deficits directly comparing ASD and ADHD (Lawson et al., 2015; Ray et al., 2014; Salcedo-Marin, Moreno-Granados, Ruiz-Veguilla, & Ferrin, 2013; Sinzig, Vinzelberg, Evers, & Lehmkuhl, 2014). Several studies directly addressed comparative analysis of symptoms in ASD, ADHD, and ASD+ADHD comorbidity (Hovik et al., 2014; Lawson et al., 2015; Salcedo-Marin et al., 2013; Samyn, Wiersema, Bijttebier, & Roeyers, 2014; Semrud-Clikeman, Walkowiak, Wilkinson, & Butcher, 2010; Sinzig et al., 2008; Sinzig et al., 2014; Tye et al., 2014). However, findings of the neuropsychological tests that rely solely on behavioral assessments can hardly be considered decisive in resolving the nature of the underlying neurobiological distinctions between autism and ADHD. That is to say, the coincidence and overlap of behavioral symptoms does not necessarily imply a similarity in underlying neurobiological pathology. Indeed, lines of research, in particular those based on pharmacological tests, have shown that behavioral symptoms for both ASD and ADHD might be mediated by different pathophysiological mechanisms. For instance, pharmacological interventions using stimulant medication that target hyperactivity and inattention in children with autism, even when proved to be effective for these particular

behavioral clinical symptoms, still did not reduce the core symptoms of autism (Hazell, 2007).

There were expectations that neuroimaging data comparing ASD and ADHD might have provided insight related to their differences. Eventually, certain neuroimaging data did show some differences in neuroanatomy. For example, brain size in ASD appears to be increased (Stanfield et al., 2008), while ADHD exhibits an opposite trend towards smaller volumes (Batty et al., 2010). Other neuroimaging studies found group differences in gyral complexity, gray white matter parcellation, and size of the corpora callosa (Casanova et al., 2009; Casanova, El-Baz, Giedd, et al., 2010; El-Baz et al., 2011; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009). Patients with ASD, as compared to neurotypical individuals, have larger brains but, at the same time, a smaller corpora callosa. Contrariwise, patients with ADHD have smaller brains but a larger corpora callosa. These morphometric differences in corticocortical connectivity may suggest a bias in short (i.e., arcuate) versus long projections (e.g., commissural fibers) that may help explain some of the behavioral manifestations observed in these conditions (Casanova, El-Baz, Vanbogaert, Narahari, & Switala, 2010). Review of 26 studies that examined executive function in children with ASD and ADHD by Craig et al. (2015) concluded that the ASD+ADHD group appears to share impairments in flexibility and planning with the ASD group, while it shares the response inhibition deficit of the ADHD group. Conversely, deficit in attention, working memory, preparatory processes, and concept formation does not appear to be distinctive in discriminating between the ASD, ADHD, or the ASD+ADHD group. Although ADHD and ASD seem very distinct in terms of core clinical symptoms, they have been shown to share some similarities in their executive functions deficit. Executive functioning skills fall under the purview of those prefrontal functions that facilitate problem-solving, flexible set-shifting and forward planning in the implementation of goal-directed behavior (Hughes, Russell, & Robbins, 1994). The executive deficits in autism have been related to specific frontal mechanisms, principally to the prefrontal and midfrontal cortices and associated neural circuitries (reviewed in Bishop, 1993; Hill, 2004). Executive deficits in ADHD are also associated with hypofunctional frontal networks (Hovik et al., 2014; Salcedo-Marin et al., 2013; Samyn et al., 2014; Semrud-Clikeman et al., 2010; Sinzig et al., 2014). Craig et al. (2015) reviewed studies comparing ASD and ADHD performance and reported that overlapping and

specific profiles for ASD and ADHD were found mainly for such neurocognitive domains as attention processing, performance monitoring, and face processing. The domain of executive functions has significant implications for developmental psychopathologies, and more rigorous studies are warranted to understand specifics of executive deficit profiles of ASD and ADHD and comorbid ASD+ADHD.

The present study focused on the possibility of differing underlying pathophysiological mechanisms in both ASD and ADHD, as well as their comorbid condition by comparing behavioral responses and patterns of event-related potentials (ERP) during performance on three-stimuli visual oddball task with illusory Kanizsa figures. It should be noted that the majority of studies examining electrocortical biomarkers of executive functions in neurodevelopmental disorders focused on ERP measures (Hoeksma, Kemner, Kenemans, & van Engeland, 2006; Jeste & Nelson, 2009; Johnston et al., 2011; Johnstone & Barry, 1996; Jonkman, Kenemans, Kemner, Verbaten, & van Engeland, 2004; Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Smith, Johnstone, & Barry, 2004; Verbaten, Roelofs, van Engeland, Kenemans, & Slangen, 1991). Analysis of ERP is a very informative method of monitoring information processing stages in the brain. Different amplitude and latency characteristics of ERP components at specified topographies reflect both early sensory perception processes and higher-level processing including attention, cortical inhibition, memory update, and other cognitive activity (Duncan et al., 2009; Polich, 2007).

Studies using oddball tasks and other attention paradigms (e.g., continuous performance, go/no-go, response choice tasks, and variety of similar tests) in ADHD have provided evidence for smaller visually evoked P300 amplitudes and prolonged latencies of P300 (Barry, Johnstone, & Clarke, 2003; Hoeksma et al., 2006; Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Polich, 2007; Townsend et al., 2001; Verbaten et al., 1991). In sum, several studies found reduced frontal amplitudes and longer latencies in ADHD, which can be taken as suggesting a deficit in selective attention. In autism, on the other hand, only few studies reported a reduced ERP response to attended visual stimuli. Therefore, the majority of ERP studies have demonstrated altered visual P300 amplitudes in both ADHD and autism; however, it should be emphasized that these stimulus-locked ERP alterations do not seem to be specific markers. One

of the important executive functions that may differentiate ASD and ADHD inputs to deficits observed in comorbid ASD+ADHD condition is response monitoring and error correction function. This function has well recognized ERP correlates in oddball tasks with motor responses. Most well validated among those is response-locked error-related negativity (ERN). This ERP component is a negative-going waveform peaking 40–140 ms after an error response or a negative feedback stimulus (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring & Knight, 2000; Miltner, Braun, & Coles, 1997). It occurs in response to response errors, response conflict, and decision uncertainty (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Conscious error processing is thought to be reflected by the error positivity (Pe), which is a positive-going potential following the ERN. It was reported that autistic children, especially those with impairments in social interaction, were more likely to fail correcting errors than controls (Henderson et al., 2006; Russell & Jarrold, 1998). Moreover, Bogte, Flamma, van der Meere, and van Engeland (2007) found that a group of autistic subjects, as compared to controls, showed no post-error normative slowing. These studies suggest decreased error awareness in autism, predicting decreased ERN and Pe amplitudes along with delayed latencies.

