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Differential Altered Auditory Event-Related Potential Responses in Young Boys on the Autism Spectrum With and Without Disproportionate Megalencephaly

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Abstract

Autism spectrum disorder (ASD), characterized by impairments in social communication and repetitive behaviors, often includes altered responses to sensory inputs as part of its phenotype. The neurobiological basis for altered sensory processing is not well understood. The UC Davis Medical Investigation of Neurodevelopmental Disorders Institute Autism Phenome Project is a longitudinal, multidisciplinary study of young children with ASD and age-matched typically developing (TD) controls. Previous analyses of the magnetic resonance imaging data from this cohort have shown that ~15% of boys with ASD have disproportionate megalencephaly (DM) or brain size to height ratio, that is 1.5 standard deviations above the TD mean. Here, we investigated electrophysiological responses to auditory stimuli of increasing intensity (50–80 dB) in young toddlers (27–48 months old). Analyses included data from 36 age-matched boys, of which 24 were diagnosed with ASD (12 with and 12 without DM; ASD-DM and ASD-N) and 12 TD controls. We found that the two ASD subgroups differed in their electrophysiological response patterns to sounds of increasing intensity. At early latencies (55–115 ms), ASD-N does not show a loudness-dependent response like TD and ASD-DM, but tends to group intensities by soft vs. loud sounds, suggesting differences in sensory sensitivity in this group. At later latencies (145–195 ms), only the ASD-DM group shows significantly higher amplitudes for loud sounds. Because no similar effects were found in ASD-N and TD groups, this may be related to their altered neuroanatomy. These results contribute to the effort to delineate ASD subgroups and further characterize physiological responses associated with observable phenotypes.

Lay summary:

Approximately 15% of boys with ASD have much bigger brains when compared to individuals with typical development. By recording brain waves (electroencephalography) we compared how autistic children, with or without big brains, react to sounds compared to typically developing

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controls. We found that brain responses in the big-brained group are different from the two other groups, suggesting that they represent a specific autism subgroup.

Keywords

autism spectrum disorder; toddlers; EEG; disproportionate megalencephaly; auditory processing

Introduction

Individuals with autism can be characterized by two core features: (a) difficulties in social interaction and reciprocity reflected by deficits in verbal and nonverbal communication skills; and (b) restricted interests and repetitive behaviors [APA, 2013]. However, the severity and expression of these impairments are highly variable from one individual to another [Lombroso, Ogren, Jones, & Klin, 2009]. It is now well accepted that autism has different etiologies and developmental trajectories that nonetheless share common features [Kim, Macari, Koller, & Chawarska, 2016]. Therefore, phenotypic heterogeneity among children presenting autistic symptoms complicates early diagnosis and limits the ability to adopt the best therapy and treatment strategy for each individual. In addition, basic understanding of the etiology and pathophysiology of autism spectrum disorder (ASD) is challenged by the inherent heterogeneity of ASD. Thus, delineation of the different phenotypic expressions of ASD is crucial. One potential approach to accomplishing this involves defining individual biological signatures such as electrophysiological responses to sensory stimuli.

Odd responses to sensory environments have long been known to be a common feature of the ASD phenotype [e.g., Bergman & Escalona, 1947] and are currently part of the DSM-5 criteria. Numerous studies show abnormal low-level sensory processing in ASD that is thought to contribute to deficits in social communication [Belmonte et al., 2004; Gerrard & Rugg, 2009; Minshew & Hobson, 2008; Valla & Belmonte, 2013] and to influence the severity of restricted and repetitive behaviors [e.g., Kargas, López, Reddy, & Morris, 2015].

Many studies have demonstrated auditory processing differences in ASD in terms of both response amplitude and timing that are seen from the earliest brainstem responses [e.g., Talge, Tudor, & Kileny, 2018] to late cortical responses [see Bomba & Pang, 2004; Jeste & Nelson, 2009; O'connor, 2012 for reviews]. Tharpe et al. [2006] showed that, despite normal auditory thresholds, brain stem responses were more variable in ASD. In terms of altered amplitude findings, Donkers et al. [2015] showed in an auditory oddball paradigm that 4- to 12-year-old children with autism had reduced early cortical sensory responses (measured by the P1 and N2 components) and reduced attentional responses (or P3a) when compared to typically developing (TD) controls. Furthermore, these response patterns were related to more atypical sensory seeking behaviors. In Khalfa et al. [2004], children and adolescents with and without ASD were presented with pure tones at different intensities and were asked to rate each sound from "low" to "too loud." Individuals with ASD judged auditory stimuli as uncomfortable at lower intensities compared to TD controls. Loudness discomfort was experienced at levels lower than 80 dB by ~63% of individuals with ASD compared to

~27% in the TD group. Interestingly, pure tone thresholds, that is, the minimal intensity to detect a sound in the absence of any other external sounds, were not significantly different between the groups. Brain responses elicited by different sound intensities were also investigated using electroencephalography (EEG). Bruneau, Roux, Adrien, and Barthélémy [1999] investigated auditory event-related potentials (ERPs) elicited by sounds of varying intensities (from 50 to 80 dB) in children with and without ASD. Children with autism were found to have, on average, differences in the ERP waveforms occurring around 150 ms poststimulus onset, with smaller amplitudes and a pronounced latency delay. Although the differences in the cortical responses as a function of loudness were present in a larger proportion of the individuals with ASD than TD children in this study, it did not represent a consistent marker for autism because a number of children with ASD displayed similar brain responses to those found in the TD group, highlighting the heterogeneity of ASD response profiles. However, such studies provide evidence that investigating physiological responses to stimuli of differing intensity can be used to identify subgroups of individuals with ASD that may reflect meaningful differences in underlying biology as well as in their expression of core deficits or co-occurring conditions.

Regarding altered timing of auditory responses in ASD, a number of studies have found delayed latencies. For example, Port et al. [2016], using magnetoencephalography (MEG), showed that children with ASD between 6 and 11 years had delayed M100 latencies in response to 45 dB above threshold simple tones when compared to age-matched TD controls. Within normal development, there is a decrease in peak latency of auditory ERPs and a narrowing of waveform peak widths with increasing age [Ponton, Eggermont, Khosla, Kwong, & Don, 2002]. Furthermore, a recent MEG study of auditory responses during sleep obtained from children with and without ASD who were 2–5 years of age showed different patterns of the impact of age on auditory response latency. TD children showed a significant reduction in latency with increasing age. The ASD group did not show this pattern: age was unrelated to latency [Stephen et al., 2017]. Regarding older children, Gage, Siegel, and Roberts [2003] and Roberts et al. [2010] also identified a decrease in M100 peak latency with increasing age in TD children (aged 8–16 years) but no change in children with ASD. Overall, children with ASD had longer M100 peak latencies than the age-matched controls, independent of age. Similar to these findings in children, Matsuzaki et al. [2018] found that the M100 component to simple sounds was delayed in adults with ASD when compared to typical adults. Latency delays have also been observed associated with larger head size in the context of individuals with 16p11.2 deletions, a genotype that has been associated with the ASD phenotype [Jenkins et al., 2015]. Taken together, there is ample evidence of altered patterns of neurophysiological correlates of auditory processing in ASD that support the phenotypic observations of odd responses to sensory input. However, the underlying neural bases of these effects are not well understood even in light of known structural brain differences in ASD.

There are a variety of alterations in neural structure in ASD compared with neurotypicals, emphasizing the heterogeneity within the autism spectrum [Amaral, Schumann, & Nordahl, 2008]. Macrocephaly (i.e., an overly large head in infants), is one of the most reported anatomical observations in individuals with autism [Grandgeorge, Lemonnier, & Jallot, 2013]. Other studies have shown that general brain enlargement is present in the first year of

life and may represent a risk for autism [Hazlett et al., 2005; Courchesne, Carper, & Akshoomoff, 2003]. Cortical thickness was also measured and was shown to have comparable values between TD and ASD children, while cortical surface area is greater in ASD than TD children [Ohta et al., 2015]. Furthermore, it has been shown that brain growth in individuals with autism undergoes an abnormal time course. For example, during the first year of life, there is a precocious growth of the brain, particularly in the frontal lobe [Carper & Courchesne, 2005; Redcay & Courchesne, 2005]. Given the altered time course of neural growth in individuals with autism, it is likely that the connectivity between brain regions is also altered. It has been proposed, for example, that there are decreases in the amount of white matter and the pattern of long-range connectivity between brain regions [for a review, see Rane et al., 2015]. At the neuronal level, postmortem differences have been observed. Casanova, Buxhoeveden, Switala, and Roy [2002] showed minicolumnar abnormalities in frontal and temporal regions in ASD. More recently, differences in minicolumnar spacing were also found in primary sensory areas, such as the auditory cortex [McKavanagh, Buckley, & Chance, 2015]. Given limited sample sizes and larger interindividual variability, the detailed localization and configuration of theses altered local and global changes in the brain remain to be determined.

