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RESEARCH ARTICLE

Reduced mismatch negativity in children and adolescents with autism spectrum disorder is associated with their impaired adaptive functioning

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Abstract

Children and adolescents on the autism spectrum display sensory disturbances, rigid and repetitive behavior, social communication problems and a high prevalence of impaired adaptive functioning. Autism is associated with slowed behavioral and neural habituation to repeated sensory input and decreased responses to sensory deviations. Mismatch negativity (MMN) reflects a pre-attentive difference in the neural response to sensory deviations relative to regularities and studies overall suggest that children and adolescents with autism tend to have smaller MMN. However, it remains unclear whether reduced MMN in autism is coupled to severity of specific autistic symptoms or more generally to lower level of adaptive functioning. To address these questions, the present study used electroencephalography (EEG) to assess whether auditory MMN in 59 children and adolescents with autism aged 7–14 years compared to 59 typically developing children and adolescents were related to specific autistic symptoms or level in adaptive functioning. As hypothesized, the autism group had a lower MMN amplitude than controls. Smaller MMN amplitudes were specifically associated with lower adaptive functioning in the autistic subjects but not in controls while no apparent relationships were observed with autistic-like social interaction and communication problems, atypical language, rigidity, stereotypy or sensory sensitivity symptoms. Our findings indicate that a blunted response to changes in sensory input may underlie or contribute to the generalized difficulties with adapting to daily life circumstances seen in children and adolescents with autism.

Lay Summary: Children and adolescents on the autism spectrum have a high prevalence of impaired adaptive functioning. Neuroimaging studies have reported that children and adolescents with autism display attenuated brain activity when discriminating sensory input. However, it is unknown whether this attenuation is related to autistic symptoms and/or adaptive functioning. The present study used electroencephalogram (EEG) to show that attenuated brain response in discrimination of novel compared to repetitive sounds in children and adolescents with autism is related to their impaired adaptive functioning.

KEYWORDS
adaptive behavior, ASD, autism, EEG, mismatch negativity

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INTRODUCTION

Autism spectrum disorders are characterized by a broad range of symptoms including difficulties in reciprocal social interaction and communication, rigid and repetitive thinking and behavior and sensory disturbances (American Psychiatric Association, 2013). Sensory disturbances have a high prevalence in children on the autism spectrum and can be observed prior to the social communication problems (Robertson & Baron-Cohen, 2017). Increased symptoms of sensory disturbance in these children are related to their social communication problems (Fernandez-Prieto et al., 2021; Hilton et al., 2007; Thye et al., 2018) and restricted and repetitive behaviors (Feldman et al., 2020).

The wide range of symptoms seen in autism may share a common neurobiological underpinning in the way sensory input are processed by the brain (Marco et al., 2011; Nordt et al., 2016). Different lines of evidence suggest that autism is coupled to impairments in the adaption to repetitive streams of sensory input (Guiraud et al., 2011; Jamal et al., 2021; Nordt et al., 2016). Functional brain imaging studies have shown that children and adults on the autism spectrum show reduced neural repetition suppression (Nordt et al., 2016) adaptation (Millin et al., 2018) and habituation (Jamal et al., 2021), even in infants at high risk of autism (Guiraud et al., 2011), and across sensory modalities (Jamal et al., 2021; Nordt et al., 2016). While the brain usually adapts to sensory regularities, it responds with heightened sensitivity to deviant sensory input (Garrido et al., 2009). Neuroimaging studies have reported that children and adults with autism show attenuated neural responses to deviant auditory input (Gomot et al., 2006; Orekhova et al., 2009; Sokhadze et al., 2009). Moreover, children with autism display an impaired ability to shift their attention to deviant visual stimuli measured with eye tracking (Vivanti et al., 2018), and lack behavioral responses to novel sensory stimulation (Baranek et al., 2013). Overall, it appears that autistic individuals show a neural and behavioral imbalance in how regular and deviant sensory input are processed.

Mismatch negativity (MMN) provides a unique window to study pre-attentive neural responses to regular and deviant sensory input. MMN can be captured with electroencephalography (EEG) and reflects the difference wave between regular and deviant sensory input (Garrido et al., 2009; Naatanen et al., 2007). There is growing consensus that MMN is attenuated in autism compared to controls. The majority of studies have reported attenuated MMN amplitudes in children and adolescents with autism (Abdeltawwab & Baz, 2015; Di Lorenzo et al., 2020; Dunn et al., 2008; Huang et al., 2018; Lepisto et al., 2005; Lepisto et al., 2006; Ruiz-Martinez et al., 2020; Vlaskamp et al., 2017), although a few studies found increased MMN amplitudes (Ferri et al., 2003; Lepisto et al., 2005; Yu et al., 2015) or no differences in MMN amplitudes (Chien et al., 2018; Gomot et al., 2011; Hudac et al., 2018; Jansson-Verkasalo et al., 2003; Weismuller et al., 2015). However, a recent meta-analysis (Chen et al., 2020) concluded that compared to controls, the MMN amplitudes in response to both speech-sound and tone-duration deviants are decreased in children but not adults with autism.

On the other hand, results on whether the timing of the MMN peak differs in autism are inconsistent, as studies report both shorter MMN latencies (Gomot et al., 2002; Gomot et al., 2011; Vlaskamp et al., 2017), prolonged MNN latencies (Abdeltawwab & Baz, 2015; Di Lorenzo et al., 2020; Huang et al., 2018) and no difference in latencies (Yu et al., 2015) in children and adolescents with autism. Many studies have additionally explored if children with autism display abnormal brain potentials as sensory deviants enters awareness. The P3a is a positive wave that peaks around 300 milliseconds after stimulus onset following MMN and is thought to reflect an involuntary orientation and switch in attention to deviant sensory input (Polich, 2007). Results on P3a in autism are likewise discrepant as the P3a amplitude is reported to be higher in children and adolescents with autism compared to typically developing children and adolescents by some studies (Ferri et al., 2003; Hudac et al., 2018; Vlaskamp et al., 2017; Yu et al., 2015) but not others (Gomot et al., 2011; Huang et al., 2018; Lepisto et al., 2005; Lepisto et al., 2006).