Several studies have found reduced ERN amplitudes in children with ADHD compared to typically developing children, suggesting that children with ADHD also present a deficit in monitoring ongoing behavior (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007). Reduced Pe amplitudes in ADHD are in accordance with the findings of reduced post-error compensatory behavior; that is, the strategic RT slowing after the commission of errors (Schachar et al., 2004; Sergeant & van der Meere, 1988; Wiersema, van der Meere, & Roeyers, 2005). Reduced error awareness may thus hamper children with ADHD in adequately adapting their behavior and consequently in learning from their mistakes. Considering that both ASD and ADHD present ERN and Pe reactivity deficits and impaired post-error normative slowing of RT, it is possible to propose that the error monitoring and correction will be even more pronounced in dual diagnosis when children with ASD have ADHD as a comorbid condition. We proposed that error detection, monitoring, and correction function—as indexed by ERN, RT accuracy, and post-error RT adjustment—will be more significantly compromised in children with ASD+ADHD as compared to ASD-alone or ADHD-

alone and will clearly differentiate these conditions from neurotypical peers.

The goal of this study was to investigate stimulus- and response-locked ERPs during performance on a visual three-category oddball task with illusory figure stimuli in children with ASD, children with ADHD, children with dual diagnosis (ASD+ADHD), and age-matched typically developing children (CNT group). We proposed that behavioral (RT, accuracy) and electrocortical (ERP, ERN, Pe) measures would provide differentiating features between the groups. We also expected to see more pronounced between group differences at the frontal topography as both ADHD and ASD typically present executive function deficits.

Methods

Participants
Participants with ASD (age range 7 to 19 years) were recruited through the University of Louisville Weisskopf Child Evaluation Center (WCEC). Diagnosis was made according to the DSM-IV-TR (APA, 2000), after 2013 according to DSM-5 (APA, 2013), and further ascertained with the Autism Diagnostic Interview – Revised (ADI-R; LeCouteur, Lord, & Rutter, 2003). They also had a medical evaluation by a developmental pediatrician. All subjects had normal hearing based on past hearing screens. Participants either had normal vision or wore corrective lenses. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality from imaging studies, or an identified genetic disorder were excluded. All participants were high-functioning persons with ASD with full scale IQ > 80 assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2004).

In the ADHD diagnosis group, male and female patients aged 8 to 18 years old meeting inclusion and no exclusion criteria were eligible for the study. Diagnosis of ADHD was based on DSM-IV and/or DSM-5 criteria (ADHD, Inattentive, Hyperactive–Impulsive, and Combined type) using a structured parent interview (DICA; Reich, 2000) and was made by a clinical psychologist and child and adolescent psychiatrist. The DSM requires that symptoms be present in at least two settings; therefore, prior to the interview, two rating scales were administered to each child's parent as well as to the teacher (parents: Achenbach Parent Form and The Conner's Parent Rating Scale-R; while

teacher: Achenbach Teacher Rating Form and Conner's Teacher Rating Scale-R). Subjects met criteria for ADHD on at least one of the two parent rating scales and on one of the two teacher rating scales. Only following these evaluations was the child considered as meeting criteria on the DICA-IV (Reich, 2000). Children with ADHD on stimulant medication were included in this study only if they were taken off medication on the day of the lab visit for tests. In addition, according to inclusion/exclusion criteria, eligible participants with ADHD had to be judged to be in generally good health and be willing and able to participate in lab tests. Exclusion criteria for this group were (a) current diagnosis of any Axis I psychiatric disorder, such as psychosis, bipolar disorder, and schizophrenia; (b) current psychiatric symptoms requiring medication other than those for ADHD; (c) severe medical, cognitive, or psychiatric impairments that preclude from the cooperation with the study protocol; and (d) inability to read, write, or speak English. The ERP procedures required the following additional exclusion criteria: (1) impaired, noncorrectable vision or hearing; (2) significant neurological disorder (epilepsy, encephalitis) or head injury.

Typically developing children (i.e., control subjects) were recruited through advertisements in the local media. All control participants were free of neurological or significant medical disorders, had normal hearing and vision, and were free of psychiatric, learning, or developmental disorders based on self- and parent reports. Subjects were screened for history of psychiatric or neurological diagnosis using the Structured Clinical Interview for DSM-IV Non-Patient Edition (SCID-NP; First, Spitzer, Gibbon, & Williams, 2001). Participants within the control, ADHD, autism, and ASD+ADHD groups were attempted to be matched by age, full scale IQ, and socioeconomic status of their family. Socioeconomic status of ASD, ADHD, ASD+ADHD, and control groups was compared based on parent education and annual household income. Participants in four groups had similar parent education levels. Participating subjects and their parents (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local Institutional Review Board (IRB). The consent and assent forms approved by the University of Louisville IRB were reviewed and explained to all subjects who expressed interest to participate. All questions were answered before consent signature was requested. If the individual agreed to participate, she or he signed and dated the consent form and received a copy countersigned by the investigator who obtained consent.

Subject Demographics
The mean age of 18 participants enrolled in the ASD group was 13.2 ± 3.5 years (range 8–18 years, 14 males, 4 females); the mean age of the 18 participants in the ADHD group was 13.4 ± 2.9 years (range 8–18 years, 14 males, 4 females); the mean age of the 18 participants in the ASD+ADHD group was 12.5 ± 3.1 (range 7–17, 15 males, 3 females); and the mean age of the 18 participants in the CNT group was 14.2 ± 3.9 years (range 9–19 years, 13 males, 5 females). The age difference between groups was not significant (p = .323). Nine subjects from the ADHD group, 8 subjects from the ASD group and 10 subjects from the comorbid ASD+ADHD group were on medication. Children with ADHD and ASD+ADHD were taking stimulants (such as Ritalin–Methylphenidate or Adderall–Dextroamphetamine). Only 3 children with ASD were taking stimulants (Ritalin, Concerta, Adderall, etc.), and 10 in ASD and 7 in ASD+ADHD were taking antidepressants (Prozac–Fluoxetine, Zoloft–Sertraline) and mood stabilizers (Depakote–Divalproex, Abilify–Ariprazole). Four children in the ASD group and three in ASD+ADHD had comorbid mild mood disorders, and five in both of these groups had anxiety disorders. Two subjects from the ADHD group had comorbid mild mood disorders, and another three had anxiety disorders. All subjects with ADHD diagnosis (in ADHD only and in ASD+ADHD groups) were included regardless of their ADHD subtype (Inattentive, Hyperactive–Impulsive, or Combined).

Three-Stimuli Visual Oddball Task with Illusory Kanizsa Figures
In this task subjects responded with a button-press to rare (25% probability) Kanizsa squares (targets) among Kanizsa triangles (rare nontarget distracters, 25% probability) and non-Kanizsa figures (standards, 50% probability). The stimuli were presented for 250 ms with intertrial intervals (ITI) varying in the range of 1100–1300 ms. A fixation point (cross) was presented during ITI. White figures were displayed on a black background on a flat monitor. Subjects were instructed to press the first button on a five-button keypad with their right index finger when a target appears and ignore nontarget Kanizsa or standard stimuli. The stimuli consisted of either three or four inducer disks which are considered the shape feature, and they either constitute an illusory figure (square, triangle) or nonillusory figure (collinearity feature). The

nontarget Kanizsa triangle was introduced to differentiate processing of task-relevant (Kanizsa square) and task-irrelevant Kanizsa figures.

