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RESEARCH ARTICLE

Auditory evoked potentials in adolescents with autism: An investigation of brain development, intellectual impairment, and neural encoding

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Abstract

Limited research has evaluated neural encoding of sounds from a developmental perspective in individuals with autism (ASD), especially among those with intellectual disability. We compared auditory evoked potentials (AEPs) in autistic adolescents with a wide range of intellectual abilities ($n = 40$, NVIQ 30–160) to both age-matched cognitively able neurotypical adolescent controls (NT-A, $n = 37$) and younger neurotypical children (NT-C, $n = 27$) to assess potential developmental delays. In addition to a classic measure of peak amplitude, we calculated a continuous measure of intra-class correlation (ICC) between each adolescent participant's AEP and the age-normative, average AEP waveforms calculated from NT-C and NT-A to study differences in signal morphology. We found that peak amplitudes of neural responses were significantly smaller in autistic adolescents compared to NT-A. We also found that the AEP morphology of autistic adolescents looked more like NT-A peers than NT-C but was still significantly different from NT-A AEP waveforms. Results suggest that AEPs of autistic adolescents present differently from NTs, regardless of age, and differences cannot be accounted for by developmental delay. Nonverbal intelligence significantly predicted how closely each adolescent's AEP resembled the age-normed waveform. These results support an evolving theory that the degree of disruption in early neural responses to low-level inputs is reflected in the severity of intellectual impairments in autism.

Lay Summary

Brain responses to sounds look different in adolescents with autism, especially for those with severe cognitive impairments, compared to younger and age-matched neurotypicals. Results support the idea that differences in how the brain encodes information from sounds are associated with intellectual impairments in those with autism.

KEYWORDS
AEPs, ASD, auditory, autism, autistic, evoked potentials, intellectual disability, intellectual impairment, neural development

INTRODUCTION

One striking feature of autism spectrum disorder (hereinafter abbreviated as autism or ASD)[1] is that many individuals diagnosed with it display atypical behavioral

[1]We attempt to respect the request of autistic self-advocates who prefer to be described using identity-first language when describing autistics with lower support needs and to respect the wishes of caregivers who prefer person-first language when talking solely about individuals with accompanying intellectual impairments and higher support needs. When talking about all autistics as a group, we use identify-first and person-first interchangeably, along with the general nomenclature of "ASD".

responses to sensory inputs. These behaviors are observed within the first few years of life and are a key manifestation of the disorder (American Psychiatric Association, 2013; Ben-Sasson & Carter, 2013). Perhaps even more striking, these behaviors are often seemingly paradoxical in nature, with the same individuals exhibiting both sensory-avoiding behaviors for certain inputs and sensory-seeking behaviors for others. For instance, a child might cover their ears in response to a sound in one setting, but in another setting, repetitively listen to a sound held close to their ear. These behaviors are evident across all sensory domains but are found to be particularly common in the auditory domain, with estimates ranging from 15 to 100 percent of this population (Baranek et al., 2006; Dunn et al., 2008; Khalfa et al., 2004; Rosenhall et al., 1999; Tomchek & Dunn, 2007). From an early age, many autistic individuals begin to show a mixture of behaviors that suggest hypersensitivity to sounds (also known as hyperacusis), unresponsiveness to sounds, and/or heightened interest in certain sounds (O'Connor, 2012; Tomchek & Dunn, 2007). Prevalence of such atypical behaviors in the auditory domain may be especially high for individuals with accompanying intellectual impairments (Patten et al., 2013; Schwartz et al., 2020).

While it is commonly accepted that these behavioral responses have a neural basis, the specific origin of such behaviors is unknown. From prior research, there is evidence to support various theories of atypical brain function that might lead to such reactions to sounds and other sensory inputs. In particular, researchers have proposed that autistic individuals have a sensory gating deficit, in which low-level systems responsible for regulating arousal and high-level systems responsible for regulating attention both fail to regulate incoming inputs (Belmonte et al., 2004; Belmonte & Yurgelun-Todd, 2003; Dawson & Lewy, 1989; Elsabbagh et al., 2013; Orekhova et al., 2014). Neural connections between areas relevant to sensory processing, including sensory auditory cortices, may also be atypical due to abnormal synaptogenesis and neuronal migration during development that ultimately interferes with transfer of sensory information (Bourgeron, 2009; Brock et al., 2002; Cherkassky et al., 2006; Gilman et al., 2011; Lewis et al., 2014; Nair et al., 2013).

Obtaining a clearer understanding of the neural origins of atypical behavioral responses to acoustic inputs is of specific interest because this might direct us toward foundational features of brain irregularities that impact a significant proportion of people with autism. Furthermore, it is important for us to understand if and how atypical neural responses to acoustic inputs could have detrimental impacts on language acquisition and general intelligence, which for normal hearing individuals, are strongly facilitated during development through aural means (Bishop, 2007; Kwok, Joanisse, Archibald, & Cardy, 2018; Kwok, Joanisse, Archibald, Stothers, et al., 2018; McArthur & Bishop, 2004; Roberts et al., 2011; Weismüller et al., 2015). Currently, it is standard to assess atypical behaviors in response to sounds and other sensory inputs in the clinic using parent report questionnaires and clinical observations (Ben-Sasson et al., 2009; Siper et al., 2017). With additional research, neural measures have the potential to be refined to similarly assess sensory processing dysfunction at the individual level (Riva, Cantiani et al., 2016; Ocak et al., 2018).

Researchers already rely on neuroimaging – commonly, electroencephalography (EEG) and magnetoencephalography (MEG) – to characterize brain activity that occurs during auditory events. These neuroimaging technologies record the obligatory neural responses that are evoked by auditory stimuli (auditory evoked potentials or AEPs), which reflect early sensory encoding of sounds in the primary auditory cortex. AEPs can be acquired through passive paradigms, which avoid confounds related to attentional control and can be adequately measured with a single mid-frontal channel and reference channel in a matter of minutes. Features like these make it an attractive tool to measure cortical response to inputs in children and those with neurodevelopmental disorders (Cunningham et al., 2000; Johnstone et al., 1996; Ponton, Eggermont, Kwong, & Don, 2000). AEPs typically occur over the span of 400 milliseconds following the onset of a sound and take the form of positive- and negative-going polarity components. These potentials are abbreviated by their polarity (positive (P) and negative (N)) and number to index the order in which the component occurs. In neurotypical adults (NT-A), the AEP includes P1, N1, P2, and N2 components. However, this complex of components matures during neurotypical (NT) child development. When neurotypical children (NT-C) are about 10 years old, their AEP signal undergoes significant morphological changes, including an increased identifiable structure of the N1 and P2 (Cunningham et al., 2000; Johnstone et al., 1996; Ponton, Eggermont, Don, et al., 2000). These changes in electrical signal are thought to reflect anatomical maturation in the auditory cortex, hypothesized to originate within superficial cortical layers II and III as a result of changes including proliferation of neurofilaments and axon myelination (Eggermont & Ponton, 2003; Moore & Guan, 2001; Morr et al., 2002; Ponton et al., 2002).

Through neuroimaging technologies, researchers have found at the group level that children with autism do not respond neurotypically to basic sounds, such as tones. Young children with autism, ages three to nine with a range of normal and impaired language and nonverbal intelligence, have smaller P1 and N1 AEP amplitudes in response to clicks or tone bursts compared to age-matched NTs (Bruneau et al., 2003; Buchwald et al., 1992; Orekhova et al., 2009; Stroganova et al., 2013). This research on obligatory AEPs to tones supplements a larger body of evidence that people with autism often have atypical neural responses to more

complex acoustic stimuli like speech or more complex auditory environments (Bomba & Pang, 2004; Jeste & Nelson, 2009; Marco et al., 2011; Schwartz et al., 2018).