So far, only a few studies have examined whether the attenuated MMN seen in autism is related to the severity of autistic symptoms. The attenuated MMN amplitude observed in children and adolescents with autism has been related to increased severity in overall autistic symptoms (Abdeltawwab & Baz, 2015) but also to less severity in autistic symptoms (Vlaskamp et al., 2017). Additionally, one study finds that attenuated MMN amplitude in children and adolescents with autism is associated with increased self-reported sensory sensitivity (Ludlow et al., 2014), while others report no relationship (Ruiz-Martinez et al., 2020) or an association between increased MMN amplitude and auditory sensitivity (Leno et al., 2018). Knowledge is still lacking on whether inter-individual variations in MMN amplitudes are coupled to the broad range of autistic symptoms and adaptive functioning in children with autism and their typically developing peers.

In summary, children and adolescents with autism tend to show attenuated MMN amplitudes but it remains unclear whether a smaller MMN amplitude is related to specific autism symptoms (Abdeltawwab & Baz, 2015; Leno et al., 2018; Ludlow et al., 2014; Ruiz-Martinez et al., 2020; Vlaskamp et al., 2017). In the present study we hypothesized that children and adolescents with autism displayed attenuated MMN compared to typically developing controls. Furthermore, we aimed to examine whether attenuated MMN in children and adolescents with autism was related to increased severity of specific autistic symptoms including social interaction and communication problems, idiosyncratic language, rigid and repetitive thinking and behavior, sensory disturbances, or more generally to

TABLE 1 Control and clinical variables for children with autism and controls

	Autism subjects ($N = 59$)	Controls ($N = 59$)
Control variables		
Age	11.89 ± 1.98	11.75 ± 2.00
Sex (female/male)	10/49	12/47
WISC-V	98.0 ± 14.0	102.3 ± 10.9
Parental education (N [%])		
Elementary school	7 (6.0%)	1 (0.8%)
Skilled worker	27 (23.1%)	28 (23.7%)
High school	8 (6.8%)	12 (10.2%)
Short higher education of 2 years or less	19 (16.2%)	17 (14.4%)
Medium higher education from 2.5 to 4.5 years	36 (30.8%)	45 (38.1%)
Long higher education of 5 years or more	20 (17.1%)	15 (12.7%)
Comorbidity		
Anxiety and stress-related disorders	9	0
ADHD/ADD	8	0
Depression	2	0
Eating disorder	1	0
Clinical assessment variables		
ABAS-2 GAC[a]*	64 (56–79)	95 (85–107)
ASRS Social Communication*	63.8 ± 7.1	45.3 ± 8.1
ASRS Unusual Behaviors*	65.0 ± 8.7	46.0 ± 6.9
ASRS Peer Socialization[a]*	66 (59–74)	43 (40–50)
ASRS Adult Socialization*	61.2 ± 8.4	47.0 ± 7.6
ASRS Social–Emotional Reciprocity*	62.9 ± 6.4	45.9 ± 6.2
ASRS Atypical Language[a]*	61 (52–68)	44 (39–48)
ASRS Behavioral Rigidity*	66.4 ± 9.1	45.9 ± 7.5
ASRS Stereotypy*	60.5 ± 9.8	49.8 ± 6.7
ASRS Sensory Sensitivity*	65.3 ± 11.8	46.4 ± 6.9
ADOS-2 Calibrated Severity Score	6.1 ± 2.0	-
ADI-R Reciprocal Social Interaction	12.6 ± 5.5	-
ADI-R Communication	11.0 ± 5.2	-
ADI-R Repetitive and Stereotype Behaviors[a]	3 (1–4)	-

Note: Data are reported with mean ± standard deviations or with medians and quartiles ([a]) if the variable significantly deviated from the normal distribution. Missing data are described in the method section. * = Significant group difference at $p < 0.001$. Abbreviations: ABAS-2 GAC, adaptive behavior assessment system-second edition general adaptive composite; ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ADI-R, the autism diagnostic interview-revised; ADOS-2, the autism diagnostic observation schedule, 2nd edition, Module 3; ASRS, autism spectrum rating scale; WISC-V, Wechsler intelligence scale for children—fifth edition.

lower adaptive functioning, which have a high incidence in children and adolescents with autism (Kenworthy et al., 2010; Pathak et al., 2019; Tillmann et al., 2019). We also investigated whether associations were of a more general nature or exclusive to symptoms of autism.

METHODS

Participants

The Regional Medical Ethics Committee (REG-116-2017) and the Danish Data Council (SJ-620) approved the study protocol. Fifty-nine children and adolescents aged 7–14 years (49 boys; 10 girls) with a diagnosis of autism spectrum disorder following the International Classification of Diseases, 10th Edition (ICD-10) (WHO, 1992) were included in the study. The participants were recruited from child and adolescent psychiatric outpatient clinics in Region Zealand, Denmark and through online advertisement. Of the 64 children and adolescents with autism initially recruited to the study, two were excluded due to intellectual disability, and three were excluded due to non-compliance. Furthermore, 59 typically developing children were included in the study as a control group, matched on age, sex, intelligence and parental education with the autism group. The recruitment of control subjects took place through schools in Region Zealand and online advertisement. Participants and their parents received written and oral information about the study and written informed consent was obtained from all parents before study initiation. Parental education was coded in one of six categories (see Table 1). One child with autism had missing data on parental education. The exclusion criteria for children and adolescents with autism and controls were premature birth (gestational age <35 weeks), intellectual disability (intelligence quotient [IQ] <70), or serious neurological or somatic illness. Additionally, controls were excluded if they had a psychiatric diagnosis or received psychopharmacological treatment. Nineteen children with autism had a comorbid diagnosis (see Table 1). Seven children with autism received psychopharmacological treatment (central stimulant medication = 4, selective serotonin reuptake inhibitor = 2, noradrenaline reuptake inhibitor = 1). Eighteen children with autism had either a mother ($N = 11$), a father ($N = 5$) or both ($N = 2$) with a self-reported psychiatric diagnosis (depression = 7, anxiety = 4, autism = 3, ADHD = 2, borderline personality disorder = 1, Post-Traumatic Stress Disorder [PTSD] = 1, ADD = 1, bipolar disorder = 1). Four of the controls had a parent with a self-reported psychiatric disorder (depression = 3, with PTSD = 1).