ERP Data Acquisition and Signal Processing

Electroencephalographic (EEG) data was acquired with a 128-channel Electrical Geodesics Inc. (EGI) system (v. 200) consisting of Geodesic Sensor Net electrodes, Net Amps, and Net Station software (Electrical Geodesics Inc., Eugene, OR). EEG data were sampled at 500 Hz and 0.1–200 Hz analog filtered. Impedances were kept under 40 KΩ. According to the *Technical Manual of EGI* (2003), this Net Sensor electrode impedance level is sufficient for quality recording of EEG with this system. The Geodesic Sensor Net is a lightweight elastic thread structure containing Ag/AgCl electrodes housed in a synthetic sponge on a pedestal. The sponges are soaked in a KCl solution to render them conductive. EEG data were recorded continuously. EEG channels with high impedance or visually detectable artifacts (e.g., channel drift, gross movement, etc.) were identified using Net Station event marker tools in "on-line" mode and removed in the "off-line" mode using Net Station Waveform Tools (NSWT). Stimulus-locked EEG data were segmented offline into 1000-ms epochs spanning 200-ms prestimulus to 800-ms poststimulus around the critical stimulus events; for example, in an oddball task: (1) rare target (Kanizsa square), (2) rare nontarget distracter (Kanizsa triangle), and (3) frequent nontarget (non-Kanizsa standards). Response-locked EEG data (for ERN and Pe analysis) were segmented off-line into 1000-ms epochs spanning 500-ms prestimulus to 500-ms poststimulus around the critical stimulus events–committed error. Data were digitally screened for artifacts (eye blinks, movements), and contaminated trials were removed using artifact rejection tools. The NSWT Artifact Detection module in off-line mode marked EEG channels "bad" if fast average amplitude exceeded 200 μV, differential average amplitude exceeded 100 μV, or if the channel had zero variance. Segments were marked bad if they contained more than 10 bad channels or if eye blinks or eye movements were detected (> 70 μV). The remaining data set was digitally filtered using 60 Hz Notch and 0.3–20 Hz bandpass filters and then segmented by condition and averaged to create ERPs. Averaged ERP data were baseline corrected and re-referenced into an average reference frame. All stimulus presentation and behavioral response collection was controlled by a PC computer running E-prime software (Psychology Software Tools Inc., PA). Visual stimuli were presented on a 15-inch display. Manual responses were collected with a

five-button keypad (Serial Box, Psychology Software Tools, Inc., PA).

Behavioral Measures

Behavioral response measures were mean reaction time (RT in ms) and response accuracy (percent of correct hits). Both commission and omission error rates were calculated. Post-error slowing was calculated as a difference between the first post-error RT and mean RT.

Event-Related Potentials (ERP)

Response-locked ERPs. Response-locked ERP dependent measures were adaptive mean amplitude and latency of two ERP peaks (i.e., ERN, Pe) within a temporal window across two region-of-interest (ROI) channel groups at the midline fronto-central area. Each ROI contained at least four electrodes. A list of dependent variables included response-averaged amplitude and latency of the fronto-central ERP components: ERN (40–150 ms poststimulus) and Pe (100–200 ms).

The frontal and fronto-central ROIs for both ERN and Pe components included the following EGI channels: midline frontal and fronto-central ROI contained Fz and FCz, and the extended fronto-central ROI contained five EEG sites—FCz, two left EGI channels 7 and 13 (between FCz and FC3 and C1), and two right EGI channels 113 and 107 (between FCz and FC2 and C2).

Stimulus-locked ERPs. Stimulus-locked ERP dependent measures were adaptive mean amplitude and latency of ERP peak (e.g., N100) within a selected temporal window across a region-of-interest (ROI) channel group. Each ROI contained at least four electrodes. A list of ERP dependent variables included stimulus-averaged amplitude and latency of the frontal ERP components: N100 (90–180 ms), P200 (180–300 ms), N200 (200–320 ms), and P300 (P3a, 300–500 ms), and the posterior (centro-parietal and parieto-occipital ROIs) ERP components N100 (80–180 ms), N200 (180–300 ms), and P300 (300–500 ms). The frontal (i.e., frontal and fronto-central) ROIs for N100, P200, N200, and P300 components included the following EGI channels: left ROI contained EGI channel 29, F3, FC1, FC3; midline ROI contained Fz, FCz, EGI channels 5, 12; and the right ROI contained EGI channel 118, F4, FC2, FC4. The parietal (i.e., centro-parietal and parieto-occipital) ROIs for N100 and P200 components included following EGI channels: left ROI contained EGI channel 67, PO3, PO7, O1; and right ROI contained EGI channel 78, PO4, PO8, O2. Midline parietal (Pz) and parieto-

occipital (POz) channels were used in combination with the left and right parieto-occipital ROIs to form a comprehensive parieto-occipital ROI containing 10 EEG channels. For parietal and parieto-occipital N200 and P300 (P3b) were used channels P1, P3, PO3, EGI channel 54 and 67 (left) and P2, P4, PO4, EGI channels 78 and 80 (right). Midline parietal channels included Pz and POz.

Social and Behavioral Questionnaires
Social and behavioral functioning of participants were evaluated using caregiver reports and clinician ratings of improvement. Selected tests that have been shown to be sensitive to behavioral and social changes expected to occur with treatment and included following the Aberrant Behavior Checklist (ABC; Aman & Singh, 1994). The ABC is a caregiver-completed rating scale assessing five problem areas: Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech based on caregiver report. In addition, we used the Achenbach System of Empirically Based Assessment (ASEBA) questionnaire (parent version) for assessing adaptive and maladaptive functioning (Achenbach & Rescorla, 2012).

Statistical Data Analysis
Statistical analyses were performed on the subject-averaged behavioral and ERP data with the subject averages being the observations. The primary analysis model is the repeated measures ANOVA, with dependent variables being reaction time (RT), accuracy, error rate, post-error RT change for behavioral responses, and ERN, Pe, and all the specific stimulus-averaged ERP components' amplitudes and latencies at selected ROIs. The data of stimulus-locked ERP dependent variable for each relevant ROI was analyzed using ANOVA with the following factors (all within-participants): *Stimulus* (Target Kanizsa, Standard, nontarget Kanizsa), *Hemisphere* (Left, Right), etc. The between subject factor was *Group* (ADHD, ASD, ASD+ADHD, CNT). The data of each response-locked ERP dependent variable for relevant midline frontal ROI was analyzed using one-way ANOVA. Post hoc analysis using Tukey test was conducted where appropriate. A priori hypotheses were tested with Student's *t*-tests for two groups with unequal variance. In all ANOVAs, Greenhouse-Geisser corrected *p*-values were employed where appropriate.

Results

Attention symptoms on ASEBA. Main group differences using Achenbach's ASEBA (Achenbach & Rescorla, 2012) were found in *Attention Deficit Hyperactivity Problem* (DSM-oriented scale) *T-scores* (57.4 ± 6.1 in ASD vs. 69.9 ± 8.3 in ASD+ADHD, $F(1, 34) = 23.24$, $p < .001$) and in general *Attention Problems T-scores* (76.3 ± 9.1 in ASD+ADHD vs. 59.1 ± 6.5 in ASD, $F(1, 34) = 31.04$, $p < .001$). Differences in *Oppositional Behavior* or *Conduct Behavior* subscale ratings between these two groups did not reach statistical significance.

ABC scores. Children in ASD, ASD+ADHD, and ADHD groups were evaluated using parental rating of symptoms of the ABC. Statistically significant group differences were present only in the *Stereotypic Behavior* subscale rating scores, $F(2, 53) = 6.74$, $p = .001$. In particular, the ASD+ADHD group showed higher scores (7.67 ± 5.39) as compared to the ASD (3.55 ± 2.39, $p = .002$) and ADHD (2.69 ± 4.64, $p = .005$) groups. Other ABC subscales (*Irritability, Lethargy/Social Withdrawal, Hyperactivity, Inappropriate Speech*) did not show any between group differences.