Findings of atypical AEPs are not exclusive to ASD. Individuals with profound intellectual impairments (often diagnosed with genetic disorders that do co-occur with the autistic phenotype–e.g., Angelman syndrome, Cornelia de Lange syndrome, Fragile X Syndrome, and Phelan-McDermot syndrome) have been reported to display similar atypical responses to sensory inputs (Fellinger, 2022; Joosten & Bundy, 2010; Heald et al., 2020). Because neuroimaging research is quite challenging to conduct on individuals with intellectual impairments, minimal research has been conducted on them to examine their neural response to sounds. In the limited research that has occurred, researchers have found individuals with profound intellectual impairments, with and without autism, display differences in the amplitude and latency of their early neural responses to sounds (Ikeda et al., 2004, 2009; Jaušovec & Jaušovec, 2000; Orekhova et al., 2008; Rotschafer & Razak, 2014). Further research is needed to characterize neural response to sounds in those with profound intellectual impairments, with or without accompanying autism.

While it is evident from prior cross-sectional research that children with autism have atypical AEPs compared to NT peers (e.g., for review, see Williams et al., 2021), limited research has been conducted to determine if these children's atypical responses are due to developmental delays that resolve by adolescence or whether they are due to an underlying system that will never act neurotypically, especially in those with profound intellectual impairments. The few longitudinal studies conducted to date find that, around age 10, children with ASD with intelligence scores within normal range undergo maturational changes that are similar to those of NTs. Six- to eleven-year-old children with autism showed a delayed M100 latency, but when the same participants were brought back after two to five years, both autistic participants and NT controls had undergone changes that led to a shortening of the M100 latency and the magnitude of the latency gap between the two groups remained constant (Port et al., 2016). Moreover, although a right hemisphere M100 response was more likely in six- to nine-year-old children with ASD than NT controls, three years later these group differences had disappeared (Green et al., 2022). Cross-sectional studies have been less conclusive regarding age-related changes. One cross-sectional study found that with increasing age, the decreases in M50 peak amplitudes and increases in M100 peak amplitudes occurred at a similar rate in ASD and NT children (Oram Cardy et al., 2004). In contrast, another cross-sectional study found that M100 latency became more delayed (relative to NTs) as a factor of age in autistic children ages eight to fourteen (Gage et al., 2003).

One promising way to investigate whether AEPs are atypical and/or developmentally delayed within the constraints of cross-sectional research is with a method called intraclass correlation (ICC) (McArthur & Bishop, 2004). With ICC, we can measure the global resemblance between an individual's waveform and an average, "age-normative" waveform that is generated from a NT sample at a certain stage of development. The global resemblance quantified by the ICC accounts for features like waveform shape, amplitude, and latency. This method also allows for a comparison between waveforms that are morphologically different, including waveforms with flatter peaks and noisier signals, like those previously noted in individuals with autism (Bruneau et al., 2014; Buchwald et al., 1992; Orekhova et al., 2009; Stroganova et al., 2013). The computation of a single index of similarity between the waveforms also allows one to conduct a single statistical test to assess differences between groups, avoiding the need for multiple comparisons. ICC has been used to study both neurotypical and atypical development and has been found to be sensitive to immature waveforms on an individual-to-individual basis (Bishop & McArthur, 2005; Kwok, Joanisse, Archibald, & Cardy, 2018; Kwok, Joanisse, Archibald, Stothers, et al., 2018; McArthur & Bishop, 2004). In these prior studies, researchers found evidence that the ICCs of children with Specific Language Impairment (SLI), also known as Developmental Language Disorder (DLD), were significantly lower than NT controls (Bishop & McArthur, 2005) and that AEPs of children with SLI/DLD – particularly the most severely impacted participants – more closely resembled those of younger NT children (Kwok, Joanisse, Archibald, & Cardy, 2018). To our knowledge, ICC has not been used in AEP studies on individuals with autism or individuals with profound intellectual impairments, but it could be an effective way to determine whether evoked potentials to acoustic stimuli are developmentally delayed in such populations. Nevertheless, we acknowledge that a cohort of younger neurotypically developing children is not a perfectly matched control for developmentally delayed children who are chronologically older; even if the cohorts have similar mental ages, the older cohort has had a longer timeframe in which to have acquired lived experiences and accompanying anatomical brain changes (Burack et al., 2004).

Here, we investigated individual differences in auditory processing by expanding on prior work that examined autistics and NT adolescents' AEPs in response to harmonic, complex tones. We studied differences in AEP response in two different ways. The first was with classically used measures of peak amplitude response. The second was with ICC, to evaluate the global resemblance between individual adolescent AEP waveforms and norm-based average AEP waveforms based on two groups of NT participants within our collected sample: prior to (ages 3–9) and post (ages 10–21) major

maturational AEP development. In addition to these measures of AEP response, we evaluated whether key phenotypic factors that varied within the autistic sample – nonverbal intelligence, verbal intelligence, age, and autism severity – accounted for variability in AEPs. We included a heterogeneous sample of autistics that ranged from those who were minimally and low verbal with accompanying intellectual impairments and high support needs to those who were verbally fluent with no accompanying intellectual impairments and low support needs. We hypothesized that AEP waveform morphology would be different in autistic adolescents compared to NT-A controls and that measures of verbal and nonverbal intelligence would further distinguish participants in the autistic group.

METHODS

The data in this study were collected as a part of two separately funded studies conducted at Boston University's Center for Autism Research Excellence – one of which focused on NT-C and the other of which focused on NT and ASD adolescents. Combination of data across two studies allowed for planned analyses that were not possible with each study alone. All participants provided either informed verbal or written assent, or, in cases where the participant was cognitively able and over 18, informed written consent. All legal guardians (for minors and individuals over 18 who were not cognitively able to provide written consent) provided informed written consent.

Participants

The study included 40 autistic adolescents that were between 10.340 and 21.190 years old ($M_{age} = 15.940$ - years). These participants had each previously received an external, formal diagnosis of autism spectrum disorder, which we confirmed using the Autism Diagnostic Observation Schedule (ADOS) Modules 3 and 4 (Lord et al., 2012) for 22 participants and the Adapted ADOS Modules 1 and 2 (Bal et al., 2020) for 18 participants. Participants who received an ADOS Module 1 or 2 were considered minimally or low verbal, producing single to phrase-level speech, while participants who received an ADOS Module 3 or 4 were considered verbally fluent, producing complex speech. All ASD participants had an ADOS calibrated severity score (CSS) of a 3 or above.

We compared autistic individuals to two groups of NT participants: 27 children ages 3.140–9.773 years old ($M_{age} = 6.804$ years) and 38 adolescents ages 10.170–20.830 years old ($M_{age} = 14.746$ years). Those in the NT groups had never received a diagnosis of ASD or related developmental disorder (e.g., attention deficit disorder, learning disability), nor did they have a sibling diagnosed with autism. All participants used English as their primary language. Furthermore, all participants reported no known hearing loss or history of traumatic brain injury. Time permitted the additional supplemental testing of 21 of the 38 NT-A – our primary group of comparison with ASD adolescents – to confirm minimal-to-no evidence of autistic characteristics as defined by a CSS of 1 or 2 on the ADOS Modules 3 and 4 (Lord et al., 2012).

We measured nonverbal intelligence (NVIQ) and verbal intelligence (VIQ) on all participants. IQ measures did differ between participants because of collection constraints; this choice is addressed further in the discussion. For NT-C (ages 3–9), NVIQ and VIQ were measured using the Kaufman Brief Intelligence, Second Edition, NVIQ and VIQ composite scores, respectively (KBIT-2; Kaufman, 2004). The KBIT-2 captures fluid (nonverbal) intelligence through a matrices test and crystallized (verbal) intelligence through a combination of prompts to label vocabulary and solve verbal riddles. It is normed for ages 4 to 90 years old. Of note, because this test is not normed for those under 4 years old, the one NT child under that age (3.140 years) was scored as a 4.0-year-old and therefore received below a 70 on their NVIQ. Given their above-average VIQ (105), likely underestimated NVIQ, and similar mental age with several of our participants with autism, we elected to include them in the study. All other NT participants had NVIQs above 85.