The development and organization of the brain in young children with ASD has been studied in the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute Autism Phenome Project (APP). The overarching goal of the APP is to investigate the heterogeneity of ASD symptoms as well as the potential links among neuropsychological, neurophysiological, genetic, and environmental factors in order to advance the basic understanding of the pathophysiology of autism and ultimately to help optimize treatment for these children. The APP is a longitudinal study that has enrolled nearly 500 children who are on the autism spectrum or are age-matched TD children. Using a multidisciplinary approach, the goal is to identify biological signatures that differentiate clinically significant subgroups of children with autism. Children on the autism spectrum are recruited shortly after diagnosis, around 2 to 3.5 years old. Although EEG data were recorded only during the first visit, other measures, such as structural magnetic resonance imaging (MRI) and neuropsychological measures, have been collected during three additional times at roughly 4, 5, and 11 years of age. One neurophenotype found in the APP cohort was characterized as disproportionate megalencephaly (ASD-DM) and was defined as having a total cerebral volume (TCV)-to-height ratio that is 1.5 standard deviations above the mean of matched TD controls [Amaral et al., 2017]. This subgroup represented approximately 15% of the young boys with ASD at the first visit. The remaining boys with ASD in the APP cohort have brains in the normal range (ASD-N; information about MRI studies in the APP cohort can be found in Amaral et al. [2017], Libero et al. [2016], Libero, Schaer, Li, Amaral, and Nordahl [2018], Nordahl et al. [2011, 2012], and Ohta et al. [2015]. Little is currently known about if, and how the enlarged brain size affects sensory processing. Furthermore, the longitudinal data collected through the APP showed that the Intelligence Quotient (IQ) deficit in the ASD-DM group became evident around the age of 5 years old. Individuals in the ASD-DM group had lower gains in IQ when compared to the ASD-N group [Libero et al., 2016; Amaral et al., 2017]. The genetics of this neurophenotype also appears to be very complex. Although one individual in this group was shown to have a loss of function

mutation of the CHD8 gene [Bernier et al., 2014], no consistent patterns of genetic mutations have been found throughout the group. As Williams, Dagli, and Battaglia [2008] summarized over a decade ago, macrocephaly is associated with a very large number of genetic conditions.

The current study investigated auditory ERPs elicited by sounds of varying intensities (from 50 to 80 dB) in young boys with ASD with and without DM and age-matched TD controls. We hypothesized that the pattern of response in both ASD subgroups (ASD-DM and ASD-N) would be different from those in the TD group. For the TD group, we expected that louder sounds would result in larger electrocortical activity. On the basis of known altered sensory responsiveness in ASD and the ERP results reported in Bruneau et al. [1999], we expected less differentiation in the electrocortical response among sound intensity levels for both autism groups. Moreover, we hypothesized that individuals in the ASD-DM group would be more likely to display odd patterns of response as compared to TD patterns of response to sounds of different intensities than those in the ASD-N group. This hypothesis, drawing on the results of Libero et al. [2016], made the assumption that altered sensory processing could contribute to increased autism severity in this group. Thus, we predicted more deviation from the TD response pattern for ASD-DM than would be observed for the ASD-N group. Given our primary interest in exploring how ERP responses track stimulus intensity (i.e., loudness dependency) we chose to focus our analyses on global measures of response amplitude rather than latency. However, given the extant data, within a given sound intensity, of latency differences between TD and ASD populations, we have, on an exploratory basis, examined latency differences in our data as well. Based on the literature, we expected to find delayed latencies for both ASD groups compared with TD group.

Materials and Methods

Participants

Participants for this study were recruited through the MIND Institute of the University of California, Davis, as part of the APP. Psychologists who specialize in autism assessment obtained the diagnostic measures including the Autism Diagnostic Observation Schedule-Generic (ADOS-G) [DiLavore, Lord, & Rutter, 1995; Lord et al., 2000], and the Autism Diagnostic Interview-Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994]. Inclusion criteria for ASD were based on DSM-IV [APA, 1994] criteria and further defined by the Collaborative Programs of Excellence in Autism network. All participants included in this study met criteria for autism or ASD on the ADOS and exceeded the ADI-R scores for autism on either the Social or Communication subscales and were within two points of this criterion on the other subscale. Because different ADOS-G modules were used for testing, we calculated ADOS severity scores to allow comparison of autism severity across participants [Gotham, Pickles, & Lord, 2009]. The Mullen Scales of Early Learning (MSEL) [Mullen, 1995] was used to measure developmental quotient (DQ), verbal quotient (VDQ), and nonverbal quotient (NVDQ) for all participants. The Social Communication Questionnaire (SCQ) [Rutter, Bailey, & Lord, 2003] was used to screen TD controls for autism traits (scores below 11). Furthermore, we only included TD controls who had developmental scores within two standard deviations on all scales of the MSEL. Sensory

processing difficulties were assessed for both groups using the Short Sensory Profile (SSP) [McIntosh, Miller, Shyu, & Dunn, 1999]. This measure is a shortened form of the Dunn's Sensory Profile caregiver questionnaire [Dunn, 1999] and contains 38 items. The SSP total score can be used as an indicator of overall sensory dysfunction (typical, probable difference, and definite difference) with lower scores indicating more impairment. Details about the inclusion criteria and other clinical measures collected in the APP can be found in previous publications [Nordahl et al., 2011; Ohta et al., 2015; Libero et al., 2016, 2018; Amaral et al., 2017].

From the larger group of participants that underwent EEG recordings, a subset of males was selected for analysis for this study. We first identified individuals in the DM group with usable EEG data and then selected individuals in the ASD-N and TD groups to match them. Data from 36 boys, of which 24 were diagnosed with ASD (two groups: 12 with DM [ASD-DM] and 12 with normal brain size [ASD-N]) and 12 TD controls (TD), were collected. All groups were matched on age (ASD-DM: [mean ± SE] 37.8 ± 1.4 months old; ASD-N: 37.6 ± 1.3 months old; TD: 37.8 ± 1.3 months old). Both ASD groups were additionally matched on DQ scores (ASD-DM: [mean ± SE] 56 ± 6.9; ASD-N: 60.4 ± 6.8; details about demographics are summarized in Table 1). As expected, DQ, VDQ, and NVDQ were significantly higher in TD controls than ASD-DM ($P \leq 0.001$) and ASD-N ($P \leq 0.001$). No significant differences were found between the two ASD subgroups (DQ: $P = 0.65$; VDQ: $P = 0.97$; NVDQ: $P = 0.38$; AD0S-G: $P = 0.89$). Participants were assigned to the DM group based on the ratio of TCV-to-height and current height. For each participant, a 3D T1-weighted magnetization prepared rapid acquisition gradient echo scan (TR 2,170 ms;TE 4.86 ms; matrix 256 × 256; 192 sagittal slices, 1-mm isotropic voxels) was obtained on a 3T Siemens TIM Trio MRI System (Siemens Medical Solutions, Erlangen, Germany) during natural sleep [Nordahl et al., 2008]. A calibration phantom (Magpham ADNI; Phantom Laboratory) was scanned at the end of each session and resulting 3D distortion map was used to remove hardware-induced distortion in the T1-weighted images (Image Owl). TCV was calculated using a template-based automated method [details have been described in Nordahl et al., 2011, 2012]. Individuals with DM were identified as having a ratio of TCV-to-height greater than 1.5 SD above the mean of age-matched and sex-matched TD males [for details, see Ohta et al., 2015; Libero et al., 2016, 2018; Amaral et al., 2017]. TD participants in our sample did not meet the criteria of DM. As expected, TD and ASD-N groups had significantly lower TCV-to-height ratios compared to the ASD-DM group (summarized in Table 1). All participants had clinically normal hearing based on their medical history provided by community services and general pediatricians prior to study enrollment (if there was a suspicion of hearing impairment, participants were not enrolled in the ERP portion of the APP). Families received a gift card as a compensation for their time. This study was approved by the UC Davis Institutional Review Board and informed consent was obtained from a parent or guardian of each participant.