Reaction time (RT) and accuracy. There were no significant group differences in RT (492 ± 111 ms in ASD vs. 523 ± 107 ms in ASD+ADD vs. 470 ± 89 ms in ADHD vs. 450 ± 97 ms in CNT, $F(3, 71) = 1.45$, $p = .236$, n.s.). Accuracy of response was different between groups, in particular total error percentage showed significant differences, $F(3, 71) = 3.78$, $p = .015$. A post hoc Tukey test yielded significant difference between ASD and CNT groups (17.9 ± 14.3 % in ASD vs. 2.4 ± 4.6 % in CNT, $p = .009$). Omission error contributed significantly to group differences, $F(3, 71) = 5.87$, $p = .001$. Post hoc analysis showed both ASD and ASD+ADHD vs. CNT difference (5.5 ± 4.9 % in ASD, 4.3 ± 5.3 % in ASD+ADHD vs. 0.4 ± 0.9 % in typical children with $p < .01$ in both comparisons). Furthermore, the ASD group had more omission errors even as compared to the ADHD group (difference was 3.80%, $p = .038$). In general children with ASD diagnosis (both ASD-only and ASD+ADHD) had more omission errors as compared to both typical controls (difference 4.36%, $p = .001$) and ADHD group (by 3.13%, $p = 0.01$). The ADHD factor (ADHD and ADHD comorbid with ASD) negatively affected total percentage of errors (12.2 ± 15.4% in combined ADHD and ASD+ADHD vs. 2.4 ± 4.6% in CNT, $p = .043$). The most pronounced group differences were found in the normative post-error RT slowing measure, $F(3, 71) = 16.45$, $p < .001$. Differences in

mean post-error reaction time changes clearly separated groups with ASD from the typical children and ADHD groups, as both ASD and ASD+ADD groups showed post-error speeding (−46.1 ± 47.4 ms in ASD, −52.1 ± 51.7 ms in ASD+ADHD), while CNT and ADHD groups showed normative slowing of RT following committed errors (49.1 ± 45.9 ms in CNT, 11.9 ± 14.2 ms in ADHD). Post hoc test confirmed that differences between ASD and ASD+ADHD group post-error RT changes vs. CNT and ADHD groups were significant (all $p < .01$). The CNT and ADHD post-error measures were not statistically different. The ASD diagnosis (combined ASD and ASD+ADHD) factored most significantly in affecting post-error RT change (−49.1 ± 48.3 ms in combined ASD vs. 49.2 ± 45.9 ms in CNT, $p < .001$). At the same time, combined ADHD (ADHD and ASD+ADHD) also showed difference in this post-error RT measure resulting in significant difference from the control group (9.7 ms, $p = .043$). Distribution of individual post-error RT values in four groups are depicted in Figure 1.
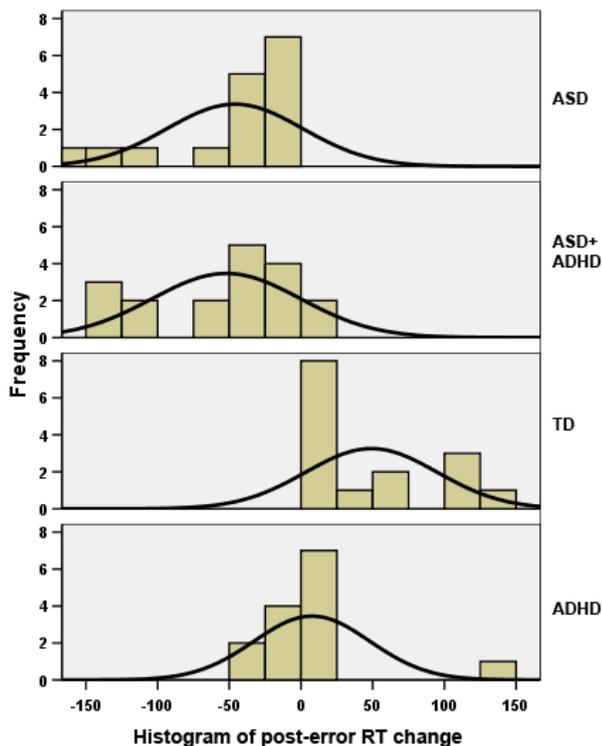

Figure 1. Histogram of distribution of individual post-error reaction time (RT) in children with autism, children with ASD+ADHD, typically developing (TD) controls, and children with ADHD. Both ADHD and control groups demonstrate slower (positive) post-error RTs compared to correct response RTs. The ASD and ASD+ADHD groups show speeding of post-error RTs with a negative peak of distribution curve.

The ADHD shows positive peak of the curve though still less expressed post-error RT slowing as compared to controls.

Response-averaged Event-related Potentials (ERP): ERN and Pe

Five subjects (4 in CNT and 1 in ADHD group) did not have enough errors to calculate reliable ERN, and their response-locket ERPs were omitted from analysis. Amplitude of the ERN measured at the midline fronto-central ROI (Fz-FCz) showed significant between group differences, $F(3, 65) = 3.15$, $p = .031$. The group differences of the ERN amplitude were better pronounced across more expanded ROIs that included five frontal and fronto-central sites, $F(3, 65) = 3.51$, $p = .02$. At these regions the differences were mostly expressed as less negative amplitudes of ERN in ASD and ASD+ADHD groups as compared to typically developing children (difference respectively −5.32 μV and −5.15 μV, both $p < .05$). The ASD-diagnosed combined group (ASD and ASD+ADHD) was statistically significantly different from the CNT group by ERN amplitude at fronto-central ROI (by 5.43 μV, $p = .005$), while combined ADHD group (ADHD and ASD+ADHD) was not different from the group of control peers ($p = .487$, n.s.), thus pointing at the more important contribution of ASD factor on attenuated ERN amplitude. Amplitude of response-locked positivity was not different between groups (e.g., for midline ROI, $p = .118$, n.s.). We could not find any statistically significant group differences either in ERN or Pe latencies.

Stimulus-averaged ERPs

Anterior event-related potentials: Frontal and fronto-central N100 and P300 (P3a). Group differences of the midline frontal and fronto-central N100 component amplitudes were statistically significant for frequent standards, $F(3, 71) = 4.95$, $p = .003$); rare nontarget Kanizsa, $F(3, 71) = 4.26$, $p = .007$); as well as target Kanizsa stimuli, $F(3, 71) = 5.73$, $p = .001$). Post hoc test showed more negative N100 in ASD group as compared to the control group in response to all the type of stimuli (standards, −2.65 ± 2.31 μV in ASD vs. −0.91± 0.90 μV in CNT, $p = .001$; nontarget distracters, −2.56 ± 2.19 μV in ASD vs. −1.20 ± 1.26 μV in CNT, $p = .036$; targets, −3.49 ± 3.15 μV in CNT vs. −1.01 ± 1.11 μV in CNT, $p = .001$). Group differences in N100 component latencies were significant only in response to task-irrelevant frequent standards, $F(3, 71) = 3.14$, $p = .028$. These differences were significant when comparing post hoc ADHD and CNT groups (145 ± 25 ms in ADHD vs. 129 ± 15 ms