For NT and ASD adolescents (ages 10–21), we used the standard score from the Peabody Picture Vocabulary Scale, Fourth Edition (PPVT-4; Dunn & Dunn, 2007) as a proxy for VIQ. It is standardized for ages 2–90 years old and, like the KBIT-2, the PPVT-4 prompts participants to label vocabulary. We measured NVIQ for NT-A with the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2; Wechsler, 2011), while autistic adolescents received the Leiter International Performance Scale, Third Edition (Leiter-3; Roid et al., 2013). The WASI-2 NVIQ is standardized for ages 6–90 and is derived from tests of block design and matrix reasoning. The Leiter-3 is standardized for ages 3–75 years old and includes tests of visual organization and pattern recognition; it can be conducted completely without verbal prompts which makes it appealing when testing individuals with poorer language skills.

Collection & Analysis of auditory evoked potentials

Brain activity was recorded from all participants using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR, sampling rate 1000 Hz). Participants sat in an electrically shielded and sound-attenuated room. They were instructed to watch a self-selected soundless movie or television show with subtitles and not worry about any weird sounds they might may hear. A 50 millisecond (ms) harmonic complex tone

stimulus was repeatedly presented binaurally from two loudspeakers, placed ±45° in front of the listener. Participants were presented with a block of 150 trials of a repeated 50 ms sound over a total of 5 min. The repeated sound was a complex tone, which was composed of 10, simultaneous pure tones that were the first ten harmonics of the fundamental frequency of 110 Hz (i.e., simultaneous pure tones of 110, 220, 330, 1100 Hz). The resulting complex tone has a strong perception of pitch, driven by its harmonic structure. The complex tone also has a strong temporal structure that drives synchronous activity in the auditory brainstem that is phase-locked to the 110 Hz fluctuations in the sound envelope, known as the envelope following response (EFR) or frequency following response (FFR) (Krizman & Kraus, 2019; Shinn-Cunningham et al., 2017). This choice of stimulus allowed us to ensure that all listeners had intact peripheral hearing that responded robustly to the input sound by measuring the EFR. This was an important test given that 45% of our autistic participants were minimally or low verbal and therefore were presumed to not be able to reliably complete standard audiometric tests that assess hearing status. The repeated complex tones, which were identical on all trials, were presented with an 867 ms interstimulus interval with 0–218 ms jitter at a level of 62 dB SPL (i.e., quite audible but not uncomfortably loud for typical listeners with good peripheral hearing).

Data were digitally filtered online with 0.1 Hz high-pass filter (Electrical Geodesics Inc., Eugene, OR). The data were then bandpass filtered offline with a passband from 0.1 to 20 Hz using the fir1 Matlab function with a Hamming window (The Mathworks Inc., 2022). The data were then referenced to the left and right mastoids and segmented into 800 ms epoch event-related potentials (i.e., one epoch per complex tone presentation trial). For the given analyses, we focused solely on a selection of 7 channels surrounding and including FCz (Figure 1; channels 5, 6, 7, 12, 13, 106, 112) based on a priori knowledge that auditory evoked potentials are well-detected and often characterized along these fronto-central midline sites in both adolescents and children (Bishop et al., 2011; Bishop & McArthur, 2005; Eggermont & Ponton, 2002; Kwok, Joanisse, Archibald, Stothers, et al., 2018; Ponton, Eggermont, Don, et al., 2000; Ponton, Eggermont, Kwong, & Don, 2000; Shafer et al., 2015; Yu et al., 2015). Event-related potentials (ERPs) were baseline corrected with respect to a 100 ms pre-stimulus baseline time. Individual trials were rejected if any channel of interest had a peak magnitude (positive or negative) that exceeded 100 uV, following baseline correction, to remove trials contaminated by movement, muscle, or other artifacts.

Each participant was required to have at least 75% usable ERP trials across all frontal electrodes to be included in the subsequent data analysis. A total of 12 ASD participants (all of whom were minimally or low verbal) were excluded because, following artifact rejection, fewer than 75% of their ERP trials remained (the number of remaining trials ranged from 73 to 111 trials, or 49% – 74%). Further data about the excluded participants are provided in the Supplementary Materials. An additional six minimally or low verbal ASD participants underwent some amount of EEG desensitization but were unable to complete the five-minute EEG paradigm with the cap. A subset of these participants has been previously described in Table 5 of Tager-Flusberg et al. (2017) under "Attempted/Successful Hearing Test".

Classic AEP measurement of adolescent participants: Amplitude

To measure AEP amplitude, we first identified positive and negative peaks in the AEP waveform. To find each peak, we used the Matlab (2022) function "findpeaks" signal function which identifies peaks in a signal. We averaged participants by group and found a mean P1-N1-P2-N2 complex at 154–190–240-342 ms for ASD adolescents and at 152–192–245-347 ms for NT-A. When averaging all adolescent participants together, the signature complex peaks were at 153–192–243-344 ms. Given there were neither clear differences in average latency between the groups, nor clear differences in latency from visual inspection of the individual waveforms, and we were most interested in capturing overall waveform morphology (as measured by ICC), between-group differences in classic measures of latency were not investigated further.

We next used the average adolescent latencies to set general guidelines for identifying individual participant AEP peaks. All peaks were confirmed with visual inspection and can be observed in Figure 3 for the ASD group. The P1 was identified as the most positive peak between a ±60 ms window around the adolescent participant average (93–213 ms). The N1 was the most negative peak between the participant's P1and the average P2 latency (243 ms). The P2 was the most positive peak between the maximum P1 latency (199 ms) and 60 ms after the average P2 latency (370 ms). The N2 was most negative peak between the participant's P2 and 60 ms after the average N2 latency (386 ms). As long as the "findpeaks" algorithm identified a peak, we considered the output valid; the minimum P1-N1 amplitude difference was 0.611 uV for ASD adolescents and 0.013 uV for NT-A, and the minimum P2-N2 amplitude difference was 0.933 uV for ASD adolescents and 0.782 uV for NT-A.

Comparisons of peak-to-peak P1-N1 and P2-N2 amplitude between ASD and NT adolescents were conducted with repeated measures analysis of variance, controlling for the number of ERP trials due to identified group-level differences. Pairwise posthoc comparisons were Bonferroni-adjusted for multiple comparisons.

