Abnormal Auditory Mismatch Fields Are Associated With Communication Impairment in Both Verbal and Minimally Verbal/Nonverbal Children Who Have Autism Spectrum Disorder

Junko Matsuzaki, Emily S. Kuschner, Lisa Blaskey, Luke Bloy, Mina Kim, Matthew Ku, James Christopher Edgar, David Embick, and Timothy P. L. Roberts

Abnormal auditory discrimination neural processes, indexed by mismatch fields (MMFs) recorded by magnetoencephalography (MEG), have been reported in verbal children with ASD. Association with clinical measures indicates that delayed MMF components are associated with poorer language and communication performance. At present, little is known about neural correlates of language and communication skills in *extremely language impaired (*minimally-verbal/non-verbal) children who have ASD: ASD-MVNV. It is hypothesized that MMF delays observed in language-impaired but nonetheless *verbal* children with ASD will be exacerbated in ASD-MVNV. The present study investigated this hypothesis, examining MMF responses bilaterally during an auditory oddball paradigm with vowel stimuli in ASD-MVNV, in a verbal ASD cohort without cognitive impairment and in typically developing (TD) children. The verbal ASD cohort without cognitive impairment was split into those demonstrating considerable language impairment (CELF core language index <85; "ASD-LI") *versus* those with less or no language impairment (CELF CLI >85; "ASD-V"). Eighty-four participants (8-12 years) were included in final analysis: ASD-MVNV: n = 9, 9.67 ± 1.41 years, ASD: n = 48, (ASD-V: n = 27, 10.55 ± 1.21 years, ASD-LI: n = 21, 10.67 ± 1.20 years) and TD: n = 27, 10.14 ± 1.38 years. Delayed MMF latencies were found bilaterally in ASD-MVNV compared to verbal ASD (both ASD-V and ASD-LI) and TD children. Delayed MMF responses were associated with diminished language and communication skills. Furthermore, whereas the TD children showed leftward lateralization of MMF amplitude, ASD-MVNV and verbal ASD (ASD-V and ASD-LI) showed abnormal rightward lateralization. Findings suggest delayed auditory discrimination processes and abnormal rightward laterality as objective markers of language/communication skills in both verbal and MVNV children who have ASD. ***Autism Res*** *2019, 00: 1–11.* © 2019 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: Brain imaging showed abnormal auditory discrimination processes in minimally-verbal/non-verbal children (MVNV) who have autism spectrum disorder (ASD). Delays in auditory discrimination were associated with impaired language and communication skills. Findings suggest these auditory neural measures may be objective markers of language and communication skills in both verbal and, previously-understudied, MVNV children who have ASD.

Keywords: minimally verbal/non-verbal children; autism spectrum disorder; magnetoencephalography; vowel mismatch fields; language and communication skill

Introduction

Autism spectrum disorder (ASD)[1] is a neurodevelopmental disorder characterized by impaired social and communication skills and repetitive and stereotyped behavior [APA, 2013]. Impairment in these core features of ASD change as a function of age, cognitive ability and language level [Risi et al., 2006]. Expressive language level is a particularly important factor regarding social - communicative deficits and predictive of long term outcomes in children who have ASD [Klein-Tasman et al., 2007, Bal et al., 2018].

Approximately 30% - 40% of children with ASD remain minimally verbal (MV) into adulthood [Howlin et al., 2013, Pickles et al., 2014, Bal et al., 2016], with MV/nonverbal (NV) defined clinically as individuals who use little or no spoken language [Jónsdóttir et al., 2007, Goods et al., 2013; Kasari et al., 2013, 2014, Norrelgen et al., 2015, Rose et al., 2016]. Approximately 31% of children who have ASD have intelligence quotients (IQs) below 70 [Baio et al., 2014,

[1]Individuals on the autism spectrum, their parents, and professionals in the field have unique and overlapping opinions regarding the use of person-first (e.g., children with ASD) or identity first (e.g., autistic child) language (Kenny et al., 2015). With respect for divided opinions, we use both approaches to terminology in this paper.

From the Department of Radiology, Lurie Family Foundations MEG Imaging Center, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (J.M., E.S.K., L.B., L.B., M.K., M.K., J.C.E., T.P.L.R.); Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (E.S.K., L.B., M.K.); Department of Linguistics, University of Pennsylvania, Philadelphia, Pennsylvania (D.E., T.P.L.R.)