Cognitive assessment

The Wechsler intelligence scale for children—Fifth edition

All participants were assessed with the Wechsler intelligence scale for children—Fifth edition (WISC-V). The

WISC-V measures general intellectual ability in children and adolescents aged 6–16 years (Wechsler, 2014). We used the Full-scale IQ score based on seven of the primary subtests. The Full-scale IQ has a mean of 100 and a standard deviation of 15.

Clinical assessment

The autism diagnostic observation schedule, 2nd edition

All subjects with autism were assessed with the autism diagnostic observation schedule, 2nd edition (ADOS-2) Module 3, which is a semi-structured interview and play assessment of social interaction, communication and idiosyncratic and stereotypical behavior (Lord et al., 2000). The ADOS-2 assessments were conducted by trained clinicians licensed at the Danish Autism Centre. The severity of autism symptoms on ADOS-2 is measured by combining a Social Affect domain (10 items; range 0–20) and a Restricted and Repetitive Behaviors domain (4 items; range 0–8). Both domains are combined to estimate a total score (range 0–28). ADOS algorithm totals can be used to derive a Calibrated Severity Score (ADOS-CSS) that ranges from 1 to 10, with higher scores indicating more severe autism symptom severity.

The autism diagnostic interview-revised

All parents to subjects with autism were interviewed by trained clinicians with the semi-structured autism diagnostic interview-revised (ADI-R; Rutter et al., 2003). The ADI-R measures the number and severity of parent-reported autistic symptoms present in the child's development. ADI-R is scored using a Diagnostic Algorithm, which provides a differentiated assessment in three domains: Reciprocal Social Interaction (15 items; range 0–30), Communication (13 items; range 0–26) and Restricted, Repetitive and Stereotyped Behaviors and Interests (6 items; range 0–12).

The autism spectrum rating scale

The severity of autistic-like symptoms within the last 4 weeks was assessed using the autism spectrum rating scale (ASRS), which is a parent-reported questionnaire for children and adolescents aged 6–18 years (Goldstein S, 2013). The ASRS measures autistic-like symptoms on the Social Communication and Unusual Behaviors scales. The Social Communication scale consists of Peer Socialization, Adult Socialization, and Social–Emotional Reciprocity subscales, while the Unusual Behaviors scale include Atypical Language, Behavioral Rigidity, Stereotypy and Sensory Sensitivity subscales. Symptom severity is rated on a 4-point Likert scale. Higher scores on the ASRS indicate more symptom severity. The internal consistency of the ASRS scales was excellent (Cronbach's alpha: 0.95).

Adaptive behavior assessment system—second edition

The adaptive behavior assessment system—second edition (ABAS-II) is a parent-report questionnaire that measures functional daily living skills in children and adolescents (Harrison & Oakland, 2003). The level of adaptive functioning is assessed with nine domains, including Communication, Community Use, Functional Academics, Home Living, Health and Safety, Leisure, Self-Care, Self-Direction and Social, which are summed to a General Adaptive Composite (ABAS-GAC) score. Questions are answered on a 4-point Likert scale. Higher scores on the ABAS-II reflect a higher level of functioning. Internal consistency for the ABAS scales was excellent (Cronbach's alpha: 0.93).

Electrophysiology

Mismatch negativity paradigm

All participants were assessed with the MMN paradigm from the Copenhagen Psychophysiological Test Battery (Vlaskamp et al., 2017). The procedures concerning MMN assessment as used in the current study were identical to the ones previously described (Vlaskamp et al., 2017). In short, children were seated in a comfortable chair in a silent room. Children were instructed to sit still, watch a muted cartoon movie and to ignore the presented sounds. Before test start, a hearing test that screened for impaired hearing at different frequencies and/or impaired right–left orientation was performed. The MMN paradigm consisted of 1800 auditory stimuli. All stimuli were presented binaurally through tubal insert earphones (EARtoneVR, Etymotic Research), by a computer running Presentation software (Neurobehavioral Systems, Inc.). The paradigm consisted of four stimuli: In 83% of the cases, a standard tone with a frequency of 1000 Hz, intensity of 75 dB and duration of 50 ms was presented. Within this sequence of standard stimuli, three types of deviants were presented, each with a probability of 6% and intensity of 75 dB: Frequency deviants of 1200 Hz and 50 ms, Duration deviants of 1000 Hz and 100 ms and Frequency-Duration deviants of 1200 Hz and 100 ms. The inter-stimulus interval (ISI) was randomized between 400 and 500 ms. The total duration of the MMN test was approximately 14 min.

Signal recording and processing

The EEG signal was recorded using a BioSemiVR system with 64 ActiveTwo electrodes placed according to the

extended 10–20 system at a sample rate of 2 kHz (2048 Hz) with low-pass filter set at 1/5th of the sample frequency (409.6 Hz), and with CMS-DRL as reference electrodes. Processing of the EEG signals was performed with Brain Electrical Source Analysis (BESA) software (version 6.0, MEGIS Software GmbH, Grafelfing, Germany). Data processing was restricted to the frontal/midline electrodes Fz, FCz, and Cz where MMN was expected to reach maximum amplitude (Oranje et al., 2008). Initially, data were resampled from the original 2 kHz to 250 Hz to allow easier file handling. Subsequently, the data were adjusted for eye-artifacts using the adaptive correction method in BESA (Ille et al., 2002). Data were epoched (from 100 ms prestimulus to 900 ms poststimulus) and corrected for movement artifacts by removing those epochs from the dataset that contained amplitude differences between maximum and minimum exceeding 75 μV in the relevant time window (see scoring below). The data were then bandpass-filtered (high-pass: 0.5 Hz, low-pass: 40 Hz), after which the average signals of each of the three deviant types was subtracted from that of the signal to standard stimuli for each individual subject. Finally, the data were re-referenced to the average reference after which minimum MMN amplitudes were scored within a time window between 70 and 170 ms after stimulus onset for the frequency and frequency-duration deviants, and between 150 and 240 ms following stimulus onset for the duration deviant. Maximum MMN latency (time from stimulus to peak amplitude) was also scored. Latency scores were based on FCz, given that maximum amplitude was reached on that electrode. Similarly to MMN, the P3a amplitudes were scored as the maximum amplitude in a window from 160 to 300 ms after stimulus onset for the frequency and frequency-duration deviants and 200–330 ms after stimulus onset for the duration deviant. Please note that we decided to carry out peak scoring, as opposed to scoring the average amplitude in a specific area, because MMN might still be developing in the age range of our population, which could potentially increase the risk that MMN of at least a number of individuals might fall outside that average scoring area.