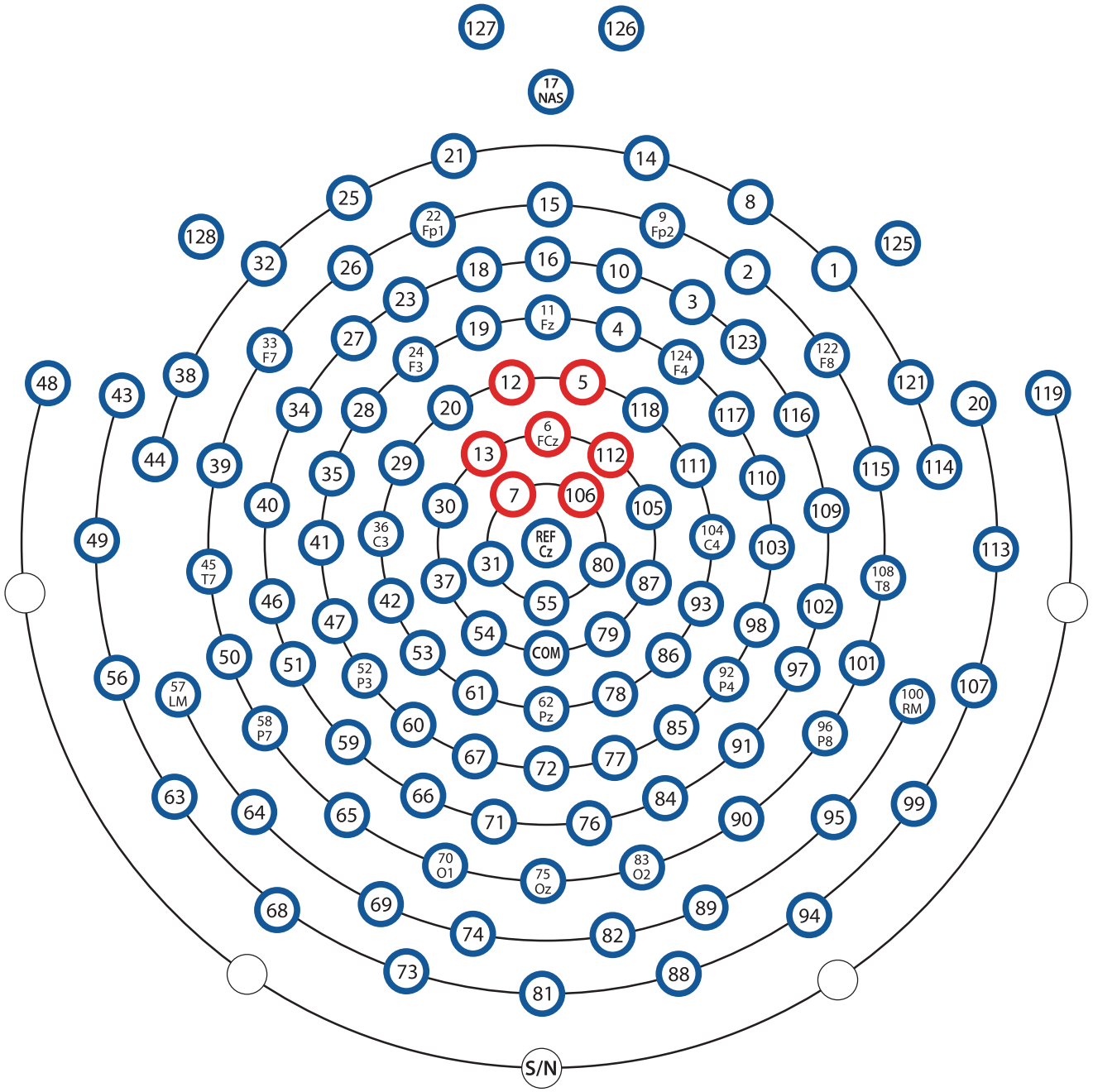

FIGURE 1 Schematic of seven fronto-central channels selected from 128-channel EGI cap for primary AEP analyses.

AEP maturity measurement: Intra-class correlation

Next, we used a measure of intra-class correlation (ICC) to determine how similar each adolescent's waveform was in comparison to grand, "age-normative" average waveforms derived from the NT-C and NT-A groups. Methods for ICC calculation were identical to those previously used to estimate the maturational state of individual's AEPs based on neurotypically-defined normed AEP waveforms (Bishop et al., 2011; Bishop & McArthur, 2005; Kwok, Joanisse, Archibald, Stothers, et al., 2018). We calculated the ICC across the AEP waveform of each ASD participant relative to the average AEP waveform of both younger, 3- to 9-year-old NT-C and age-matched, 10- to 21-year-old NT-A participants. We then calculated the ICC between the AEP of each NT-A and the average AEP waveform of the NT-C and NT-A participants. To prevent bias within the NT-A calculations, data from each NT-A was excluded from the NT-A average waveform to which it was compared. As was done in previous studies using this method (Bishop et al., 2011; Bishop & McArthur, 2005; Kwok, Joanisse, Archibald, Stothers,

et al., 2018), we normalized ICC values data using Fisher's z transformation. We conducted a univariate analysis of variance to compare the age-appropriate ICCs of the NT and ASD adolescents.

In addition to considering the ICC of every ASD and NT adolescent relative to the NT-A normative waveform, we measured whether the global resemblance ICC value was larger when each adolescent participant's AEP was compared to the child- or adolescent-based normative waveform. We continued to follow analyses laid out by Bishop and McArthur (2005) by considering the proportion of ASD to NT adolescents who more closely resembled the child normative waveform than the age-equivalent adolescent waveform and considered the significance of those proportions with a one-sided Fisher's exact-test.

AEP maturity measurement: Pearson correlations

Again, in keeping with prior work by Bishop and McArthur (2005), we measured whether groups differed using Pearson's correlations rather than ICC to consider the global morphology of the waveforms independent of amplitude.

Regression analyses

We entered phenotypic data, including age, NVIQ, VIQ, and ADOS CSS, along with number of ERP trials, into a stepwise linear regression model to consider which variables accounted for the variance in ICC within the heterogeneous ASD sample. Adjusted R squared values were used to determine the percent of variance in ICC accounted for by the model.

Posthoc investigation was conducted with Pearson's correlations across and within each adolescent group to identify trends between NVIQ and AEP ICC. Further investigation was conducted with a stepwise linear regression on the full sample of adolescents with ICC as a dependent variable and group, NVIQ, and the interaction term as independent variables.

Secondary analyses were also conducted to consider the effect of age, NVIQ, VIQ, ADOS CSS, and number of ERP trials on variance of a linear combination of P1-N1 and P2-N2 amplitude within the ASD group.

RESULTS

Demographics

Adolescents with and without ASD were compared across demographic characteristics (Table 1). The distribution of IQ scores across the three groups are displayed in Figure 2. NVIQ scores were normally distributed within each of the three participant groups, as defined by Shapiro–Wilk's test. A total of 40% of the ASD group scored a 70 or below on the Leiter-3 NVIQ measure and can be described as having a comorbid intellectual disability. VIQs were negatively skewed within the ASD group ($W = 0.847$, $p < 0.001$) and ADOS CSS scores were positively skewed within the ASD group ($W = 0.914$, $p = 0.005$). The number of ERP trials used to generate waveform averages was also positively skewed across all groups (NT-C: $W = 0.925$, $p = 0.052$; NT-A: $W = 0.802$, $p < 0.001$; ASD: $W = 0.934$, $p = 0.022$). To address this deviance from normal distributions, nonparametric tests were used for demographic comparisons; VIQ, CSS scores, and number of ERP trials were normalized with z-scores for all subsequent analyses.

The two adolescent groups were not statistically different in terms of age, gender ratio, race, ethnicity, or the number of usable ERP trials, although the autistic adolescents did tend to be older than the NT-A group. The NT adolescent group had significantly higher NVIQ, VIQs, and lower ADOS CSS than ASD peers. In addition, it was confirmed that ASD and NT adolescent groups were not significantly different in their gender ratio, race, ethnicity, or number of accepted ERP trials relative to the NT child group.

Classic AEP measurement: Amplitude

All 40 ASD adolescent participants presented with a P1-N1-P2-N2 AEP morphological structure that could be identified by our algorithm (Figure 3). 35 of the 38 NT participants showed this identifiable P1-N1-P2-N2 structure as well. Multivariate analyses revealed that group, but not number of ERP trials, significantly contributed to the variation observed in peak-to-peak amplitudes. There was a significant interaction between repeated measures of P1-N1 and P2-N2 amplitude and group while controlling for covariates ($F(1,72) = 12.379$, $p < 0.001$, $\eta_p^2 = 0.147$). Comparisons revealed lower P1-N1 ($F(1,72) = 21.146$, $p < 0.001$, $\eta_p^2 = 0.227$) and P2-N2 ($F(1,72) = 36.888$, $p < 0.001$, $\eta_p^2 = 0.339$) peak-to-peak amplitudes in adolescents with ASD relative to NT adolescents (Table 2; Figure 4). There was also a main effect of group such that NT-A peak-to-peak amplitude was overall greater than ASD participants ($MD = 2.760$ ($SE = 0.438$), $F(1,72) = 39.672$, $p < 0.001$, $\eta_p^2 = 0.355$) and no main effect of the number of accepted ERP trials ($F(1,72) = 0.040$, $p = 0.842$, $\eta_p^2 = 0.001$).

AEP maturity measurement: Intra-class correlation

Our collected NT-C and NT-A average waveforms resembled those which have been shown in prior work,

TABLE 1 Demographics.