Stimuli and Procedure

Stimuli were 50 ms (including 5 ms rise and decay time) complex tones (i.e., a combination of multiple frequencies spanning from ~200 to 3,000 Hz) chosen to activate a large portion

of the primary auditory cortex. These tones were of different loudness (50, 60, 70, and 80 dB SPL) and were presented via headphones in a random order.

Electrophysiological data were collected from all conditions throughout the duration of the experiment. Presentation software (neurobehavioral systems; www.neurobs.com) was used to control stimulus delivery. Pediatric headphones were used for stimulus delivery (Sony MDR-222KD) and were calibrated using a B&K artificial ear model 4153 coupled to a B&K model 2229 sound level meter. A total of ~1,200 stimuli (300/intensity level in random order) were presented with a random 1–2 s inter-stimulus interval. Children were passively listening to the sounds while sitting on their caregiver's lap in a dimly lit audiometrically quiet electrically shielded testing room and were watching a quiet movie of their choice to ensure that they remained alert during the recording session. Given the variability in sound intensity of any movie soundtrack across time, and the additional variability of using different films, we relied on the robustness of the recording protocol where each stimulus at each intensity level was randomly interleaved and repeated 150–300 times so that the effects of co-occurring auditory input from the film would be expected to be averaged out in the course of deriving the auditory ERPs. The experiment was designed to be child-friendly, with breaks occurring on demand. The average duration of the recording session after electrode application was about 40–45 min.

EEG Acquisition and Preprocessing

Continuous EEG was acquired at 1,000 Hz (Compumedic Neuroscan Synamp II) using soft electrode caps with 61 equidistant electrodes (www.easycap.de) referenced to Cz. EEG preprocessing was performed with Brain Electrical Source Analysis Software (BESA 5.2; www.besa.de). EEG data were average-referenced and band-pass filtered offline with a low cutoff filter at 0.4 Hz (12 dB/octave roll-off). For each participant, bad channels were removed and single trials spanning 200 ms prestimulus to 900 ms poststimulus onset were screened for extreme amplitudes. Trials were excluded from analyses if large movement artifacts or high amplitude spikes were present. The remaining trials were submitted to Second-Order Blind source Identification [SOBI: Belouchrani, Abed-Meraim, Cardoso, & Moulines, 1997; SOBI applied to EEG: Tang, Sutherland, & McKinney, 2005] to remove the remaining non-neural artifacts (such as muscle tension, eye movements, blinks, and 60 Hz contamination) from the ERPs using a semiautomatic artifact removal tool (SMART; https://stanford.edu/~saggar/Software.html). Additional details about artifact identification and removal using SOBI and SMART can be found in Saggar et al. [2012]. Artifact-free single trials were then reconstructed for each participant and averaged ERPs were individually calculated for the four experimental conditions. The total number of trials per condition did not statistically differ between groups (Table 2). Prior to group-averaging, data from excluded channels from each subject were interpolated using a 3-dimensional spline [Perrin, Pernier, Bertnard, Giard, & Echallier, 1987]. Epochs used for the analyses spanning 50 ms prestimulus to 350 ms poststimulus onset were filtered (second order Butterworth with −12db/octave roll-off; 0.1 Hz high-pass; 40 Hz low-pass) and baseline corrected using the prestimulus interval using Cartool [Brunet, Murray, & Michel, 2011]. ERPs for the four experimental conditions were calculated for each participant.

Statistical Analysis of ERPs

The effect of the presence or absence of DM, compared to typical development, on brain responses was quantified by assessing the modulations in the electric field strength at the scalp surface for each condition using the global field power (GFP). GFP is calculated as the square root of the mean of the squared amplitude value recorded at each electrode of the 61-channel montage (vs. the average reference) and represents the spatial standard deviation of the electric field at the scalp [Lehmann & Skrandies, 1980]. Specifically, GFP yields larger amplitudes for stronger electric fields, and GFP peaks indicate that the underlying neural sources are maximally synchronized [Michel & Murray, 2012]. This measure represents a reference-free estimate of the electrocortical response strength. We decided to use the GFP approach instead of the classical one or few selected electrodes method to perform our analysis for the following reasons. First, selecting electrodes with the highest ERP response based on the grand average waveforms does not necessarily represent the location of maximal activity at the single subject level. The GFP, however, by taking activity at all electrodes into account is insensitive to differing spatial distribution at the individual subject level. Second, the location of such single electrode maxima is dependent of the choice of the reference. In other words, the choice of the reference will change the shape of the electrode waveforms (see Murray, Brunet, & Michel, 2008 for more details).

Because we were primarily interested in the differences in early, low-level auditory processing between groups, we report effects prior to 200 ms poststimulus. Periods of interest were determined by a time point 3 × 4 ANOVA with the factors of group (ASD-DM; ASD-N; and TD) and loudness (50, 60, 70, and 80 dB) using Statistical Toolbox for Electrical Neuroimaging (STEN; http://doi.org/10.5281/zenodo.1164038). To account for multiple comparisons, only effects with a P-value ≤0.05 sustained for at least 15 consecutive time-frames (15 ms) were considered to be significant (cf. table 1 in Guthrie & Buchwald, 1991). When appropriate, separate one-way ANOVAs for each group as well as t-tests (two-tailed) were conducted to analyze differences between intensities. Results with $P \leq 0.05$ were considered to be significant. All statistical analyses were performed by using SPSS statistics, version 25.0 (IBM, Tokyo, Japan).

During periods of significant effects, the relations between GFP amplitudes and other measures, including ADOS severity scores, DQ, VDQ, and NVDQ scores, chronological age and head circumference were tested using Pearson correlations. Data from the SSP questionnaires were too sparse to further analyze. However, it is important to note that after examination of the distribution of the SSP scores in both ASD groups, individuals with the lowest scores, that is, who are more likely to exhibit sensory processing issues, were mostly in the ASD-DM group.

During periods of significant effects, additional tests were performed to account for the heterogeneity of the data. Individual mean GFP values were calculated for each intensity over the period showing a significant effect. For each period, the standard deviation of the four intensities was calculated for each participant and compared between groups (ASD-DM, ASD-N, and TD) using a one-way ANOVA.

Latency Analysis

The latency analysis was undertaken in the following manner: for each group, and for each intensity level, the GFP peak of the main auditory response was identified. The latency of this peak defined the center of a 100 ms-wide window subsequently used to identify individual subject peak GFP latencies for each loudness condition by group. In the TD group, the period of interests were the following: for 50 dB 74–174 ms (peak at 124 ms), for 60 dB 61–161 ms (peak at 111 ms), for 70 dB 55–155 ms (peak at 105 ms), and for 80 dB 50–150 ms (peak at 100 ms). In the ASD-N group, the period of interests were the following: for 50 dB 70–170 ms (peak at 120 ms), for 60 dB 55–155 ms (peak at 105 ms), for 70 dB 43–143 ms (peak at 93 ms), and for 80 dB 43–143 ms (peak at 93 ms). In the ASD-DM group, the period of interests were the following: for 50 dB 69–169 ms (peak at 119 ms), for 60 dB 55–155 ms (peak at 105 ms), for 70 dB 43–143 ms (peak at 93 ms), and for 80 dB 44–144 ms (peak at 94 ms). When the peak latency occurred at the end of the window, that is, when the GFP waveform was still increasing, we looked for the first peak occurring after that. Only one participant had a peak latency that was significantly outside of the defined periods. This participant was in the ASD-DM group and was not excluded from the analyses. Differences for peak latency between the three groups were tested with a 3 × 4 ANOVA with the factors of group (TD, ASD-N, and ASD-DM) and loudness (50, 60, 70, and 80 dB) using SPSS. Effects with a *P*-value ≤0.05 were considered to be significant. When appropriate, separate one-way ANOVAs for each group as well as *t*-tests (two-tailed) were conducted to analyze differences between intensities. Results with *P*-value ≤0.05 were considered to be significant.

The relation between peak latency to other measures, including chronological age, ADOS scores, and DQ, VDQ, and NVDQ scores was tested using Pearson correlations.