Statistical analysis

Statistical analyses were conducted using SPSS 28. A p-value below 0.05 was considered significant. Continuous variables with a significantly non-normally distributed skewness above or below $Z \pm 1.96$ (two-sided $p < 0.05$) in the patients and/or controls were Rankit-transformed and used in the statistical analyses. ABAS-GAC, ADI Restricted, Repetitive and Stereotyped Behaviors and the majority of the MMN and P3a amplitudes of interest were significantly non-normally distributed ($p < 0.05$), except amplitudes to the duration deviant for electrodes Fz and Cz. We normalized all MMN and P3a amplitudes and latency scores with Rankit-transformation to keep the outcome measures in scale to each other. Group differences in age, Full-scale IQ, ASRS Social Communication, ASRS Unusual Behaviors and ABAS-GAC were tested with two-tailed t-test and Chi-square was used to test for differences in sex and parental education.

We used a three-way repeated measures ANOVA to test the hypothesis that the autistic subjects displayed a smaller MMN amplitude compared to controls. Group was entered as the between-subject factor. The electrodes (Fz, FCz and Cz) were entered as the first within-subject factor while deviant types (Duration, Frequency and Duration-Frequency) were entered as the second within-subject factor. Group differences in MMN latency were explored using two-way repeated measures ANOVA with group as the between-subject factor while deviant types were entered as the within-subject factors. We used three-way repeated measures ANOVA to test group differences in the P3a amplitudes. Group was entered as the between-subject factor while the electrodes were entered as the first within-subject factor and deviant types as the second within-subject factor.

A two-tailed Student's t-test was used to confirm if observed group differences were related to lower MMN amplitudes in the autism group. We used multiple linear regression models to ensure that likely confounders did not mediate group differences. All multiple linear regression models were visually inspected to ensure normal distribution of the residuals and that covariates fulfilled criteria of noncollinearity defined as a tolerance >0.3. Initially, group was entered as the predictor of interest. The first model was controlled for comorbidity and psychopharmacological medication, while a second model was controlled for age, sex, parental education and Full-scale IQ. Because linear regression modeling is not able to model non-binary categorical covariates, parental education was recoded into lower education (elementary school, skilled worker, high school or short higher education of 2 years or less) and higher education (medium to long higher education).

Subsequently, we corrected the multiple linear regression model for the ASRS Social Communication score, ASRS Unusual Behavior score, and the ABAS-GAC score in separate linear regression models together with age, sex, parental education and Full-scale IQ. Subsequently, we explored whether the MMN amplitude was coupled to ASRS Social Communication score, ASRS Unusual Behavior score, and/or the ABAS-GAC score. Therefore, we included an interaction term for group by the ASRS Social Communication score, the ASRS Unusual Behavior score, and the ABAS-GAC score, respectively, to examine if inter-individual variations in MMN amplitude were uniquely associated with autism symptoms or adaptive functioning in the autism group compared to controls. If an interaction term was significant, within-group analyses were performed entering the ASRS Social Communication score, ASRS