	Group	Neurotypical		Autistic	Adolescent groups comparison	
	Subgroup	Children	Adolescents	Adolescents	Significance	Effect
Participants	*N*	27	38	40		
Age (years)	*Mean (SD)*	6.804 (2.018)	14.746 (3.143)	15.940 (2.717)	$F(1,76) = 3.229$, $p = 0.076$	$\eta^2 = 0.407$
	Range	3.140–9.773	10.340–21.190	10.170–20.830		
F:M	*Ratio*	15:12	17:21	11:29	$X^2(1) = 2.516$, $p = 0.113$	$V = 0.180$
Race						
	Asian	2	3	2	$X^2(6) = 8.598$, $p = 0.198$	$V = 0.332$
	Black/African American	1	4	2		
	Caucasian/White	14	24	30		
	Multiple Races	6	7	3		
	Pacific Islander or Native Hawaiian	0	0	1		
	Prefer not to respond	4	2	2		
Ethnicity						
	Hispanic	2	1	3	$X^2(2) = 2.881$, $p = 0.237$	$V = 0.192$
	Non-Hispanic	22	36	33		
	Prefer not to respond	3	1	4		
NVIQ	*Mean (SD)*	107.519 (15.639)	109.710 (14.571)	86.500 (33.296)	$F(1,76) = 15.616$, $p < 0.001$	$\eta^2 = 0.170$
	Range	67–133*	86–140	30–160		
VIQ	*Mean (SD)*	114.889 (12.157)	111.842 (13.079)	69.850 (44.205)	$U(1,76) = 387.500$, $p < 0.001$	$r = 0.422$
	Range	85–137	86–138	20–135		
ADOS CSS: Total	*Mean (SD)*	N/A	1.333 (0.483)	7.500 (1.935)	$U(1,59) = 0.000$, $p < 0.001$	$r = 0.864$
	Range	N/A	1–2	3–10		
Number of ERP Trials	*Mean (SD)*	139.889 (8.446)	140.895 (10.785)	135.925 (10.897)	$U(1,76) = 1001.500$, $p = 0.015$	$r = 0.274$
	Range	119–150	112–150	113–150		

Note: Verbal IQ (VIQ) was derived from either the PPVT-4, WASI-2 Verbal IQ, or KBIT-2 Verbal IQ. Nonverbal IQ (NVIQ) was derived from WASI-2, Leiter-2, or KBIT-2 Performance IQ. Effect size for ANOVAs were measured with eta squared. Effect size for Mann–Whitney U Tests were measured with r (Conroy, 2012). Effect size for Chi-Squared tests measured with Cramer's V. Autism Diagnostic Observation Schedule Calibrated Severity Scores (ADOS CSS) are only reported for 21 NT-A. *All NT-C scored above an 85 on NVIQ with the exception of one 3-year-old, whose score was underestimated because they were compared to 4-year-old standardized norms.

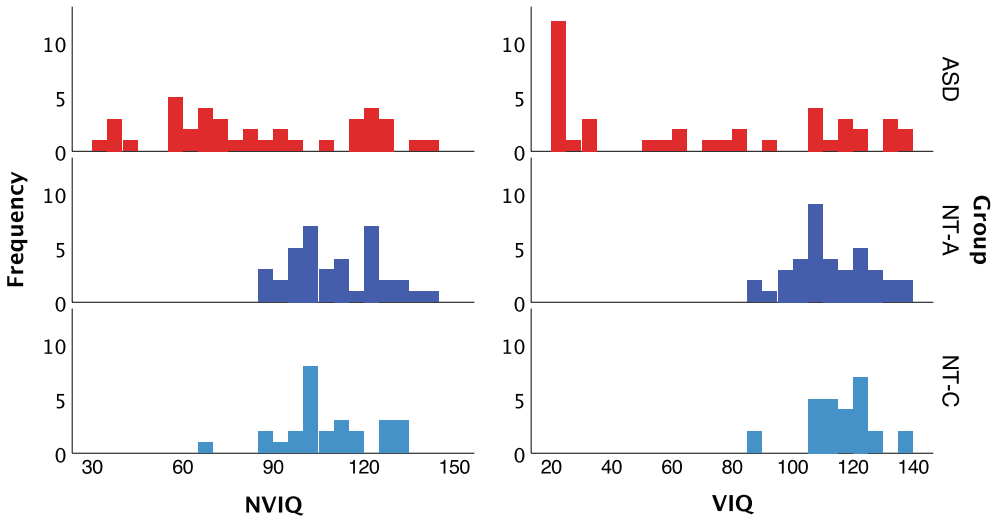

FIGURE 2 Histogram of intelligence scores (x-axis), with Nonverbal IQ (NVIQ) and Verbal IQ (VIQ), respectively. Bars are binned with an interval width of 5 points along the x-axis. Horizontal panels display histograms for autistic (ASD), neurotypical adolescent (NT-A), and neurotypical child (NT-C) groups.

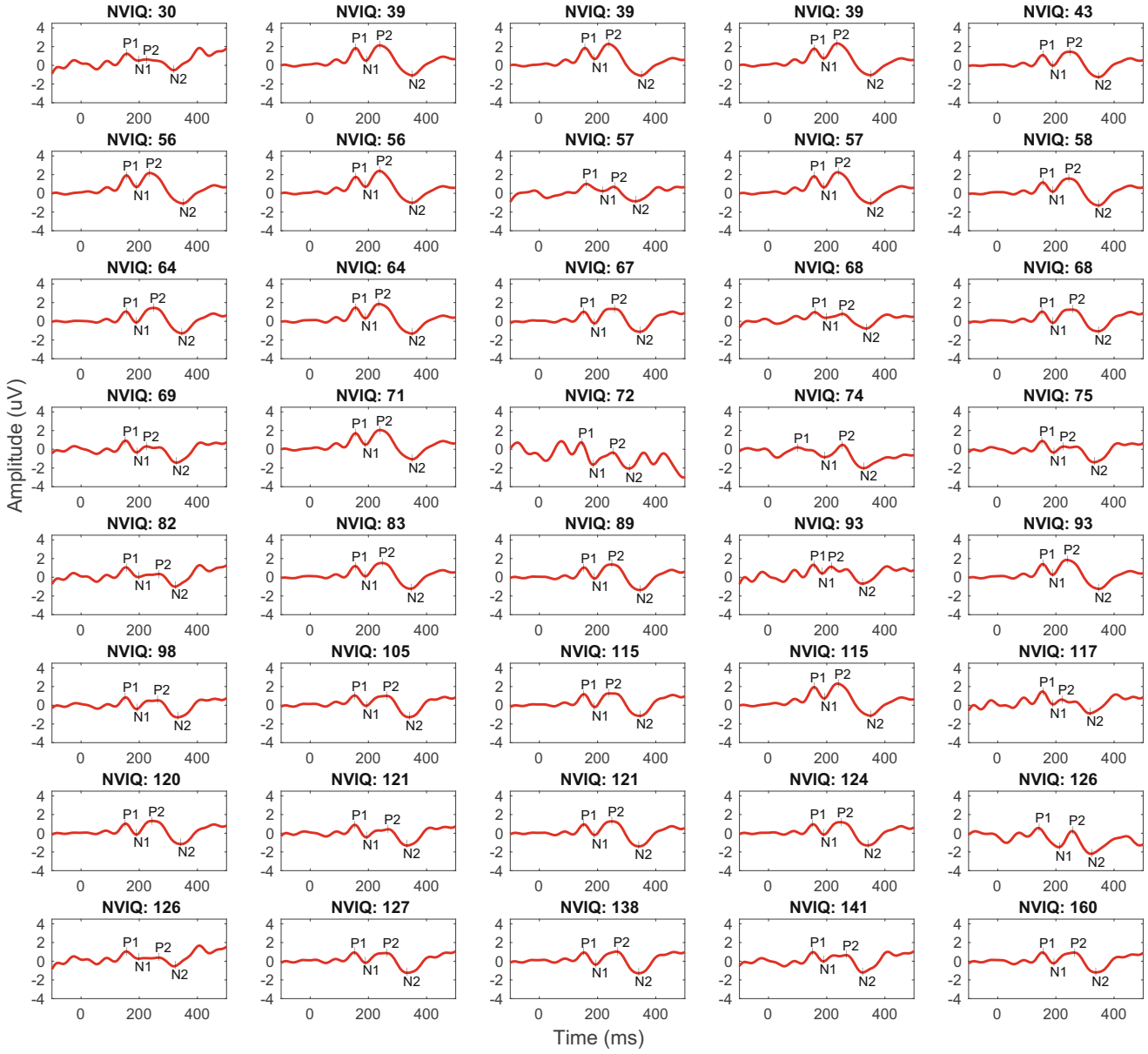

FIGURE 3 Evidence of P1-N1-P2-N2 AEP wave morphology in adolescents with ASD. Y-axis is amplitude (uV) and x-axis is time relative to stimulus onset (ms).

with a N1-P2 complex that is present in NT adolescents but not in NT children under the age of ten (Figure 5). After Fisher's z-transformation, ASD adolescents showed an ICC value with the NT-A waveform that averaged to −0.167 ($SD = 0.949$). This compared with the NT-A group whose average z-scored ICC was 0.466 ($SD = 0.800$). The NT-A group's ICC values were significantly higher than the ASD group's ICC values ($F(1,75) = 9.327$, $p = 0.003$, $d = 0.854$). In the ASD group, 57.5% (23 out of 40) of the ASD participants' ICCs more closely resembled the NT-A group's AEP than the NT-C group's AEP. In the NT-A group, 71% (27 out of 38) of the ICCs more closely resembled the NT-A group's age-normative AEP than the younger NT-C group's age-normative AEP. This difference in the proportion of ASD cases with immature waveforms compared to NT-A controls did not reach significance (Fisher's exact-test, one-sided, $p = 0.156$).