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Timothy P. L. Roberts, Oberkircher Family Chair in Pediatric Radiology and Vice-Chair Research, Department of Radiology, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA, 19104. E-mail: robertstim@email.chop.edu

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Bal et al., 2016], the cutoff for intellectual disability [APA, 2013]. Thus, both language-specific ability and general cognitive ability are key features, impaired in many children who have ASD.

A number of studies have reported abnormal auditory processing in ASD and/or other disorders such as schizophrenia, measured by magnetoencephalography (MEG), electroencephalography (EEG), and auditory brainstem responses (ABR). Previous electrophysiology studies have also observed prolonged latencies of other components in clinical populations compared to neurotypically developing controls, with delayed auditory responses observed at mid-brainstem levels as well as primary/secondary auditory cortex [Oram Cardy et al., 2005, Roberts et al., 2012, Rojas., 2014, Kikuchi et al., 2015, Damaso et al., 2015, Berman et al., 2016, Schwartz et al., 2018, Talge et al., 2018, Matsuzaki et al., 2019]. The ability to detect an auditory change (e.g., pitch, frequency, syllable) is an important feature of the auditory system, with impaired change detection likely contributing to downstream language and communication impairment [Schwartz et al., 2018]. MEG and ERP studies in ASD have reported neural correlates of abnormal auditory discrimination, measured by the mismatch negativity (MMN) potential or its magnetic counterpart, the mismatch field (MMF), both assessing an individual's ability to detect change and thus interpreted as reflecting neural discrimination processing [Näätänen et al., 1978, 2007, Oram Cardy et al., 2005, Roberts et al., 2011]. Kujala et al., [2010] reported MMF findings on children with Asperger syndrome (AS, age 8 to 12 years), a neurodevelopmental disorder now subsumed within the ASD label, and with these individuals showing no or very mild cognitive problems [WHO, 1993]. Kujala et al., [2010] found that the children with AS had larger MMN responses to intensity-changed stimuli compared to typically developing peers, indicating that the children with AS had atypical early cortical speech - sound processing. Tecchio et al., [2003] reported that moderately to severely impaired verbal individuals with ASD (age 8 to 32 years) demonstrated a weak or absent MMF response compared with controls, and they suggested that impaired implicit auditory discrimination in ASD may hinder the development of language. On the other hand, Ferri et al., [2003] reported that individuals with ASD who also had intellectual disability (age 6 to 19 years) demonstrated larger MMN responses compared with TD controls, suggesting that MMNs in ASD can reflect a temporal cortex dysfunction that influences the pre-perceptual processing of auditory sensory information. Such discrepant findings in the literature may be attributed to small sample sizes or differences in recruitment and/or methodology.

Importantly, most previous MMN/MMF studies have focused on *verbal* children who have ASD without significant cognitive impairment (ASD). Children who have limited or no speech, and those who have intellectual disability, have frequently been excluded from research given anticipated barriers such as tolerating loud sounds and other sensory experiences associated with magnetic resonance imaging and remaining still during an imaging exam [South et al., 2013].

To better understand auditory language discrimination processes in ASD-MVNV, MEG measured cortical responses to an auditory oddball paradigm with vowel stimuli (/a/ and /u/). Stimuli were identical to those used in Roberts et al., [2011]. MEG is well-suited for the study of auditory function for the following reasons [Tobimatsu et al., 2016]. First, the MEG device (unlike MRI) does not make any sound during measurement and we can measure brain neural activity in silence. Second, MEG can well resolve signals produced by the auditory cortices located bilaterally in the temporal lobes, due to the tangential orientation of neurons in the sulci of the superior temporal gyri. Left and right superior temporal gyrus (STG) MMFs in ASD-MVNV were compared to STG MMFs in age-matched verbal children with ASD (with and without language impairment) as well as TD. Hypotheses were: 1) MMF STG latencies would be delayed in ASD-MVNV compared to verbal ASD and TD, and 2) delayed MMFs latencies would be associated with language and communication skills in all children, with longer MMF latencies indexing greater language impairment. Given prior reports of atypical rightward laterality of language processing in ASD [Flagg et al., 2005, Knaus TA et al., 2010, Lindell & Hudry, 2013], hemispheric laterality of MMF amplitude was also explored.