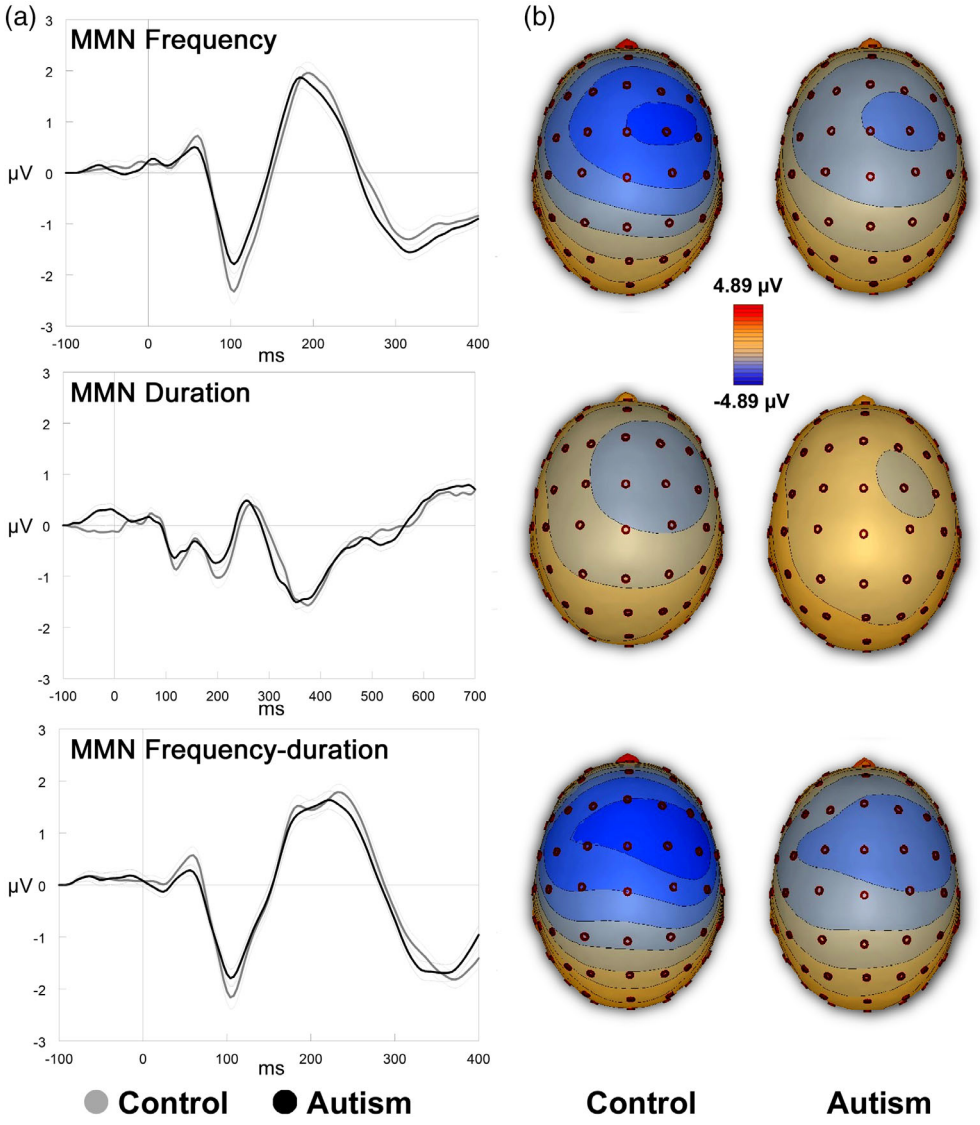

FIGURE 1 The grand averages of the mismatch negativity (MMN) amplitudes from electrode FCz are displayed in (a) for each type of deviant in children with autism and controls, while (b) shows where maximum amplitudes were reached on the scalp for each of the deviant types in children with autism and controls. Positivity is illustrated upwards. Children with autism are coded in black and controls are coded in gray. The standard error of the mean (SEM) is displayed with stippled lines for each waveform.

Unusual Behavior score, and the ABAS-GAC scores together in the same linear regression model controlling for age, sex, parental education and Full-scale IQ. Otherwise, whole-group analyses were performed instead. Lastly, multiple linear regression models were performed in the autism group to explore if inter-individual variations in MMN amplitude were related to the ADOS-CSS or ADI scores controlled for age, sex, parental education and Full-scale IQ.

RESULTS

Groups did not differ in age, sex, parental education or Full-scale IQ ($p > 0.05$) but did differ significantly in ASRS Social Communication, ASRS Unusual Behaviors and ABAS-GAC. Visual inspection of the MMN waves (see Figure 1a) indicated that the MMN response was successfully captured in children with autism and controls. As expected, maximum amplitudes were observed at the frontal and midline electrodes in children with autism and controls (see Figure 1b). Figure 2 shows the amplitudes to the standard tones and each of the three MMN deviants. The MMN and P3a amplitudes and latencies for the group of children and adolescents with autism and the control group are displayed in Table 2.

Group differences in MMN and P3a

The repeated measures ANOVA showed a main effect of group across electrode and deviant types ($F[1116] = 5.086$; $p = 0.026$) with no significant interactions for group by electrode ($F[2, 232] = 0.047$; $p = 0.89$), group by deviant type ($F[2, 232] = 0.457$; $p = 0.61$) or group by electrode by deviant type ($F[4, 464] = 0.764$; $p = 0.53$). No significant main effect of group or interaction effects were observed for neither MMN latencies, P3a amplitudes nor P3a latencies ($p > 0.05$).