in CNT). We did not find any group differences in either amplitude or latency of the anterior P200 component. Amplitude of the midline frontal and fronto-central P300 (i.e., P3a) ERP component yielded group differences only in response to target Kanizsa figures, $F(3, 71) = 2.96$, $p = .038$). Post hoc test revealed statistically significant higher amplitude of the P3a in ASD group as compared to ADHD group (6.23 ± 4.67 μV in ASD vs. 4.27 ± 2.21 μV in ADHD, $p = .041$). Analysis of P3a latencies at the midline ROI revealed significant group differences for all three conditions—frequent standards, $F(3, 71) = 8.80$, $p < .001$; rare nontargets, $F(3, 71) = 7.31$, $p < .001$; targets, $F(3, 71) = 8.60$, $p < .001$. Post hoc

analysis demonstrated that differences were significant when ASD and ASD+ADHD groups were compared with the ADHD group. For instance, in ADHD group latency to nontarget Kanizsa stimuli was 52 ms longer than in ASD, 73 ms longer than in ASD+ADHD, and 79 ms longer than in the CNT group (all ps < .01). However, in response to target stimuli only ASD and ADHD groups P3a latencies were statistically distinct (66 ms longer in ADHD, $p = .002$). Similar trends of P3a latency differences were found not only for midline but also for all other frontal and fronto-central ROIs. Grand averages of frontal ERP in four groups are shown in a Figure 2.
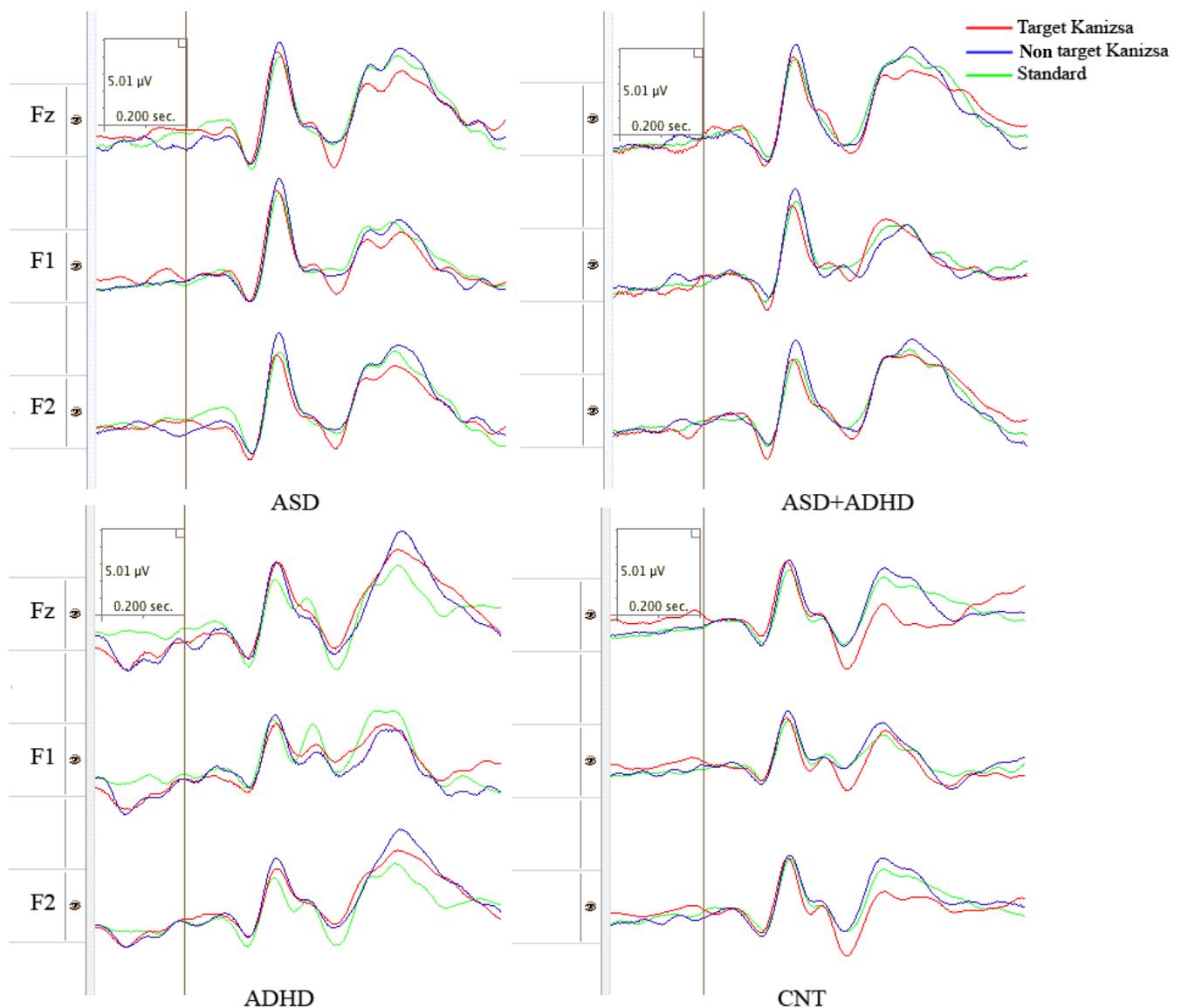

Figure 2. Frontal (Fz, F1, F2) ERPs to target Kanizsa, nontarget Kanizsa and standard stimuli in ASD, ASD+ADHD, ADHD, and CNT groups ($N = 18$/per group).

Posterior ERPs: Parietal and parieto-occipital N100, N200, and P300 (P3b). There were no significant between group differences found for amplitude and latency of the parietal and parieto-occipital N100 and N200 components. The parietal P3b ERP component did not show any statistically significant between group differences in amplitude. Between group differences in the latency of P3b were found only for frequent standards, $F(3, 71) = 2.67$, $p = .046$ across both left and right hemisphere; while at the right parietal and parieto-occipital ROI $F(3, 71) = 3.64$, $p = .015$. Post hoc analysis yielded statistically significant difference in latency (31 ms, $p = .011$ at the right ROI; 26 ms, $p = .047$ across both ROIs) between ADHD and typical controls, with more prolonged latency being noted in the ADHD