AEP maturity measurement: Pearson correlation

The mean Pearson correlation between the NT-A average waveform and ASD participant waveforms was 0.399 (Fisher z-transformed $M = -0.193$, $SD = 0.931$), compared to a mean Pearson correlation of 0.620 (Fisher z-transformed $M = 0.502$, $SD = 0.786$) between the NT-A average waveform and NT-A participants. The difference between correlations was significant ($t(76) = -3.556$, $p < 0.001$, $d = 0.864$), even after accounting for each participant's number of ERP trials ($F(1,75) = 11.630$, $p = 0.001$, $d = 0.920$). Results indicated that observed ICC differences between NT and ASD adolescents were not solely due to differences in AEP amplitude, as this metric captures global morphology independent of amplitude.

TABLE 2 Peak-to-Peak Amplitudes in ASD and NT adolescents, controlling for z-scored number of ERP trials. There was a significant main effect of group on ERP peak-to-peak amplitude ($F(1,72) = 39.672$, $p < 0.001$, $\eta_p^2 = 0.355$). There was no main effect of z-scored number of trials ($F(1,72) = 0.040$, $p = 0.842$, $\eta_p^2 = 0.001$). There was a significant interaction between repeated ERP measures and group while controlling for number of ERP trials as a covariate ($F(1,72) = 12.379$, $p < 0.001$, $\eta_p^2 = 0.147$). Compared to NT adolescents, ASD adolescents had significantly smaller P1-N1 ($F(1,72) = 21.146$, $p < 0.001$, $\eta_p^2 = 0.227$) and P2-N2 ($F(1,72) = 36.888$, $p < 0.001$, $\eta_p^2 = 0.339$) peak-to-peak amplitudes.

Domain	Mean difference (NT – ASD)	Std. error	Sig (p)
P1-N1	1.816	0.395	<0.001
P2-N2	3.703	0.610	<0.001

Note: All significance values are Bonferroni-corrected for multiple comparisons.

Regression analyses

A linear combination of all five entered independent variables (age, NVIQ, VIQ, ADOS CSS, and number of ERP trials) accounted for 13.5% of the variance in ICC within the ASD sample ($F(5, 34) = 2.213$, $p = 0.076$). From a stepwise linear regression model, NVIQ was identified as the single best predictor of ICC, accounting for 15.5% of the variance (Table 3; $F(1,38) = 8.137$, $B = 0.420$, $p = 0.007$). Age ($B = -0.211$, $p = 0.155$), z-scored VIQ ($B = 0.116$, $p = 0.670$), z-scored ADOS CSS ($B = 0.074$, $p = 0.627$), and z-scored number of ERP trials ($B = -0.036$, $p = 0.821$) were excluded from this model as nonsignificant factors.

In an additional post hoc analyses, we found that Pearson's correlation between age-normed ICC and NVIQ was significant across the full adolescent group ($r(78) = 0.414$, $p < 0.001$), as well as across ASD adolescents alone ($r(40) = 0.420$, $p = 0.007$), but not across NTs adolescents alone (*NS*) (Figure 6). To further investigate if the relationship between NVIQ and ICC significantly differed by group, we conducted linear and stepwise linear regressions on the full sample of adolescents with ICC as a dependent variable and group, NVIQ, and the interaction term as independent variables. We found that a linear combination of NVIQ, group,

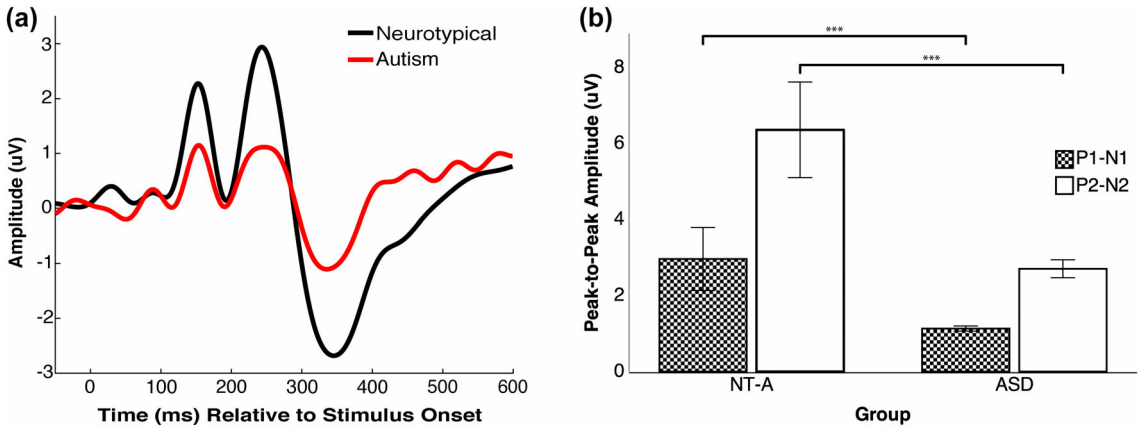

FIGURE 4 AEPs across adolescents who are neurotypical (NT-A, $n = 38$) and who have autism ($n = 40$) displayed by (a) ERP traces and (b) Bar plots of P1-N1 and P2-N2 peak-to-peak amplitudes. Error bars indicate 95% confidence intervals. Significance values based on repeated measures ANOVAs described in detail in Table 2 (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