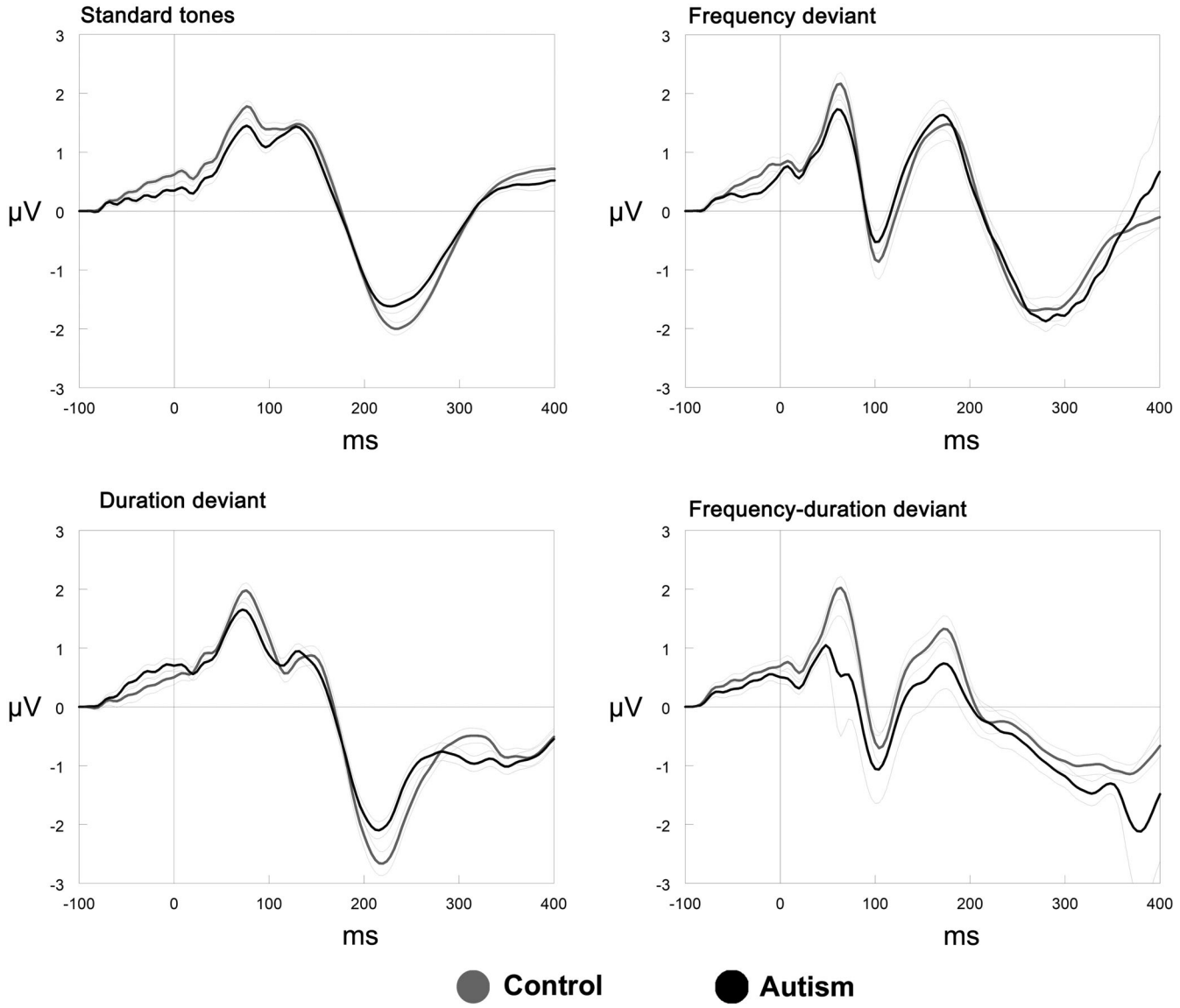

FIGURE 2 The figure shows the amplitudes to the standard tones and each of the three mismatch negativity deviants. Children with autism are coded in black and controls are coded in gray. The standard error of the mean (SEM) is displayed with stippled lines for each waveform.

A two-tailed *t*-test confirmed that the autism group had a smaller average MMN amplitude ($t[116] = -2.255$; $p = 0.026$; Cohen's $d = 0.63$) regardless of the type of deviant. Group differences stayed significant when controlling for comorbidity and psychopharmacological medication ($t[114] = 2.368$; $B = 0.303$; SE = 0.128; $\beta = 0.238$; $p = 0.020$). Group differences likewise survived correction for age, sex, parental education and Full-scale IQ ($t[112] = 2.312$; $B = 0.273$; SE = 0.118; $\beta = 0.214$; $p = 0.023$; see Figure 3a). The group difference in average MMN amplitude remained significant when additionally correcting for either the ASRS Social Communication scale ($p = 0.021$), ASRS Unusual Behavior scale ($p = 0.006$), but not when corrected for the ABAS-GAC scale ($p = 0.15$).

MMN amplitude associated with autism symptoms and adaptive functioning

We observed a significant interaction for group by the ABAS-GAC score ($t[110] = -2.011$; $B = -0.316$; SE = 0.157; $\beta = -0.183$; $p = 0.047$) but not for group by ASRS Social Communication or group by ASRS Unusual Behavior with the MMN amplitude ($p > 0.05$). In the whole-group analysis, attenuated MMN amplitude was significantly related to lower scores of ABAS-GAC corrected for ASRS Social Communication scale and ASRS Unusual Behavior scale ($t[110] = -2.877$; $B = -0.282$; SE = 0.098; $\beta = -0.438$; $p = 0.005$). In the within-group analyses, attenuated MMN amplitude was significantly related to lower scores on the ABAS-GAC

TABLE 2 MNN amplitudes of the frequency, duration and frequency-duration deviants on electrode Fz, FCz and Cz, respectively

	Autism subjects ($N = 59$)		Controls ($N = 59$)	
	Amplitudes			
	MMN	P3a	MMN	P3a
Frequency Fz	−1.85 (−3.07–1.29)	1.58 (0.76–2.45)	−2.24 (−3.87–1.64)	1.62 (0.89–2.67)
Frequency FCz	−2.10 (−3.14–1.41)	2.69 (1.41–3.88)	−2.63 (−3.93–1.70)	2.81 (2.02–3.79)
Frequency Cz	−1.38 (−2.38–0.60)	2.35 (1.52–3.20)	−1.73 (−2.83–0.97)	2.20 (1.27–3.71)
Duration Fz	−1.43 (−1.92–0.72)	0.44 (−0.01–1.41)	−1.54 (−2.52–0.67)	0.75 (0.22–1.26)
Duration FCz	−1.55 (−2.25–1.01)	0.84 (0.24–1.73)	−1.72 (−2.69–0.88)	1.22 (0.59–1.76)
Duration Cz	−1.19 (−1.94–0.47)	0.62 (−0.06–1.14)	−1.34 (−2.22–0.64)	0.99 (0.07–1.77)
Freq-Dur Fz	−1.80 (−2.75–1.49)	1.81 (1.11–2.51)	−2.13 (−3.18–1.47)	1.64 (1.01–2.31)
Freq-Dur FCz	−2.54 (−2.99–1.68)	2.39 (1.79–3.63)	−2.58 (−3.76–1.73)	2.59 (2.12–3.33)
Freq-Dur Cz	−1.58 (−2.04–0.95)	2.06 (1.26–2.79)	−1.74 (−2.54–1.14)	2.26 (1.0.43–2.84)
	Latency			
	MMN	P3a	MMN	P3a
Frequency FCz	104 (100–112)	200 (180–224)	104 (100–120)	200 (188–232)
Duration FCz	196 (172–216)	256 (240–276)	208 (180–220)	268 (244–288)
Freq-Dur FCz	108 (96–112)	208 (188–232)	104 (100–120)	228 (188–248)

Note: Data are reported with medians (lower quartile–upper quartile), because the majority of the variables significantly deviated from the normal distribution. Amplitudes are measured in μV and latencies are measured in ms. Freq-Dur, frequency-duration.
Abbreviation: MMN, mismatch negativity.