group. Stimulus type (standard, nontarget Kanizsa, target Kanizsa) had main effect, $F(2, 67) = 5.75$, $p = .004$, partial sigma squared = 0.107, observed power = 0.85. Stimulus x Group interaction was significant, $F(3, 66) = 2.39$, $p = .029$, partial sigma squared = 0.069, observed power = 0.81. This effect can be described as a delayed latency to target and nontarget Kanizsa stimuli in ADHD, and similar latency to all stimuli in the ASD and at a lesser extent in the ASD+ADHD group, whereas typical controls showed longer latency to targets, shorter to both task-irrelevant stimuli (Figure 3). Grand averages of posterior (parietal and parieto-occipital) ERPs for four groups are presented in Figure 4.
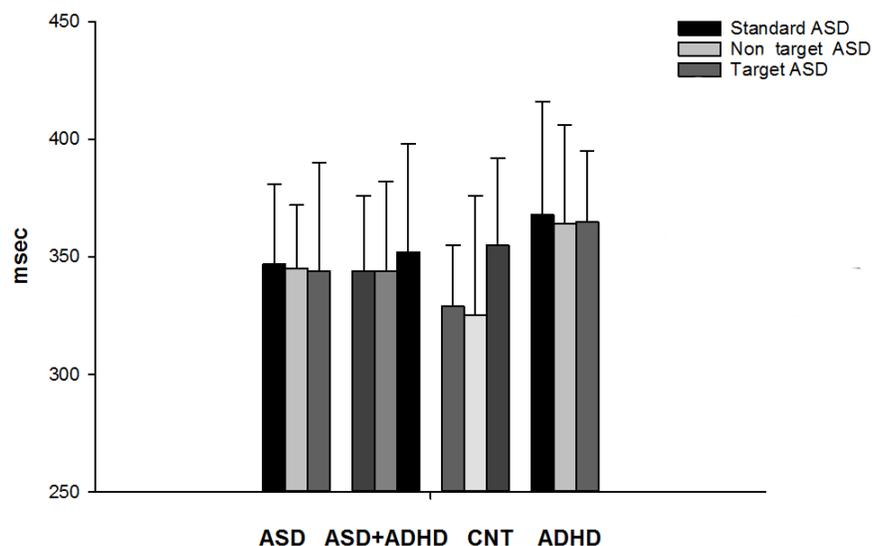

Figure 3. Latency of parietal P3b ERP component (mean with standard deviations) in response to standard, nontarget Kanizsa and target Kanizsa figures in visual oddball task in four groups of children (ASD, ASD+ADHD, CNT, ADHD, *N* = 18/per group). Stimulus x Group interaction was significant (*F* = 2.39, *p* = .029). Children with ADHD have delayed latencies to all type of stimuli, while ASD-only group is featured by similar latency to both task relevant and task-irrelevant stimuli. Note that control children (CNT group) showed shorter latency to both task-irrelevant items (standard and nontarget Kanizsa).
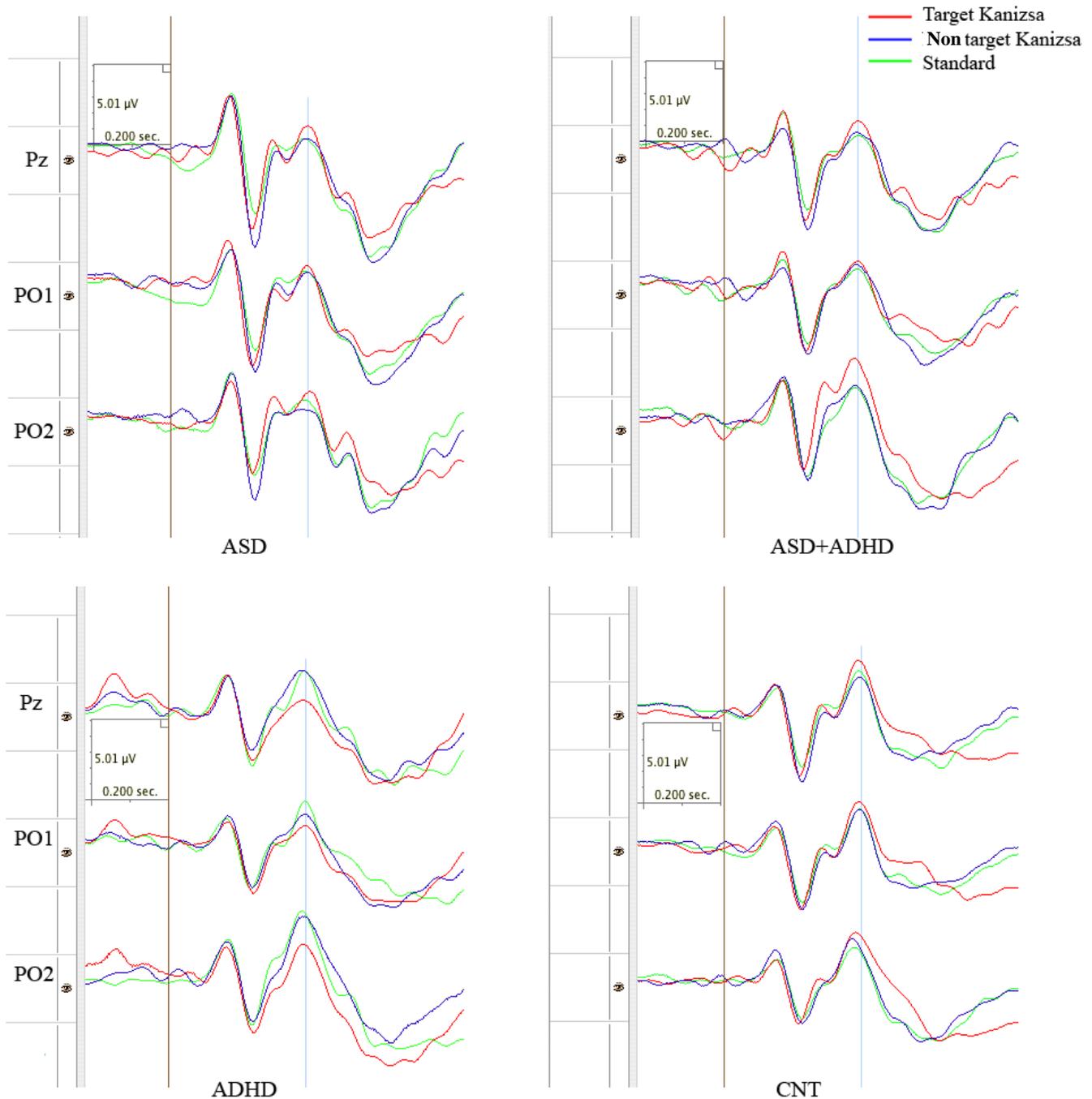
Figure 4. Parietal and parieto-occipital (Pz, P01, P02) ERP to target and nontarget Kanizsa and standard stimuli in ASD, ASD+ADHD, ADHD, and CNT groups. P3b component is marked by a blue line.

Discussion

The present study investigated differences in the behavioral (RT, accuracy, error rate, post-error slowing) and neurophysiological (ERP, including response-locked ERN and Pe) correlates of

executive functions during task performance in children with ASD, ADHD, ASD+ADHD, and neurotypical controls (CNT). Our study also explored whether these prospective biomarkers were shared or distinct in comorbid ASD+ADHD by using a behavioral screening (RT, error rate, post-