Results

Modulations of the Auditory Response Strength Over the 55–115 ms Poststimulus Period

Visual inspection of group-averaged GFP waveforms suggested a difference in amplitude for the four intensities at early latencies (around the 50–100 ms range) for each of the three groups (Fig. 1, waveforms). The time-wise analysis of the GFP of all participants confirmed this pattern, revealing a significant temporally sustained main effect of loudness over the 55–115 ms period ($F_{3,105} = 16.29$; $P \leq 0.001$, $\eta_p^2 = 0.32$; Fig. 1, period shown with a pink box). GFP, averaged over this period, was modulated according to the level of intensity, with very soft sounds (50 dB) having the lowest electric field strength amplitude and very loud sounds (80 dB) having the highest amplitude (Fig. 2A). Over the 55–115 ms period, electric field strength was weaker for 50 dB sounds as compared to 60 dB sounds ($t_{35} = -2.2$; $P = 0.03$), 70 dB sounds ($t_{35} = -4.23$; $P \leq 0.001$) and 80 dB sounds ($t_{35} = -5.69$; $P \leq 0.001$);they were weaker for 60 dB sounds as compared to 70 dB sounds ($t_{35} = -2.47$; $P = 0.02$), and 80 dB sounds ($t_{35} = -5.09$; $P \leq 0.001$); and they were weaker for 70 dB sounds as compared to 80 dB sounds ($t_{35} = -2.24$; $P = 0.03$). These results demonstrate the feasibility of recording clear auditory ERPs in young children. Specifically, the loudness-dependent responses occurred in the expected time domain of the main auditory cortical response (i.e., ~100ms).

We also investigated group differences in the pattern of response during this period of time. Figure 2B shows the GFP amplitudes averaged over the 55–115 ms window for the four experimental conditions in ASD-DM, ASD-N, and TD. Although ASD-DM and TD show expected loudness-dependency during this period, the ASD-N group demonstrated a different pattern of response. The electrocortical responses primarily differed between soft (50 and 60 dB) vs. loud (70 and 80 dB) sounds rather than responding in a graded fashion. We tested these assumptions with a 3 × 4 ANOVA with group and loudness as factors. We found a significant main effect of loudness ($F_{399} = 17.48$; $P \leq 0.001$; $\eta_p^2 = 0.35$) and an interaction between loudness and group ($F_{699} = 2.28$; $P = 0.04$; $\eta_p^2 = 0.12$) but no significant main effect of group ($F_{2,33} = 1.74$; $P = 0.19$; $\eta_p^2 = 0.09$). Separate one-way ANOVAs for each group (ASD-DM, ASD-N, and TD) revealed that the GFP was modulated by intensity of the presented sounds in ASD-DM ($F_{3,33} = 9.7$; $P \leq 0.001$; $\eta_p^2 = 0.47$) and TD ($F_{3,33} = 8.99$; $P \leq 0.001$; $\eta_p^2 = 0.45$) but not in ASD-N ($F_{3,33} = 2.22$; $P = 0.11$; $\eta_p^2 = 0.17$). Within ASD-DM, post-hoc *t*-tests showed that the electric field strength was weaker for 50 dB as compared to 60 dB ($t_{11} = -2.19$; $P = 0.05$), 70 dB ($t_{11} = -4.81$; $P = 0.001$), and 80 dB ($t_{11} = -4.37$; $P = 0.001$), and weaker for 60 dB as compared to 80 dB ($t_{11} = -2.69$; $P = 0.02$). Within TD, post-hoc *t*-tests showed that the electric field strength was stronger for 80 dB as compared to 50 dB ($t_{11} = -5.29$; $P \leq 0.001$), 60 dB ($t_{11} = -3.22$; $P = 0.008$), and 70 dB ($t_{11} = -3.34$; $P = 0.007$), and weaker (trend) for 50 dB as compared to 60 dB ($t_{11} = -1.99$; $P = 0.07$) and 70 dB ($t_{11} = -2.07$; $P = 0.06$). Taken together, these results suggest that, at least at the group-level, loudness-dependent mechanisms are present in ASD-DM and TD but not in the ASD-N group. This suggests that the ASD-N group demonstrates a different profile of sensory sensitivity.

Based on the preceding analyses, the two ASD groups appeared to differ in their loudness-dependent electrophysiological responses. We formally tested this assumption with a 2 × 4 ANOVA with the factors of group (ASD-DM vs. ASD-N) and loudness (50, 60, 70, and 80 dB). A significant interaction between these factors was found ($F_{3,66} = 2.85$; $P = 0.04$; $\eta_p^2 = 0.12$). Although none of the post-hoc unpaired *t*-tests were significant between the two ASD groups at any intensity, the pattern of response within each group is different, as shown in Figure 2B. Taken together, these data suggest that the presence of ASD and DM may involve distinct underlying brain processes compared to individuals with ASD and more normative brain size.

No statistically significant correlations between amplitude growth and ADOS severity scores, DQ, VDQ, and NVDQ scores, chronological age or head circumference were found.

Modulations of the Auditory Response Strength Over the 145–195 ms Poststimulus Time Period

The time-wise analysis of GFP revealed a significant temporally sustained interaction of group and loudness over the 145–195 ms poststimulus period ($F_{699} = 2.72$; $P = 0.02$, $\eta_p^2 = 0.14$; Greenhouse-Geisser corrected: $F_{4.2,68.9} = 2.72$, $P = 0.03$, $\eta_p^2 = 0.14$; Fig. 1, period shown with a dashed box). Separate one-way ANOVAs for each group (ASD-DM, ASD-N, and TD) revealed that the GFP was modulated by the intensity of the presented sounds in

ASD-DM ($F_{3,33}$ = 5.09; P = 0.005, η_p^2 = 0.32: Greenhouse-Geisser corrected: $F_{1.7,18.7}$ = 5.09, P = 0.02, η_p^2 = 0.32), but not in ASD-N ($F_{3,33}$ = 0.15; P = 0.93, η_p^2 = 0.01; Greenhouse–Geisser corrected: $F_{1.7,18.3}$ = 0.15, P = 0.82, η_p^2 = 0.01) or TD ($F_{6,99}$ = 2.21; P = 0.11, η_p^2 = 0.17; Greenhouse–Geisser corrected: $F_{2.2,24.6}$ = 2.21, P = 0.13, η_p^2 = 0.17). Within ASD-DM, post-hoc *t*-tests showed that the electric field strength was weaker for 50 dB as compared to 70 dB (t_{11} = −2.68; P = 0.02) and 80 dB (t_{11} = −2.51; P = 0.03; Fig. 3).

No statistically significant correlations between amplitude growth and ADOS severity scores, DQ, VDQ and NVDQ scores, chronological age or head circumference were found.

Individual Modulations of the Auditory Response Strength Over the 55–115 ms and 145–195 ms Periods

To further investigate individual differences in sensory-related brain responses in ASD-DM compared to ASD-N and TD, we compared individual patterns of responses over the two periods shown to be significant in the time-wise GFP analysis: 55–115 ms and 145–195 ms. Figure 4 shows GFP values averaged over the 55–115 ms (left panels) and 145–195 ms (right panels) periods for the four intensities and for each participant (TD [top panels], ASD-DM [middle panels], and ASD-N [bottom panels]). These scatter plots show: (a) inter-individual variability of the response patterns in the three groups over the two periods; (b) over the 55–115 ms, when the main auditory response occurs, most individuals display higher amplitudes to 70 and 80 dB sounds and lower amplitudes for 50 and 60 dB sounds in TD and ASD-DM, but less so in ASD-N; (c) most individuals in the TD group seem to discriminate the four intensities during the first period (55–115 ms) and then demonstrate minimal differences between the four intensities during the second period (145–195 ms); (d) some of the individuals in the ASD-DM group seem to discriminate between the four intensities in the first period (55–115 ms) but not in the second period (145–195 ms), and the remaining individuals in this group seem to show the inverse pattern with minimal difference between intensities over the 55–115 ms period and a discrimination between the four intensities over the 145–195 ms period; and (e) individuals in the ASD-N group predominantly display minimal differences between the four intensities over the two periods. To examine if the three groups differ in terms of inter-individual variability, we compared the dispersion of the data within each group using the within-individual standard deviation across the four intensities, with low standard deviation values representing minimal differences between the four intensities. Differences in data dispersion between the three groups were tested with a one-way ANOVA over the 55–115 ms and 145–195 ms periods, separately. Mean standard deviation values were not significantly different over the 55–115 ms period ($F_{2,35}$ = 2.29; P = 0.12). Over the 145–195 ms period, a slim difference was found between the three groups, although not reaching statistical significance, with ASD-DM seemingly displaying the highest standard deviation compared to ASD-N and TD ($F_{2,35}$ = 2.8; P = 0.075). Individual measures of dispersion over this period (displayed in Fig. 5, left panel) showed that only the ASD-DM group has individuals with a high standard deviation (Fig. 5). The discrimination between the four intensities may take longer in subjects in the ASD-DM group as compared to those in the ASD-N and TD groups, providing possible evidence for different mechanisms involved in auditory processing in ASD-DM.