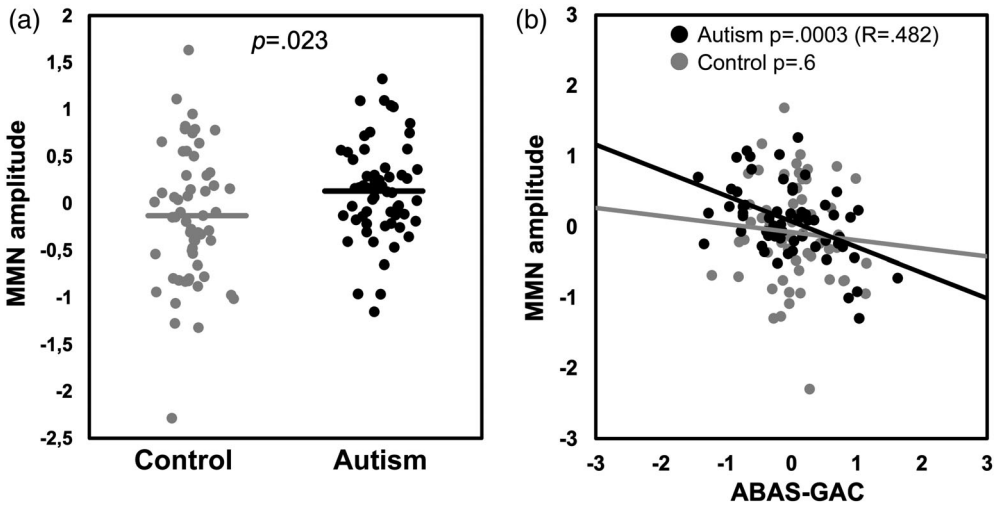

FIGURE 3 The partial plots derived from the multiple linear regression models display the group difference in the Rankit-normalized average MMN amplitudes in children with autism and controls (a) and the within-group analyses in children with autism and controls of the associations between the Rankit-normalized MMN amplitudes and the ABAS-GAC score (b). The regression analyses are controlled for age, sex, full-scale IQ, parental education, ASRS social communication scale and ASRS unusual behavior scale. Children with autism are coded in black and controls are coded in gray. The MMN amplitudes are the average of the three deviants and three electrodes (Fz, FCz, Cz) of interest. The values displayed on the y-axes and x-axes are the regression model residuals. ABAS-GAC, adaptive behavior assessment system-general adaptive composite; ASRS, autism spectrum rating scale; MMN, mismatch negativity.

corrected for ASRS Social Communication scale and ASRS Unusual Behavior scale in the autism group (t [51] = −3.924; B = −0.360; SE = 0.092; β = −0.526; p = 0.0003; see Figure 3b) while no apparent association was seen in the control group (t[51] = −0.543; B = −0.107; SE = 0.016; β = −0.107; p = 0.59). Whole-group analyses did not indicate that average MNN amplitude was related to the ASRS Social-communication or ASRS Unusual Behaviors scores ($p > 0.05$) across the autism group and controls. Neither

the ADOS-CSS nor the ADI-R social interaction score were related to average MMN amplitude in the autism group.

DISCUSSION

The primary aim of the present study was to examine whether attenuated MMN in children and adolescents with autism was associated with increased severity of the core autistic symptoms and lower level of adaptive functioning. As hypothesized, we observed that children and adolescents with autism on group average had a reduced auditory MMN amplitude of moderate effect size relative to their typically developing peers across all the deviants and electrodes that were analyzed. Notably, a lower MMN amplitude related significantly with decreased levels in global adaptive functioning, specifically in the autism subjects but not controls. MMN amplitudes showed no apparent relationship with autistic-like social interaction and communication problems, atypical language, behavioral rigidity, stereotypy or sensory sensitivity. We observed no group differences in MMN latency where prior findings have been highly divergent (Chen et al., 2020; Yu et al., 2015). Consistent with the majority of previous reports, we observed no group difference in P3a amplitude (Gomot et al., 2011; Huang et al., 2018; Lepisto et al., 2005) regardless of the type of deviant.

Our finding that children and adolescents with autism had a smaller MMN amplitude compared to controls is in line with the majority of MMN studies in autism (Abdeltawwab & Baz, 2015; Di Lorenzo et al., 2020; Dunn et al., 2008; Huang et al., 2018; Lepisto et al., 2005; Lepisto et al., 2006; Ruiz-Martinez et al., 2020; Vlaskamp et al., 2017) and a recent meta-analysis (Chen et al., 2020). Others studies however, have reported a higher MMN amplitude in children and adolescents with autism (Ferri et al., 2003; Lepisto et al., 2005; Yu et al., 2015) or no group differences in MMN amplitude (Gomot et al., 2011; Jansson-Verkasalo et al., 2003; Weismuller et al., 2015) but these studies included small sample sizes ($n < 20$) and were therefore more vulnerable to error variance such as random outliers. While the MMN amplitude is attenuated in children with autism, meta-analyses indicate that the MMN is normal in adults with autism (Chen et al., 2020; Schwartz et al., 2018). The lack of significant findings of attenuated MMN in autistic adults may be due to methodological shortcomings in study design (Schwartz et al., 2018). However, population studies have consistently observed that the MMN diminishes with age (Czigler et al., 1992; Pekkonen et al., 1996), so it seems plausible that group differences may get undetectable in adults.

Children with autism show delayed neural adaptation to repeated sensory input (Gomot et al., 2011; Jamal et al., 2021; Millin et al., 2018; Nordt et al., 2016) and reduced neural responses to sensory novelty (Gomot et al., 2006; Orekhova et al., 2009), which may explain why MMN is lower in autism. The failure to discriminate sensory regularities from sensory deviants is also seen behaviorally in children and adolescents with autism who have been shown to be impaired in shifting their attention to deviant visual stimuli (Vivanti et al., 2018), and lack behavioral responses to novel sensory stimulation (Baranek et al., 2013).

The predictive coding framework has gained increasing traction as a way to explain the core symptoms of autism (Lawson et al., 2014; Sinha et al., 2014; Van de Cruys et al., 2014). Shortly, the predictive coding framework assumes that when top-down predictions computed by the brain do not fit with bottom-up sensory input, a so-called prediction error occurs (Friston, 2005). Prediction errors are sometimes contextually informative but are at other times noisy and then better ignored. Children, adolescents and adults with autism are thought to display an inherent deficit in their ability to flexibly weighting whether prediction errors are noisy or informative (Van de Cruys et al., 2014). At the neuronal level, imprecise weighting of how informative prediction errors are may cause overfitted predictions that are not generalized to novel and unexpected situations (Lawson et al., 2014; Van de Cruys et al., 2014). This deficit is suggested to underlie the attenuated MMN response in autism as the steady stream of trivial sensory input are not optimally discriminated from novel and potentially informative input (Garrido et al., 2009). While some studies have reported impaired predictive coding in children and adults with autism (Gonzalez-Gadea et al., 2015; Goris et al., 2018; Grisoni et al., 2019; Kinard et al., 2020; Landa et al., 2016; Thillay et al., 2016), others found no evidence to support that predictive coding is atypical in autism (Beker et al., 2021; Knight et al., 2020). However, a recent, EEG study observed no apparent differences between children with autism and controls in making behavioral or neural predictions about upcoming events, but rather that autistic children displayed impaired neural entrainment and anticipatory activity (Beker et al., 2021). Thus, whether or not the attenuated MMN in autism is explained by deficits in predictive coding mechanisms remains to be clarified.