error RT adjustment) and ERP paradigm (ERP at frontal and parietal sites, response-averaged error-related negativity, and error-related positivity) that we implemented in previous studies (Sokhadze, Baruth, et al., 2009; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Sokhadze, Tasman, Sokhadze, El-Baz, & Casanova, 2016). Our findings indicate a dissociation between disorders on the basis of distinct stages of illusory figures processing during performance on Kanizsa task. In particular, children with ASD diagnosis (both ASD-only and ASD+ADHD) showed alterations at the early stages signal processing along with impairments in habituation to task-irrelevant stimuli, committed more errors and presented deficits in error monitoring and post-error response adjustment and correction; while children with ADHD displayed abnormalities at a later processing stage, mostly by displaying delayed ERP latencies of cognitive potentials. The comorbid ASD+ADHD group presented only partially as an additive condition with the ASD diagnosis factoring more in response monitoring and correction functions. The role of ADHD factor was better pronounced in latencies of the late ERP components. This supports the use of objective neural measurement of complex signal processing to delineate pathophysiological mechanisms in complex overlapping neurodevelopmental disorders such as ASD and ADHD. Our results show that children with ASD, ADHD, and ASD+ADHD do not differ on mean reaction time, but they commit more errors than neurotypical children. Furthermore, children with ASD and ASD+ADHD do not present normative post-error slowing of RT indicative of impaired error correction capacity. As evidenced by a higher rate of response errors (total errors and omission errors) and impaired post-error normative RT slowing and lower amplitude of ERN, the ASD+ADHD group appears to share impairment in performance monitoring and error detection and correction with the ASD group. This combined group, as compared to ASD-only group, had higher attention deficits scores and higher general ASEBA attention *T*-score and higher stereotype behavior rating scores on the ABC subscale emphasizing that ADHD diagnosis factors in severity of attention-related symptoms and stereotype behaviors. In addition, ADHD comorbidity affects latency of cognitive potentials (P3a, P3b) at the frontal and parietal topographies, especially in response to nontarget distracter stimuli. Latencies of both P3a and P3b in ADHD and ASD+ADHD groups were significantly delayed. Conversely, other stimulus-locked ERP measures (e.g., amplitude to targets) do not appear to be distinctive in discriminating between the ASD, ADHD, or ASD+ADHD groups. On the basis of performance monitoring and correction phenotype, the common co-occurrence of this particular executive function deficit seems to reflect a comorbidity of two separate conditions with distinct impairments. Our study showed certain similarities and differences in executive functioning between ASD, ADHD, and ASD+ADHD groups. Identification of group differences among children with ASD-only, ADHD-only, ASD+ADHD, and neurotypical (CNT) children during performance on attention task may lead to better understanding of clinical phenotypes (Gadow, DeVincent, & Schneider, 2009).

One of the most significant findings of this study was that response-locked ERN is less negative both in ASD and ASD+ADHD groups as compared to both ADHD and control groups, thus supporting our prior findings of differences in error monitoring impairment extent in ASD and ADHD. In this regard it is very important to emphasize the importance of such frontal response-locked potentials as ERN, as it may provide a viable biomarker for differentiation of the impact of ASD and ADHD in the comorbid ASD+ADHD condition. Combination of such behavioral response measures as RT, accuracy, post-error slowing, and frontal ERN/Pe indices of error-processing in children with ASD, ADHD, ASD+ADHD, and in typical children allows us to assess the ability to monitor ongoing behavior and exercise adaptive control. It is therefore of interest that our prior studies reported on several deficits in error monitoring function in autism (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze et al., 2014). There are somewhat less reports about performance monitoring abnormalities in ADHD using ERN/Pe measures. Several studies addressed neural correlates of error processing and behavioral monitoring measures in children and adults with ADHD (Burgio-Murphy et al., 2007; Groom et al., 2010; Hermann et al., 2010; Liotti et al., 2005). For instance, the Groen et al. (2008) study used ERN/Pe using ERP technique considering error processing specifics as a useful method for dissociating ADHD from ASD and elucidating pharmacotherapy effects on performance monitoring in ADHD. Our prior study (Sokhadze, Baruth, El-Baz, et al., 2010) also discussed error processing measures as useful biomarkers of executive dysfunctions in children with ASD. The current study contributes to these investigations by adding an ADHD group as well as comorbid ASD+ADHD and a group of typically developing children as contrast groups.

Our prior study (Sokhadze, Baruth, El-Baz, et al., 2010) found substantial differences in error monitoring measures (e.g., in ERN and post-error adjustment) between the ASD and ADHD groups; though both groups showed more deficits compared to the typical individuals. However, we could not find group differences in amplitude and latency of Pe measure. Our current study suggests that impaired conflict monitoring is more pronounced in ASD than in ADHD and neurotypical children and that ASD probably contributes more significantly to error detection and correction deficit in the comorbid ASD+ADHD group. Our study specifically found that children with ASD and those with ASD+ADHD have more performance monitoring deficit (lower ERN, impaired post-error slowing of RT) compared to ADHD alone and CNT children. The neuronal source of ERN has been recognized as frontal and localized in the anterior cingulate cortex (ACC) (Taylor, Stern, & Gehring, 2007). The ERN is hypothesized to reflect phasic ACC activity in response to reinforcement signals from the mesencephalic dopamine system that serves as a trigger for further processing of the event and further deliberate compensatory behavior (Holroyd & Coles, 2002). In our prior studies (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012ab, 2018), we already examined the possibility that children with ASD exhibit a deficiency in the processing of error, reflected by a reduction and delays in the ERN and Pe response-locked brain potentials. Our results showed that ASD patients had high rate of errors in the visual oddball task. In addition, in neurodevelopmentally normal subjects, it has been observed that after an error has been committed, subjects show slower RT and decreased error rates. These changes have been interpreted as revealing alterations in the speed–accuracy strategy of the subjects possibly due to error-induced control processes and concomitant corrective adjustments. The patients with ASD showed opposite response: faster post-error RT instead of slowing down. We found as well lower ERN amplitude and prolonged Pe in ASD as compared to typical controls. The reduced ERN along with a lack of post-error RT slowing in autism was interpreted as an insensitivity to detect and monitor response errors and reduced ability of execute corrective actions (Sokhadze, Baruth, El-Baz, et al., 2010). Results were indicative of reduced error awareness and a failure in stimulus-response mapping adjustment in ASD when dealing with situations where erroneous responses may occur.

At the frontal topography, the ASD group and combined ASD+ADHD show higher stimulus-locked early ERP component (N100) amplitude to all stimuli (i.e., standards, nontarget and target Kanizsa figures) and delayed latency to nontargets as compared to controls. These groups showed higher P3a amplitude as compared to the ADHD group. Children with ADHD showed delayed latency of the frontal P3a to nontargets as compared to the ASD, ASD+ADHD and typical controls. At the posterior topographies, the ADHD group had longer latencies to each type of stimuli, while the ASD group along with ASD+ADHD had similar latency to all stimuli. It should be noted that we found group differences predominantly in frontal ERP components indicating that these neurodevelopmental groups exhibit frontal function deficits. Most behavioral and ERP measures in this study show that the ASD group is significantly different from controls on many measures, but to a lesser extent different from the ADHD group. The most pronounced was the difference in reactivity to nontarget items. Autistic children showed excessive response to frequent standards and rare nontarget distracters. Differences between ADHD groups (ADHD and ASD+ADHD) and typical controls were minimal and were mostly manifested in prolonged latencies of ERP. Shorter latency and higher amplitude of the early frontal negativity (N100) in the autism group with minimal differentiation of response magnitude to either target or nontarget stimuli is an interesting finding that replicates our earlier report (Sokhadze, Baruth, et al., 2009; Sokhadze, Baruth, Tasman, et al., 2010) where different visual oddball task was used. Visual processing is based on a core system consisting of occipito-temporal regions in extrastriate visual cortex (Haxby, Hoffman, & Gobbini, 2002) although parietal (Posner & Petersen, 1990) and frontal (Clark, Fan, & Hillyard, 1994) regions also play a role in directing visual attention. The visual N100 is considered an index of stimulus discrimination (Hopf, Vogel, Woodman, Heinze, & Luck, 2002; Vogel & Luck, 2000); Visual N100 over frontal electrode sites most likely is reflective of frontal generators (Clark et al., 1994). The visual N100 generally is augmented during attentional stimulus processing, which is also known as the N1-effect (Hillyard, Hink, Schwent, & Picton, 1973), and is larger towards task-relevant target stimuli (Hillyard, Mangun, Woldorff, & Luck, 1995; Luck, Heinze, Mangun, & Hillyard, 1990). Therefore, augmented and undifferentiated N100 in response to all stimuli regardless of their task relevance in the ASD group probably reflects deficient discrimination capacity.