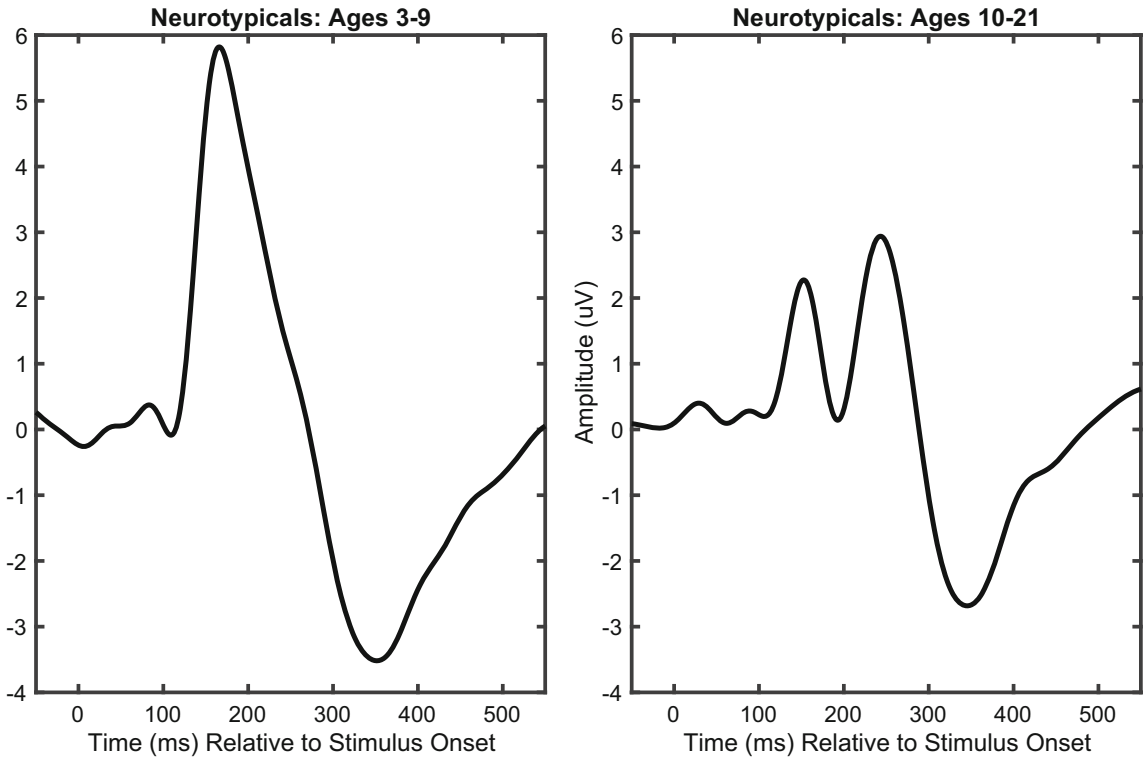

FIGURE 5 Comparison between the AEP waveforms of neurotypical children, ages 3–9 ($n = 27$) and neurotypical adolescents, ages 10–21 ($n = 38$). As described in prior research, this morphology changes between the age of 8–12 in neurotypical children, including the more pronounced formation of an N1-P2 complex.

TABLE 3 Stepwise regression analysis within the ASD Group identified NVIQ as the only significant predictor of ICC (Model 1). Age ($B = -0.211$, $p = 0.155$), z-scored VIQ ($B = 0.116$, $p = 0.670$), z-scored ADOS CSS ($B = 0.074$, $p = 0.627$), and z-scored number of ERP trials ($B = -0.036$, $p = 0.821$) were excluded from this model as nonsignificant factors.

	Model 1			
Variable	***B***	***SE B***	***t***	***Sig (p)***
(*Constant*)		0.389	−3.098	0.004
NVIQ	0.420	0.004	2.853	0.007
Adj R^2	0.155			
SE	0.873			
F	8.137			

and NVIQ by group interaction term accounted for 18% of the variance in norm-based ICC ($F(3,74) = 6.661$, $p < 0.001$). From a stepwise linear regression model, NVIQ continued to be the sole significant predictor of ICC, predicting 16% of the variance (Table 4; $F(1,76) = 15.693$, $p < 0.001$; $R^2_{adj} = 0.160$, $B = 0.014$, $p < 0.001$). Group ($B = 0.207$, $p = 0.070$) and NVIQ by group interaction ($B = 0.194$, $p = 0.102$) were excluded from this stepwise model as nonsignificant independent variables.

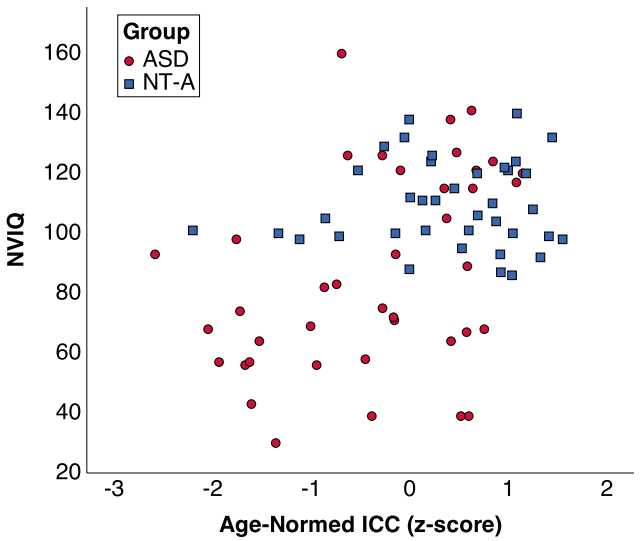

FIGURE 6 Nonverbal IQ (NVIQ) was the single best predictor of age-normed ICC in ASD adolescents ($R_{adj}^2 = 0.21$, $B = 0.48$, $p = 0.002$). Pearson's correlation between age-normed ICC was significant across all adolescents ($r(78) = 0.414$, $p < 0.001$), as well as across ASD adolescents alone ($r(40) = 0.420$, $p = 0.007$), but was not for NT adolescents (NT-A) alone (*NS*). From a stepwise linear regression across the full adolescent sample, we found no effect of group or interaction between NVIQ and group; NVIQ was the only significant factor and predicted 16% of the variance ($F(1,76) = 15.693$, $p < 0.001$; $R^2_{adj} = 0.160$, $B = 0.014$, $p < 0.001$).

TABLE 4 To determine if there was a Group x NVIQ interaction impacting ICC, we conducted a second stepwise regression of all adolescent participants with the factors of NVIQ, group, and NVIQ * group interaction. NVIQ remained the only significant predictor of ICC (Model 1). Group ($B = 0.207$, $p = 0.07$) and Group * NVIQ interaction ($B = 0.194$, $p = 0.102$).

	Model 1			
Variable	***B***	***SE B***	***t***	***Sig (p)***
(Constant)	−1.190	0.350	−3.403	0.001
NVIQ	0.014	0.003	3.961	<0.001
Adj R^2	0.160			
SE	0.852			
F	15.693			

No inputted phenotypic variable significantly predicted P1-N1-P2-N2 amplitude within the ASD group ($F(5,35) = 0.335$, $p = 0.888$).

DISCUSSION

The objective of this study was to investigate early sensory cortical neural responses to sound inputs in adolescents with autism with a wide range of intellectual abilities and to compare autistics not only to age-matched NT-A but also to NT-C. Having a comparison group of younger NTs enabled us to investigate whether neural differences can be explained by developmental delays, particularly given that pronounced NT maturational changes in AEPs occur around the age of ten. Further, by including autistic participants with a wide range of intellectual abilities, we were able to take a more precise look at whether profound intellectual impairments – which may be particularly impacted by disruptions in atypical neural activity – are associated with atypical obligatory responses to sounds. Finally, measures of ICC between individual waveforms and child- and adolescent-normative waveforms enabled us to consider the overall shape of the signal and not just peak amplitude or latency. Our findings of ICCs around 0.5 in the neurotypical control group were similar to that described in the prior literature (Bishop & McArthur, 2004; McArthur & Bishop, 2004, 2005).

In line with prior evidence of a diminished AEP response in children with autism, we found that adolescents with autism collectively showed significantly smaller P1-N1 and P2-N2 peak amplitudes to complex tones than their NT peers (Bruneau et al., 2003; Buchwald et al., 1992; Orekhova et al., 2009; Stroganova et al., 2013). However, our algorithm was also able to identify a N1-P2 complex in every adolescent with autism, appropriate for their maturational age; this is consistent with the prior report that NT and autistic adolescents show similar rates of maturational change in P1 and N1 MEG homologs (Oram Cardy et al., 2004). Furthermore, our primary analyses revealed that the global resemblance (ICC) between individual waveforms and age-appropriate NT-based norms was weaker in autistic adolescents compared to NT adolescents, and that amplitude alone did not account for these differences. This pattern was generally more pronounced in ASD adolescents with more severe nonverbal intellectual impairments. Like the classic amplitude-based analyses, we found no evidence from analyses of global resemblance to suggest that autistic adolescents' AEPs more closely resembled younger, NT children's AEPs than those of same-aged, NT peers. We interpret these findings in conjunction with prior work to suggest that AEPs of autistic adolescents – particularly those with more pronounced intellectual impairments – look different from NT peers, but that such differences are not due to development delays. We theorize this presentation reflects a combination of neurotypical maturation within the superficial layers of the auditory cortex during middle childhood and atypical neural connectivity within the auditory cortex that persists through middle childhood into adolescence.