Latency Analysis Results

At the group level, the peak latencies in the TD group were (mean ± SE) 125.6 ± 3.8 ms for 50 dB, 118.3 ± 4.5 ms for 60 dB, 118.5 ± 6.9 ms for 70 dB, and 112.5 ± 8.1 ms for 80 dB; peak latencies in the ASD-N group were 140.4 ± 6.7 ms for 50 dB, 128.5 ± 6.3 ms for 60 dB, 114.6 ± 9 ms for 70 dB, and 107.5 ± 7.8 ms for 80 dB; peak latencies in the ASD-DM group were 139.5 ± 10 ms for 50 dB, 130.8 ± 11.9 ms for 60 dB, 133.6 ± 10.5 ms for 70 dB, and 117.8 ± 6.7 ms for 80 dB (mean peak latencies as well as individual data are displayed in Fig. 6).

The analysis of the peak latency revealed a significant main effect of loudness ($F_{2,33}$ = 6.3 89, P = 0.002, η_p^2 = 0.38). Peak latency was different according to level of intensity, with soft sounds (i.e., 50 and 60dB;[mean ± SE] 135.2 ± 4.3 ms and 125.9 ± 4.8 ms, respectively) having the latest peak latency and loud sounds (i.e., 70 and 80dB;[mean ± SE] 122.2 ± 5.3 ms and 112 ± 4.4 ms) having the fastest peak latency (Fig. 6). Post-hoc *t*-tests revealed that 50 dB had a peak significantly later than 80 dB (t_{35} = 3.69; P = 0.001) and 70 dB (trend: t_{35} = 1.944; P = 0.06), and 60 dB had a peak significantly later than 70 dB (t_{35} = 2.97; P = 0.005) and 80 dB (t_{35} = 2.34; P = 0.025). No significant main effect of group ($F_{2,33}$ = 1.264, P = 0.296, η_p^2 = 0.071) and no significant interaction between loudness and group ($F_{6,99}$ = 0.787, P = 0.583, η_p^2 = 0.069) were found. The analysis of latency revealed a significant delayed processing for soft sounds when compared to loud sounds.

No statistically significant correlations between latency and ADOS severity scores, DQ, VDQ, and NVDQ scores, chronological age or head circumference were found.

Discussion

Previous publications from the APP using MRI suggest that DM is present in ~15% of young boys with autism [Nordahl et al., 2011;Amaral et al., 2017] and can be considered as a subgroup within the autism spectrum [Ohta et al., 2015;Libero et al., 2016, 2018;Amaral et al., 2017]. In the current study, we investigated electrophysiological responses to auditory stimuli in toddlers between 28 and 47 months old with ASD, and those who were TD, recruited through the APP. More specifically, we focused on characterizing differences in ERP response patterns to sounds of increasing loudness to test the impact of DM on the known altered auditory responses in ASD, as well as to relate them to typical development. As expected, we found that both ASD subgroups have different patterns of response as compared to TD controls. More interestingly, we found that ASD-DM and ASD-N differ in their electrophysiological patterns of response. Finally, individuals in all groups showed substantial variability in their response patterns.

We tested the validity of our experiment with a time-wise analysis of the GFP which revealed a period, spanning from 55 to 115 ms poststimulus onset, when responses to increasing sound intensity also result in increasing GFP amplitude, as expected. GFP values averaged across this period showed a linear increase in amplitude as a function of intensity, with soft sounds (50 dB) having the lowest amplitude and very loud sounds (80 dB) having the highest amplitude. These differences occur during a period overlapping with the N1

auditory component [corresponding to the P1 component in very young children as described in Ponton et al. [2002]] that reflects low-level auditory processing [e.g., Wunderlich, Cone-Wesson, & Shepherd, 2006 for the maturation of auditory ERPs from newborns to adults; Bruneau et al., 1999 and Ponton et al., 2002 for auditory ERPs in 4–8 years old children, and Näätänen & Picton, 1987 for auditory ERPs in adults]. Taken together, the data demonstrate the feasibility of obtaining high quality auditory ERPs in toddlers with and without autism that show the expected relationship between the sound intensity and their elicited brain response.

Although the three groups did not differ in their overall response to sounds across intensity, probably caused by a lack of statistical power because of our modest sample, they did differ in their loudness-dependent electrophysiological response patterns. In the 55–115 ms poststimulus window, both ASD-DM and TD groups showed loudness-dependency responses, with smaller GFP associated with soft sounds and greater GFP associated with very loud sounds, whereas ASD-N showed no reliable differences between intensities. Although abnormal auditory responses are well known in autism [Belmonte et al., 2004; Gerrard & Rugg, 2009;Minshew & Hobson, 2008;Valla & Belmonte, 2013; for reviews, see Bomba & Pang, 2004; Jeste & Nelson, 2009], the two ASD subgroups differed in their response patterns during this early period, suggesting that they may have different ASD-related neural alterations. Although ASD-DM shows a loudness-dependency, ASD-N shows a soft vs. loud discrimination, suggesting differences in sensory sensitivity. Most children in the ASD-N group have minimal differences in the GFP amplitudes averaged over the 55–115 ms period.

Interestingly, a significant interaction between the factors of loudness and group was found in the 145–195 ms poststimulus window, driven by the ASD-DM response pattern that shows significant differences between intensities, suggesting differences in effective sensory processing in this group. Children whose brain responses still discriminate between the intensities in this time period are more likely to be in the ASD-DM group. Because no similar effects were found in the ASD-N and TD groups, this may be related to the altered neuroanatomy of individuals with DM. Other studies have shown a relationship between morphological differences and sensory processing in healthy participants. For example, a study using MRI data and scores from the Sensory Profile Questionnaire [Brown, Tollefson, Dunn, Cromwell, & Filion, 2001] showed a positive association between individual differences in sensory processing and gray matter volumes in the primary or secondary sensory areas for visual, auditory, touch, and taste modalities in healthy adults [Yoshimura et al., 2017]. Another MRI study found a significant correlation between partial hearing loss and altered brain volume in hearing-impaired adults as compared to normal-hearing controls [Alfandari et al., 2018]. In our study, we were not able to test the relationship between SSP scores and response amplitudes because of the small sample size. However, we observed that individuals in the ASD-DM were most likely to have the lowest scores. Our results confirm that auditory processing in autism is different than in typical development. Because ASD-DM and ASD-N also differ from each other, it suggests that DM has a significant impact on the underlying mechanisms in sensory processing. Models of the neuropathology of ASD suggest abnormal patterns of cortical connectivity [Belmonte et al., 2004; Just, Cherkassky, Keller, Kana, & Minshew, 2006] and altered ratios of cortical excitation to inhibition [e.g.,

Rubenstein & Merzenich, 2003], which could both contribute to deficits in sensory processing. The maintenance of sensory-induced activations in this late period in ASD-DM could be related to this altered inhibitory-excitatory balance. Further studies designed to examine the underlying mechanisms in sensory processing in DM are needed.

The results of our latency analysis revealed, within the context of large interindividual differences, particularly for the ASD groups, a pattern of decreased latency of the main auditory response as stimulus intensity increased. Interestingly, no group differences were found. However, examination of individual data (Fig. 6) shows that, compared to the TD group, most individuals in both ASD groups appear to have delayed latencies consistent with prior findings in the literature [e.g., Port et al., 2016; Gage et al., 2003; Matsuzaki et al., 2018]. The lack of group differentiation within the latency data in terms of loudness-dependency points to the importance of using amplitude measures in studies examining neural responses to stimuli of differing intensity, an understudied area of characterizing auditory atypicality in ASD [Foss-Feig, Stone, & Wallace, 2012].