A few earlier studies have explored whether attenuated MMN amplitude in children and adolescents with autism was related to the severity of autism symptoms but so far, results seem to be mixed. While one study reported that attenuated MMN amplitude in autistic children and adolescents was coupled to increased severity of general autism symptomatology in autistic but not control children and adolescents (Abdeltawwab & Baz, 2015), another study found the opposite relationship as reduced MMN amplitude in children and adolescents with autism was associated with less autistic-like symptoms (Vlaskamp et al., 2017). Studies that have explored if sensory disturbances in autism were related to attenuated MMN amplitude are likewise mixed (Leno et al., 2018; Ludlow et al., 2014; Ruiz-Martinez et al., 2020). More sensory sensitivity has been associated

with attenuated MMN amplitudes (Ludlow et al., 2014), but also with increased MMN amplitude (Leno et al., 2018) while others found no apparent relationships (Ruiz-Martinez et al., 2020). The present study aimed to reconcile these inconsistencies as we examined whether attenuated MMN in autistic children and adolescents was related to specific core symptoms of autism, and/or to a more generalized impairment in global adaptive functioning, frequently reported in children and adolescents with autism (Kenworthy et al., 2010; Pathak et al., 2019; Tillmann et al., 2019). Notably, we observed that attenuated MMN amplitude in children and adolescents with autism was moderately associated with deficits in global adaptive functioning reflecting a moderate effect size, while no apparent relationships was seen with severity of autism symptoms. Of note, we assessed core autistic symptoms using a standardized clinical observation tool, as well as parent-reports on developmental history and present severity of autism symptoms. To our knowledge, this was the first study to show that attenuated MMN amplitude in children and adolescents with autism was linked to their adaptive behavior problems. Our findings may have clinical implications as the results emphasize that children and adolescents with autism tend to display a neurobiological vulnerability in the processing of auditory input that are generalized to global impairments in adaptive behaviors across a wide range of settings highlighting their need for well-structured and low-noise learning environments. Children and adolescents with autism have a high incidence of impaired adaptive functioning (Kanne et al., 2011; Kenworthy et al., 2010; Pathak et al., 2019; Tillmann et al., 2019) and maladaptive behaviors in childhood predispose to adverse outcomes later in life such as not being able to live independently, hold a job or develop meaningful relationships (Lord et al., 2020; Woolf et al., 2010). Adaptive behaviors are context-dependent and necessitate the ability to flexibly navigate through a continuously changing environment (Bertollo et al., 2020; Pugliese et al., 2016; Uddin, 2021). Recent lines of evidence indicate that the lower level of adaptive functioning in autism may partly be connected to the lack of neurocognitive flexibility seen in these children and adolescents (Bertollo et al., 2020; Uddin, 2021). Whether the inflexibility in the weighting of prediction errors formulated by the predictive coding framework is linked to the impaired level in adaptive functioning remains to be studied.

While a lower MMN response is frequently reported in children and adolescents with autism, it is not specific to the diagnosis of autism spectrum disorders. Reduced MMN has been observed in a wide range of mental and neurological disorders in particular in adolescents (Rydkjaer et al., 2017) and adults (Higgins et al., 2021; Light & Braff, 2005; Naatanen & Kahkonen, 2009) with schizophrenia, but also in adults with multiple sclerosis (Jung et al., 2006) as well as in children with epilepsy (Korostenskaja et al., 2010; Naatanen et al., 2014), specific language impairment and dyslexia (Chen et al., 2020; Naatanen et al., 2014), and ADHD (Cheng et al., 2016). Thus, rather than being a specific diagnostic biomarker, attenuated MMN is likely a more dimensional and transdiagnostic marker of vulnerability to mental or neurological disorders. This notion fits well with observations that attenuated MMN amplitudes in adults with first episode psychosis or schizophrenia are associated with impaired level of adaptive and social functioning (Higgins et al., 2021; Light & Braff, 2005; Naatanen et al., 2011), consistent with the findings of the present study. Indeed, the complex interplay between genetic predispositions and atypical maturational trajectories of basic brain functions as biomarkers of vulnerability to later development of psychopathological symptoms and consequently reduced level in adaptive functioning has recently given rise to theories that aim to capture the dynamic course of autism from a translational psychiatric framework (Aggernæs, 2020).

The present study has several strengths as well as limitations. We carefully matched groups and statistically controlled for age, sex, parental education and intelligence. Our auditory MMN paradigm consisted of three types of deviant conditions so to limit potential stimulus-specific responses. Despite these efforts, firm inferences on the causality of the observed relationships are prevented by the cross-sectional design of the study. Due to the moderate sample sizes of the autism and control groups, the study may have lacked power, which possibly was an issue concerning the analyses within the autism group correcting for multiple covariates. Further, the study was limited by relying solely on parent-reports to assess adaptive behavior, while the inclusion of multi-informant reports from teachers as well as clinicians might have added valuable information.

In conclusion, MMN amplitude was attenuated in the autism group compared to their typically developing peers as hypothesized. This is in line with a growing body of evidence, which has demonstrated that children and adolescents with autism tend to display pre-attentional abnormalities in the discrimination of auditory input. Importantly, attenuated MMN amplitude was coupled to a general impairment in adaptive functioning rather than to severity of specific autism symptoms. This finding suggests that a blunted response to changes in sensory input may underlie or at least worsen problems with flexibly adapting to a continuously changing environment. Our study contributes with novel insight to the understanding of the dynamic neurobiological underpinnings of autism. Hopefully, the present findings may contribute to guide future interventions aimed at improving the quality of life in children and adolescents with autism and their families.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Regional Medical Ethics Committee (REG-116-2017) and the Danish Data Council (SJ-620) approved the study protocol. Participants and their parents received written and oral information about the study and written informed consent was obtained from all parents before study initiation.

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