The results from this study expand on a growing body of literature that draws parallels between the extent to which sensory input-evoked neural activity is atypical and the severity of intellectual impairment in individuals with autism (Andersson et al., 2013; Brandwein et al., 2014; Dinstein et al., 2012; Gomot et al., 2011; Jao Keehn et al., 2017; Linke et al., 2018; Roberts et al., 2011; Stroganova et al., 2013; Taylor et al., 2018; Weismüller et al., 2015). Our finding of global differences in the autistic group's AEP signals points to differences not only in the overall strength of those signals but also differences in their shape. As a result of ineffective sensory gating, attentional regulation, and excitatory-inhibitory control, it has been hypothesized that sensory inputs in those with autism are masked by excess noise (Belmonte et al., 2004; Gliga et al., 2014; Rubenstein & Merzenich, 2003). In particular, various researchers have postulated that autistic people are more prone to becoming overaroused, with a heightened neural excitation in response to inputs that leads to difficulties distinguishing important series of stimulus inputs from competing noise (Belmonte et al., 2004; Belmonte & Yurgelun-Todd, 2003; Dawson & Lewy, 1989; Dinstein et al., 2012; Hussman, 2001; Liss et al., 2006). This heightened neural excitation is coupled with an inability to adequately regulate incoming sensory inputs with attentional modulation (Belmonte et al., 2004; Courchesne et al., 1994). While more research is needed to support this claim, the evidence to date suggests that distortions in simple processing of sensory inputs caused by these noisy signals could have cascading effects on more complex, higher-order processing, thus impacting not only simple processing but more generalized

cognitive functioning (Belmonte et al., 2004; Chang & Merzenich, 2003). We suspect that the flatter neural signals we measured in individuals with profound intellectual impairments reflect inefficient sensory modulation and gating systems that interact closely with the processes underlying general intellectual function (Belmonte et al., 2004; Gliga et al., 2014; Rubenstein & Merzenich, 2003). Further research is needed to determine whether intellectual deficits and neural atypicalities to acoustic inputs arise from a jointly impacted neural system.

The identified relationship between neural response to sounds and intellectual impairment in autism suggests that the practice of comparing individually measured AEPs to established age-based normative data could be refined as a tool in clinical settings to do an initial screening of abnormal neural encoding of information. As demonstrated above, AEPs can easily be acquired with a few mid-frontal and reference channels and a short, five-minute presentation of complex tones, which allows simultaneous assessment to confirm that the auditory periphery responds robustly to the sounds without having to rely on standard audiometric tests. EEG is relatively inexpensive for a neuroimaging tool and should be considered in the future development of clinical measures aimed at capturing automatic response to sounds in young children at risk for intellectual disabilities and neurodevelopmental disorders. The early detection of a possible atypical neural response to sounds could serve as a foundation for clinicians to seek additional targeted testing, as well as treatments to alleviate overarousal of the sensory system, before sensory processing impairments fully manifest or potentially impact cognitive development (Marco et al., 2011).

RESEARCH LIMITATIONS

This research has a number of notable limitations. First, there are limitations with our sample and how data were collected. While the enrollment efforts strived to have a racially and ethnically diverse sample and did achieve this to some extent, Black and African American participants were underrepresented compared to the general United States population. In addition, current EEG collection techniques are limited in terms of how well they work on coarse and curly hair typically found in people who are Black or of African descent (Bradford et al., 2022). Although we did not need to exclude a disproportionately high number of non-White individuals because of this (see Supplementary materials), continued efforts should be dedicated to expanding racial and ethnic diversity in autism and neuroimaging research (Bradford et al., 2022).

One of the strengths of this study is the successful collection of EEG data from many ASD participants who were minimally and low verbal and had accompanying intellectual impairments. However, it is important to note that our retention rate of these participants was only about 50%. Of the 36 participants who received an Adapted ADOS 1 or 2, 13% could not wear the cap for the five-minute study and an additional 27% did not have enough usable ERP trials to be easily compared with our neurotypical samples, whose data was relatively less noisy. This means that researchers should expect a high attrition rate when conducting research on individuals who are minimally and low verbal and/or have a profound intellectual disability and/or be prepared to. Furthermore, because this research did not include a control sample of adolescents with intellectual impairments or language disorders without autism, we cannot make any firm conclusions that our findings are specific to individuals with ASD. In fact, given similar findings of auditory processing differences in individuals with developmental language disorders (Bishop & McArthur, 2004; Kwok, Joanisse, Archibald, & Cardy, 2018) and intellectual impairments (Ikeda et al., 2004, 2009; Jaušovec & Jaušovec, 2000; Orekhova et al., 2008; Rotschafer & Razak, 2014), and our hypothesis that distortions in simple processing of sensory inputs may have cascading impacts on generalized cognition, we do not necessarily expect our findings to be specific to autistic individuals. Non-autistics who are impacted by similar difficulties with low-level processing may also show similar results. Further research on those populations would be worthwhile, albeit difficult given the common overlap of autism and profound intellectual disability and the common challenges with neuroimaging such populations.

Another potential limitation of this research is the use of different IQ measures across participants, particularly NVIQ (WASI-2, KBIT-2, Leiter-3), due to constraints around collection. This was largely due to the nature of combining two separately designed, independently funded research studies with the primary goal to investigate a particular hypothesis about possible maturational lags in morphology of AEP response. In the study designed for adolescents, the Leiter-3 was selected as an optimal measure of NVIQ to capture the wide range of cognitive abilities in our autistic sample because it is designed for those with cognitive delays and can be implemented with minimal verbal cues (Tsatsanis et al., 2003). Prior research has found that there is a moderately strong correlation between Leiter and Weschler tests, but that individuals generally score higher on the Leiter than Weschler tests (Lewis & Lorentz, 1994; Renaud et al., 2022; Shah & Holmes, 1985). This suggests that if anything, our measures of NVIQ in the NT-A group are slightly lower than they would have been on the Leiter. Despite this limitation, we do not believe the differences in the NVIQ measure between adolescent groups impact the interpretation of our results, as we find that AEP waveform global resemblance to the NT

age-normative waveform is associated with NVIQ across participants and do not see a main effect of group or interaction between NVIQ and group.

There are also several limitations with our ERP analyses to be acknowledged. First, it is possible our artifact rejection procedures, which did not include hand editing or independent component analysis, may not have sufficiently captured all noise and motion artifacts. Second, we also conducted artifact rejection on only seven target channels, but surrounding channel noise could have still impacted our target region. Our rationale for limiting the region of interest was to identify if this set of analyses could work with only a few channels, thus optimizing utility for clinical settings where findings might be inferred from only a few electrodes. Of note, the average waveforms in this region generally looked clean from visual inspection. Third, we did not analyze any of the classic latency measures often used in ERP studies. In general, studies seem to find small but sometimes significant differences in latency between autistic and control groups (Williams et al., 2021). We chose not to conduct this analysis because we focused on metrics that are more robust to noise than extracting the exact times of specific individual peaks (the ICC and differences in the magnitude from peak to peak); this choice is validated by the observation that there were no clear latency differences across groups in average waveforms, even though there are clear differences in both response shape (captured by the ICC) and overall response magnitude (captured by peak-to-peak magnitudes; see Figure 3). Further, any systematic differences in latency would affect the ICC, if present.

CONCLUSION

Despite the limitations noted above, we believe that our results provide an important contribution to the research field by characterizing auditory evoked responses in a relatively large sample of understudied individuals with moderate-to-profound intellectual impairments. AEPs of autistic adolescents, particularly those with low nonverbal intelligence, look different than those of NTs, but those differences are regardless of age and do not appear to be due to a developmental delay.

The findings described here may be explained in part by the hypothesis that the brains of autistic individuals have an overarching imbalance of excitatory to inhibitory activity (Casanova, 2006; Rubenstein & Merzenich, 2003). Flattened AEPs could be the result of sensory input processing masked by excess noise due to this imbalance of excitatory-inhibitory activity, along with ineffective sensory gating and attentional regulation (Belmonte et al., 2004; Gliga et al., 2014; Rubenstein & Merzenich, 2003). Moreover, distortions in simple processing of sensory inputs caused by these unfiltered and noise-contaminated signals could have cascading effects on more complex, higher-order processing that rely on clear, low-level sensory inputs, thus impacting not only simple processing but also more generalized cognitive functioning (Belmonte et al., 2004; Chang & Merzenich, 2003). Further research is needed to investigate if and how the measure of neural responses to low-level, early sensory inputs (particularly sounds) might be used to capture processes of sensory gating, attentional regulation, and excitatory-inhibitory control that are foundational for general cognitive functioning.

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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All components of these studies were approved by Boston University's Institutional Review Board.

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