During the recordings, children were listening to sounds of varying intensities while watching a quiet movie of their choice. The presence of the video ensured that they remained alert during the long recording session (approximately 45 min) and allowed for the collection of a large number of trials to permit examination of ERPs at the individual level. Although it can be argued that visual attention might impact the auditory response, we think that this is unlikely. First, several studies presenting a quiet movie during an auditory task showed no impact on the auditory responses in children with ASD using speech sounds [e.g., Otto-Meyer, Krizman, White-Schwoch, & Kraus, 2018], multisensory stimulations [e.g., Russo et al., 2010], and pure tones [e.g., Roberts et al., 2010]. Second, this setting mimics everyday life situations and gives an ecological validity to our experiment. Moreover, because of the simplicity of our paradigm, we were able to recruit a broader range of individuals on the autism spectrum, including prelinguistic or nonlinguistic children or children with intellectual disability. Our study does have some limitations. The first is the small size of our sample which may have limited the power of our statistical analyses. Nonetheless, we did see meaningful effects sustained over time that were further supported by individual data. Second, the effect of megalencephaly on auditory ERPs was only tested in toddlers with autism. Future studies should include TD children with megalencephaly as an additional control group. Third, EEG data were only collected once, when participants were between 2 and 3.5 years old, and did not allow longitudinal comparison of electrophysiological patterns. Other studies from the APP showed that the IQ deficit in the ASD-DM boys became evident only when the children were 5-years-old [Amaral et al., 2017; Libero et al., 2016]. This highlights the need for comprehensive longitudinal studies. Fourth, we only investigated electrophysiological response patterns in young boys. Further studies are needed to understand whether similar mechanisms are involved in girls, although existing data suggest that the DM neurophenotype is rare in females with ASD [Amaral et al., 2017]. Finally, although GFP has advantages as a reference-free means of global neural activity, it does not provide information about the spatial distribution of the response to sensory stimulation. We are currently collecting data for a new project that addresses many of these issues.

Despite these limitations, the results of the current study show that ASD-DM may involve different brain processes related to loudness-dependent responses compared to individuals with ASD but without DM. These results contribute to the effort to delineate ASD subgroups and to further characterize physiological responses associated with observable neurophenotypes of autism.

Given that this is the first attempt to study, at a neurofunctional level, megalencephaly identified on the basis of TCV-to-height ratios, our main goal was to answer the question of whether the ASD-DM group displayed a distinct electrophysiological phenotype compared to the ASD N group. We have shown that they are different from TD and ASD-N groups, adding evidence to the proposition that they should be considered a distinct subgroup of ASD. The specific mechanisms or more detailed manifestations of the DM phenotype cannot be determined from this study. However, our group is now engaged in a large study with goals of characterizing the ASD-DM at structural, functional, and molecular levels. In addition, this project is examining TD individuals with megalencephaly in order to tease apart aspects of brain size differences that may be expressed differently in terms of phenotype. The present study was a first step towards these goals we are now trying to define the effects of megalencephaly more specifically. Further mechanistic studies that relate neuroanatomical differences in surface area of different brain regions [e.g., Ohta et al., 2015] and/or probabilistic tractography [Berman et al., 2016] to electrocortical responses represent future directions for more mechanistic characterization of the brain differences underlying variations in loudness-dependency within subgroups of the ASD population [see also Foss-Feig et al., 2012]. In addition, studies designed to further examine the balance of excitatory and inhibitory processes activated by stimuli of graded intensity will importantly contribute to understanding the mechanistic basis of our findings [Foss-Feig et al., 2017].

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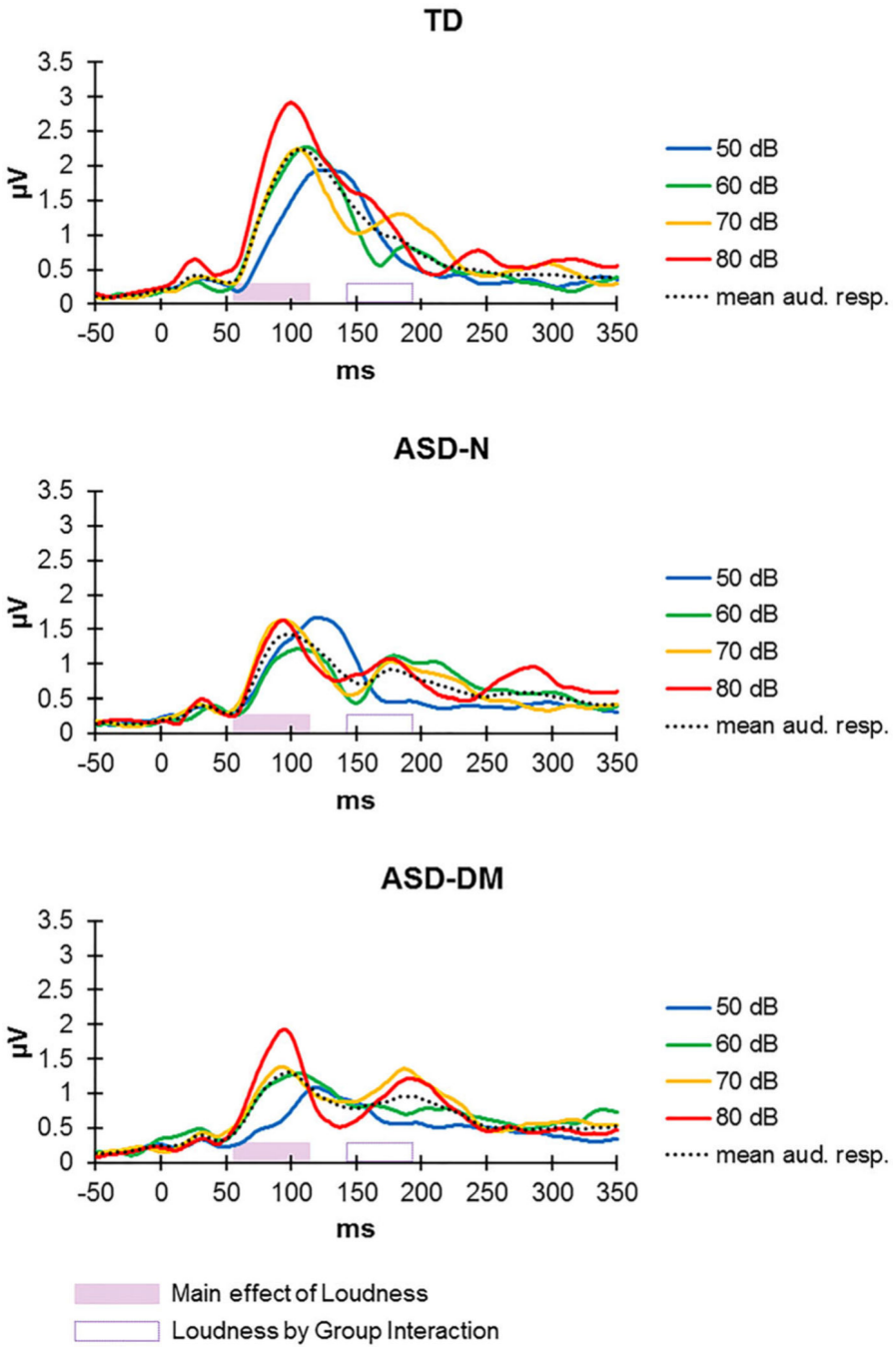

Figure 1.

Global field power (GFP) analysis over time. GFP waveforms are displayed by group for the four intensities and the mean auditory response: typically developing (top graph), autism spectrum disorder (ASD) without megalencephaly (middle graph), and ASD with disproportionate megalencephaly (bottom graph). Two time intervals showed significant effects: 55–115 ms for the main effect of loudness (pink) and 145–195 ms for the group by loudness interaction (dashed). Zero milliseconds = stimulus onset.