Most investigations into visual processing in ASD have focused predominantly on P300 (Courchesne,

Courchesne, Hicks, & Lincoln, 1985; Courchesne, Lincoln, Kilman, & Galambos, 1985; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Hoeksma et al., 2006; Kemner et al., 1999; Polich, 2007; Townsend et al., 2001; Verbaten et al., 1991). As compared to cognitive P300 component, there have been significantly fewer studies focused on the early stage of visual perceptual processing in ASD (Jeste & Nelson, 2009). In our prior ERP studies (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze et al., 2017) on novel distracters processing in children with ASD and neurotypical children, we reported that ASD group showed higher amplitudes and longer latencies of early ERP components such as parieto-occipital P100 and frontal and fronto-central N100 to novel distracter stimuli in both hemispheres. Studies of P300 in ADHD have suggested that children with this diagnosis have attenuated P300 to both auditory and visual stimuli (Barry et al., 2003). In children with ADHD, especially with those with the combined type of ADHD as compared to inattentive type, a decreased P300 at centro-parietal sites has been reported in conjunction with an augmentation at frontal sites (Banaschewski et al., 2003; Banaschewski, Roessner, Dittman, & Santosh, 2004; Dimoska, Johnstone, Barry, & Clarke, 2003; Duncan et al., 2009; Johnston et al., 2011; Johnstone & Barry, 1996; Klorman et al., 1983; Smith et al., 2004). In ADHD population, some selective attention studies found a smaller early frontal negativity in ADHD as compared to controls, suggesting deficiencies as well in early attention processes (Jonkman et al., 2004; Satterfield, Schell, & Nicholas, 1994; van der Stelt, van der Molen, Gunning, & Kok, 2001). For the P300, the findings were inconsistent, demonstrating no differences in amplitude, a smaller amplitude or a deviation in scalp distribution but majority reported delayed latencies of most ERP components in response to target stimuli (Dimoska et al., 2003; Jonkman et al., 1997, 2004; Smith et al., 2004). Interesting results in our study were found for the P3a (sometimes referred to as the novelty P300 or attention-orienting P300). This is a fronto-central wave occurring within a time window of 300 to 520 ms that reflects an aspect of the orienting response and has been related to evaluative attentional processes (Hruby & Marsalek, 2003; Polich, 2003). The ASD group shows clearly augmented and delayed frontal P3a that might have resulted from an impaired early differentiation of target and nontarget items (e.g., on N100 stage) and more effortful compensatory strategies involved for successful target identification and correct motor response selection. In general, the autistic group

showed prolonged latencies to standard and rare nontarget illusory figures, and relatively unaffected response to targets. These results suggest that individuals with autism probably over-process information needed for the successful differentiation of task-relevant and task-irrelevant stimuli. The P3b is a centro-parietal wave occurring between 320 and 560 ms that has been linked to task-relevance and the decision-related character of the eliciting stimulus; it reflects memory-updating processes and/or processing closure (Picton, 1992). Most studies agree that the P3b has multiple dipole sources (Halgren, Marinkovic, & Chauvel, 1998; Knight, 1997; Townsend et al., 2001). Considering that most studies on P3b in ADHD report attenuated amplitude and prolonged latency of this cognitive component (Banaschewski et al., 2003, 2004; Barry et al., 2003; Dimoska et al., 2003; Duncan et al., 2009; Jonkman et al., 2004; Satterfield et al., 1994; Smith et al., 2004; van der Stelt et al., 2001), our finding of delayed latencies in the ADHD group is in good concordance with prior reports, even though amplitude differences did not reach significance levels. In general, our study found only minimal group differences in posterior stimulus-locked ERP components, as most ERP differences were at the anterior (frontal and fronto-central) topographies.

Our results show significant differences both in behavioral and electrocortical responses between ASD, ADHD, ASD+ADHD, and typical controls during performance on illusory figure test. In autism, a model of local hyperconnectivity and long-range hypoconnectivity explains many of the behavioral and cognitive deficits present in the condition, while the inverse arrangement of local hypoconnectivity and long-range hyperconnectivity in ADHD explains some deficits typical for this disorder (Williams & Casanova, 2010). Casanova, Buxhoeveden, and Brown (2002) proposed that information processing exists within a connectivity spectrum that affects the excitation/inhibition ratio of the cerebral cortex. A similar theory was later elaborated by Rubenstein and Merzenich (2003). Because local- and long-range cortical coordination is a finely tuned relationship of the signal-to-noise ratios, extremes of either edges of the spectrum can disrupt functionality and result in similar behavioral manifestations (e.g., attention deficits) despite opposing underlying etiologies in autism and ADHD. Following the hypothesis suggested in Williams and Casanova (2010) while considering dyslexia and autism conditions, it is possible to propose that ASD and ADHD are two conditions that share aspects which are also "cortical opposites." This idea may help explain why some children with ASD may

present with attention disorders similar to those seen typically in ADHD. Indeed, the present study identified distinct patterns of behavioral and ERP measures in ASD versus ADHD, and in co-occurring ASD+ADHD diagnosis suggesting that there may be distinct neural mechanisms underlying the expression of each these conditions (Ray et al., 2014).

Several limitations of this study should be noted. There was no differentiation of ADHD patients according to their subtypes (Inattentive, Hyperactive, or Combined) providing for clinical heterogeneity within our study groups. Our efforts were also very selective for our stated goals and did not include analysis of several ERP components (e.g., frontal P2a, parietal N2b, etc.) that could have provided additional markers of cognitive processes specifics in ASD and ADHD. Finally, the majority of the patients in this study were high-functioning individuals with ASD, ADHD, and ASD+ADHD, and generalization of results to more severe cases should be pursued with caution.

Conclusion

The current ERP study supports the proposed suggestion that some between group differences (e.g., ASD vs. ADHD vs. ASD+ADHD vs. CNT) could be manifested in the frontal ERP indices of executive functions during performance on illusory figure categorization task. Our study suggests that investigation of quantitative EEG and ERP biomarkers of executive function abnormalities and other behavioral performance deficits present in ASD and ADHD is a feasible research strategy that may contribute to the better understanding of nosology of these two disorders and their co-occurrence. Efforts to define the common or distinct phenotype of these two disorders are important as they may help to improve classification systems and enhance the assessment of these dual diagnosis (ASD+ADHD) cases for better targeted and more specific treatment strategies. The study supports the use of objective neurophysiological biomarkers such as ERP and behavioral (e.g., reaction time and accuracy) measures to delineate pathophysiological mechanisms in such complex and often overlapping disorders. These findings have significant implications for both shared and discrete symptom presentations for the two conditions. Moreover, they can help delineate the boundaries and overlap between ADHD and ASD, especially if children with ADHD-alone and ASD-alone are compared with those with dual ASD+ADHD diagnosis, and further

compared to neurotypical children used as a normative contrast group.

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