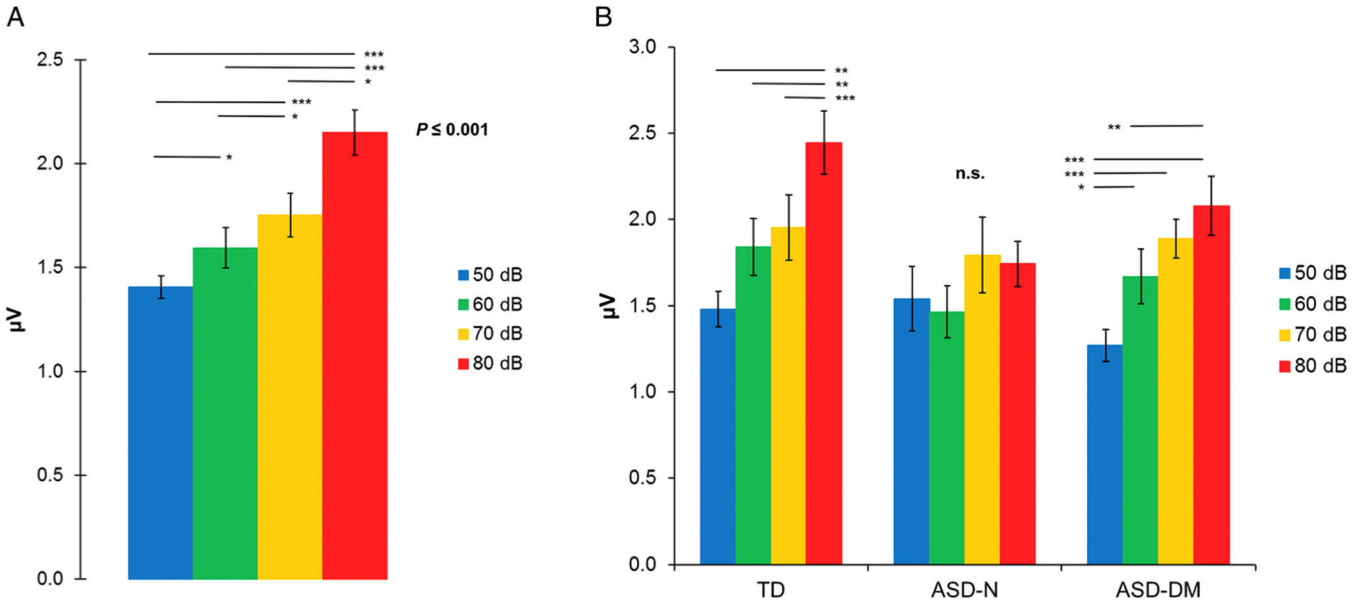

Figure 2.

Results of global field power (GFP) analysis, main effect of loudness over the time-window 55–115 ms. (**A**) Bar graphs visualizing the mean GFP to each intensity across all participants. (**B**) Bar graphs visualizing the mean GFP to each intensity by group. $*P \leq 0.05$, $**P \leq 0.01$, $***P \leq 0.001$, n.s.: not significant; error bars, standard error. Individual data for each group and condition during the 55–115 ms time period are represented in Figure 4, left panels.

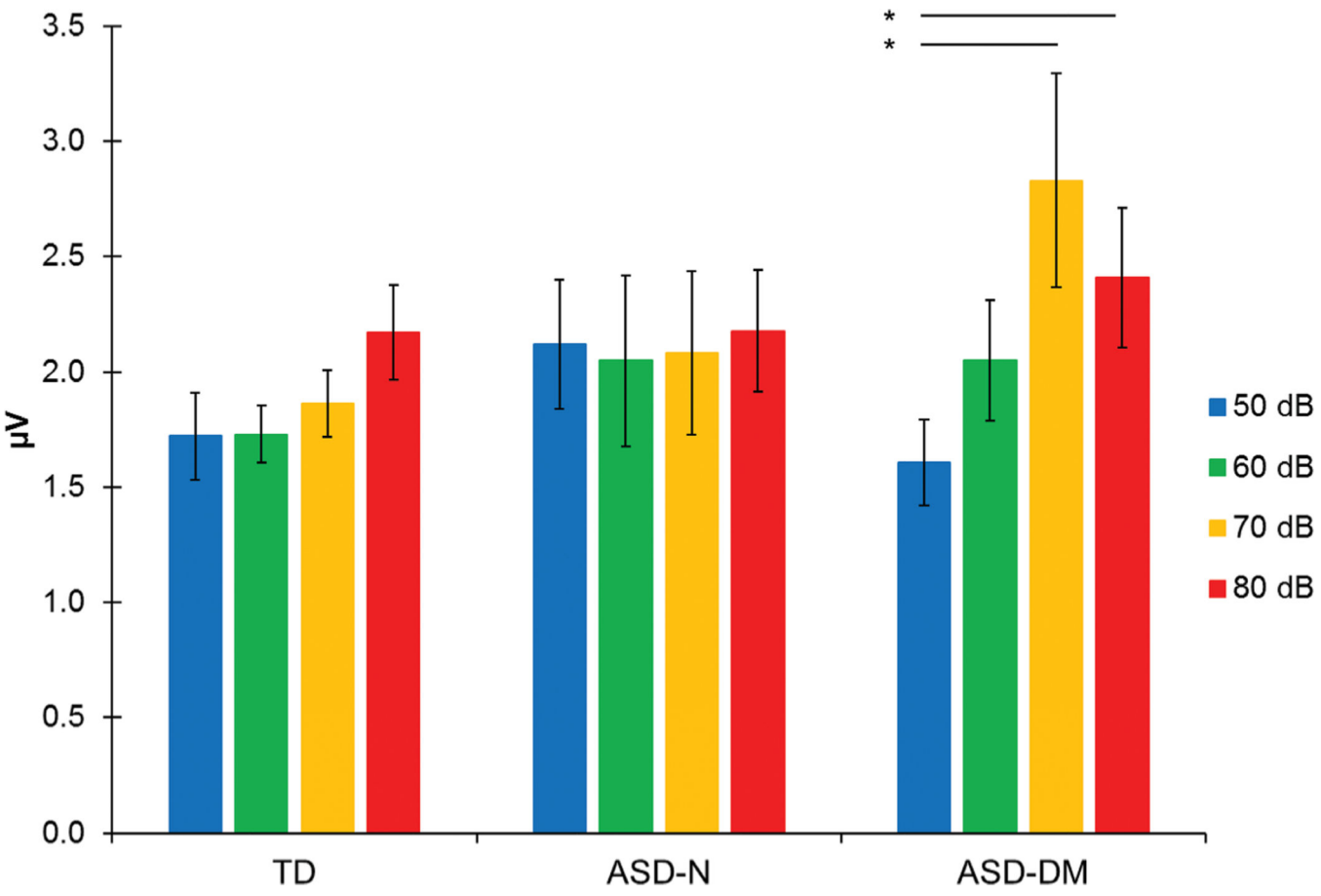

Figure 3.

Results of the global field power analysis, group by loudness interaction over the 145–195 ms window. Modulations in response strength were quantified over the 145–195 ms period by group for each intensity. Mean ± SE values are displayed and asterisks indicate significant effects between intensities within a group at $P \leq 0.05$. Individual data for each group and condition during the 145–195 ms time period are represented in Figure 4, right panels.

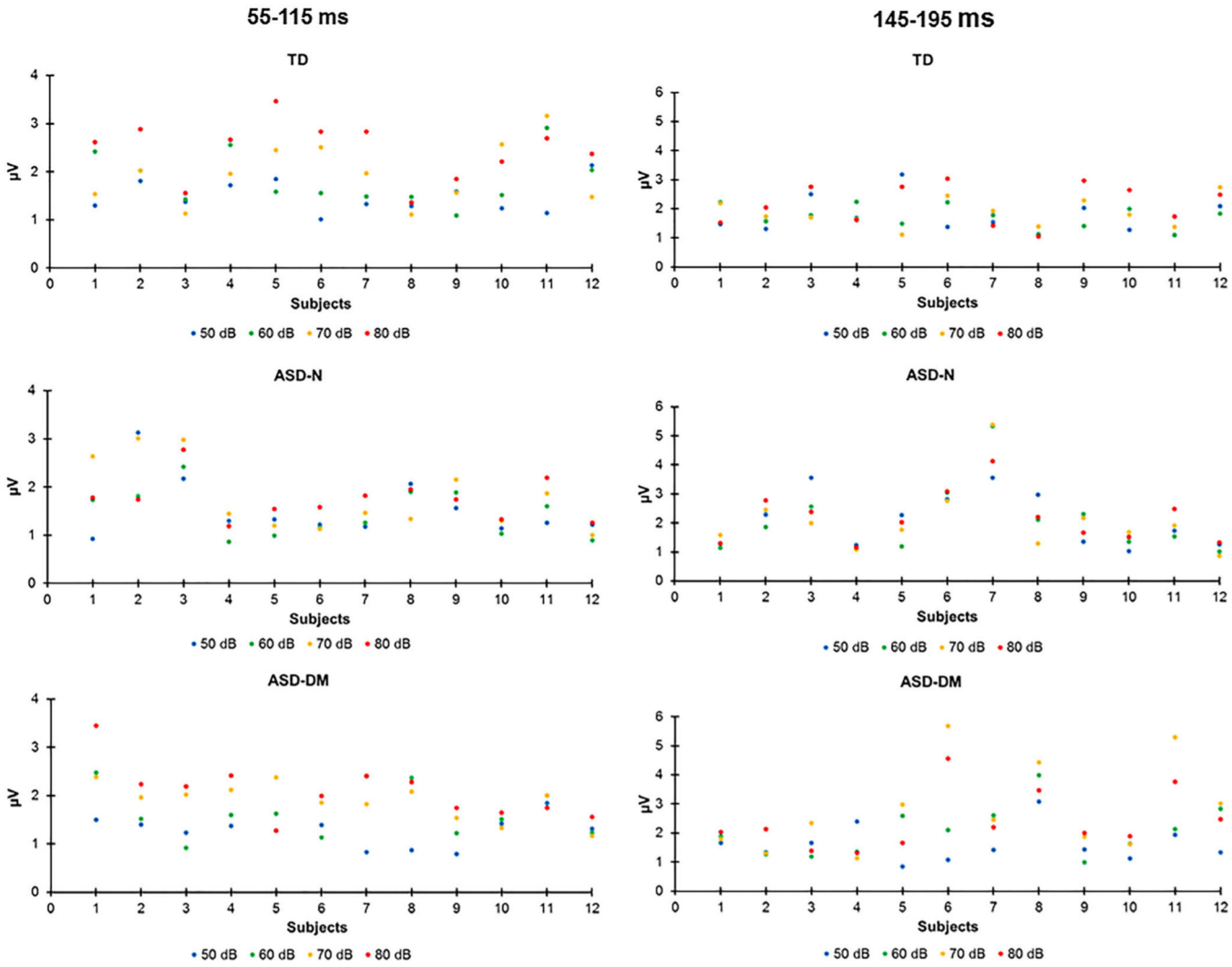

Figure 4.

Individual data. Mean global field power values were calculated over the 55–115 ms (left panels) and 145–195 ms (right panels) windows for the four intensities for each participant in typically developing (top panels), autism spectrum disorder (ASD) without megalencephaly (middle panels), and ASD with disproportionate megalencephaly (bottom panels).

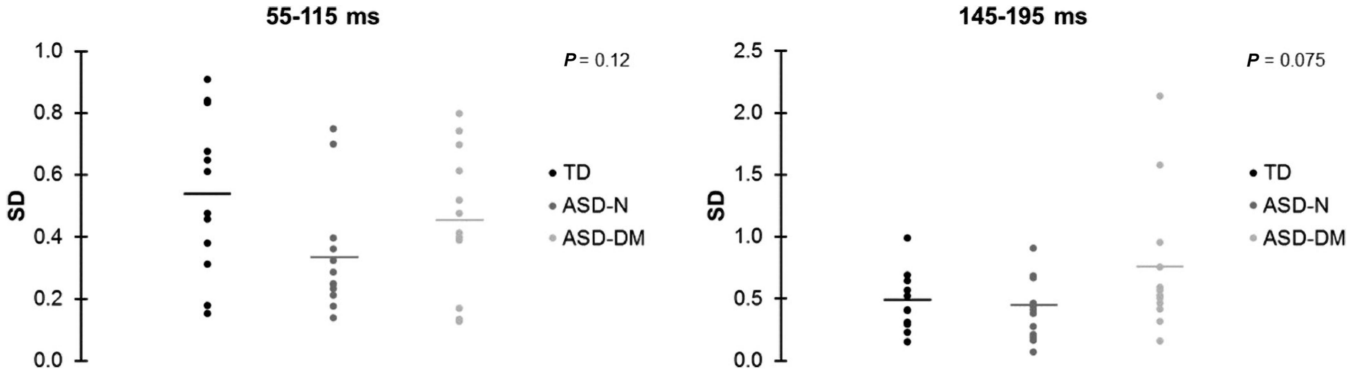

Figure 5.

Dispersion measures. Individual mean standard deviations are displayed for each group over the 55–115 ms (left panel) and 145–195 ms (right panel). The horizontal bars represent the group average.

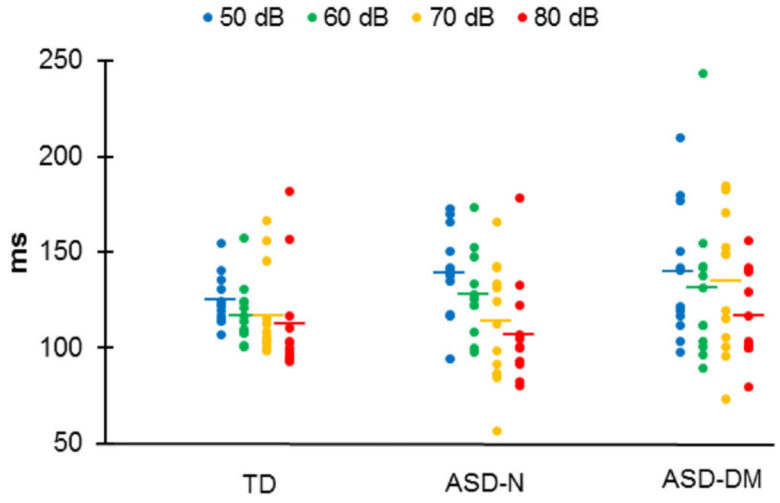

Figure 6.

Results of the latency analysis. Individual latency values are displayed for each intensity and each group. The horizontal bars represent the group average for each intensity level.

Table 1.

Demographic and Clinical Characteristics

	TD (*n* = 12)		ASD-N (*n* = 12)		ASD-DM (*n* = 12)	
	Mean ± SE	**Range**	**Mean ± SE**	**Range**	**Mean ± SE**	**Range**
Age in months	37.8 ± 1.3	27.6–43.5	37.6 ± 1.3	28.1–44.4	37.8 ± 1.4	28–46.1
ADOS severity	n.a.		8.1 ± 0.4		8.2 ± 0.5	
DQ	111 ± 3.8[a,b]	89.7–131.9	60.4 ± 6.8[a]	30.2–100	56 ± 6.9[b]	33.7–114.2
VDQ	113.9 ± 4.7[a,b]	89.7–138.9	49.9 ± 6.6[a]	22.1–88.7	49.5 ± 8.6[b]	26.7–116.2
NVDQ	108.7 ± 3.2[a,b]	89.7–125	70.7 ± 7.2[a]	38.4–118.6	62.5 ± 5.7[b]	37.2–112.2
SSP	164.1 ± 5.4 (*n* = 9)		128.8 ± 4.8 (*n* = 5)		122.3 ± 4.7 (*n* = 9)	
Head circumference (cm)	52 ± 0.5	49.5–55	51.2 ± 3.2	50–52	51.1 ± 0.5	48.5–54
TCV/height ratio	26.6 ± 0.32[b]	25.3–28.43	27.9 ± 0.31[c]	26.03–29.39	31.1 ± 0.32[b,c]	29.97–33.05

Note. Data are presented as mean ± SE.

[a]Statistical differences between ASD-N and TD ($P \leq 0.001$).

[b]Statistical differences between ASD-DM and TD ($P \leq 0.001$).

[c]Statistical differences between ASD-DM and ASD-N ($P \leq 0.001$).

Abbreviations: TD, typical development; ASD, autism spectrum disorder; ASD-N, ASD without megalencephaly; ASD-DM, ASD with disproportionate megalencephaly; ADOS, Autism Diagnostic Observation Schedule; DQ, developmental quotient; VDQ, verbal DQ; n.a., not applicable; NVDQ, nonverbal DQ; SSP, short sensory profile; TCV, total cerebral volume.

Table 2.

Average Number of Trials Per Condition for Each Group

	TD	ASD-N	ASD-DM
50 dB	214.8 ± 17.8	221.4 ± 14	216.4 ± 13.7
Range	[123, 316]	[135, 303]	[141, 301]
60 dB	210.7 ± 16.7	214.3 ± 14.3	208.9 ± 12.5
Range	[130, 310]	[125, 286]	[146, 292]
70 dB	219.8 ± 18.2	229.6 ± 13	221.1 ± 12.7
Range	[137, 327]	[140, 303]	[152, 300]
80 dB	213.3 ± 17.2	222 ± 14.4	211.5 ± 12.3
Range	[125, 316]	[131, 297]	[146, 299]

Note. Data are presented as mean ± SE, as well as the range. There was no significant interaction between the factors of group and intensity.

Abbreviations: TD, typical development; ASD, autism spectrum disorder; ASD-N, ASD without megalencephaly; ASD-DM, ASD with disproportionate megalencephaly.