Methods

Participants

Recruitment and inclusion/exclusion criteria. Participants were recruited from The Children's Hospital of Philadelphia (CHOP). Participants made two visits to CHOP. During the first visit (2–3 weeks prior to the MEG exam), clinical and diagnostic testing was performed to confirm or rule out ASD diagnosis, administer cognitive and language assessments, and ensure that all participants met study inclusion/exclusion criteria.

Clinical assessments were performed by a licensed child psychologist with expertise in ASD. Children with ASD had a prior diagnosis, typically made by an expert clinician in CHOP's Regional Autism Center or, more rarely, by community providers. Confirmation of ASD diagnosis was made using the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2; Lord et al., 2012) and parent report on the Social Communication Questionnaire (SCQ) [Rutter et al., 2003a]. If the SCQ did not corroborate diagnosis, exceeding empirically established cut-offs by parent report on *both* the Social Responsiveness Scale and Autism Spectrum Rating Scale, in combination with the ADOS, also led to ASD diagnostic confirmation. The parent-completed Autism Diagnostic

Interview-Revised (ADI-R; Rutter et al., 2003b) was administered with parents for any participants who entered the study without a formal ASD diagnosis made by an expert clinician (e.g., ASD educational classification only) and for any child with a prior ASD diagnosis for whom a diagnostic discordance existed during the evaluation (e.g., a child who exceeded ADOS-2 diagnostic cut-offs but was below SCQ cut-off). Dimensional symptom severity indices were obtained from the ADOS-2 Calibrated Severity Score metric [Gotham et al., 2009]. For the verbal ASD and TD cohorts, cognitive ability was characterized using the Wechsler Intelligence Scale – Fifth Edition (WISC-V; Wechsler, 2014), or the Differential Ability Scale – Second Edition (DAS-II, Elliott, 2007). To rule out global cognitive delay in TD and verbal ASD (both ASD-V and ASD-LI), participants were required to score at or above the 2nd percentile (SS > 70) on the nonverbal reasoning composite score of the administered cognitive assessment. For the ASD-MVNV cohort, nonverbal cognitive ability was assessed with the Leiter International Performance Scale, 3rd Edition (Leiter-3; Roid et al., 2013).

To assess language ability in the ASD and TD participants, the Clinical Evaluation of Language Fundamentals - Fifth Edition (CELF-5, Wiig et al., 2013) was administered. In the ASD group, the verbal children with language impairment (ASD-LI) was comprised of subjects with a CELF-5 core language score at or below 85. The verbal children without language impairment (ASD-V) performed above 85 on the CELF-5 core language score. Given significant spoken language limitations in the ASD-MVNV group, there was not a common assessment of language ability that was valid and appropriate across all three cohorts. Thus, the Communication Domain Score from the Vineland Adaptive Behavior Scale, Second Edition (Vineland-II; Sparrow et al., 2005) or Vineland Adaptive Behavior Scale, Third Edition (Vineland-III; Sparrow et al., 2016), a parent-report questionnaire of adaptive behavior skills, was used as a proxy for communication skill. For the ASD-MVNV, in addition to a diagnosis of ASD, MVNV status was operationally defined during ADOS-2 administration as an expressive vocabulary of fewer than 30 words/phrases used spontaneously and communicatively which was operationalized as language appropriate for administration of Module 1 on the ADOS-2 (i.e., use of only single words or rote phrases during the ADOS-2). Inclusion criteria for all participants included 1) males or females ages 8–12 years old, and 2) English as a first language in the family home. Additional inclusion criteria for the TD children included no significant cognitive impairment (described above) and scoring below the cut-offs for ASD on all domains of the ADOS-2 as well on parent questionnaires of ASD symptoms. For the ASD cohorts, stimulant medications were withheld for at least 24 h prior to each study visit (when possible, and with parental consent). In fact, six ASD children were prescribed stimulant medications at the time of participation. Data from these participants did not show evidence of forming an outlier cluster in terms of MMF responses and so these data were retained. Exclusion criteria for all participants included 1) claustrophobia, 2) metallic implanted prosthetic or stimulation device including cardiac pacemaker, 3) excessive metallic dental work including braces, non-removable retainer or other non-removable metal in the body, 4) nonverbal mental age less than 18 months, 5) history of seizure disorder, 6) known neurological (e.g., cerebral palsy, epilepsy) disorders, severe tics, or severe head trauma that affected brain functioning or sensory (hearing, visual) impairments, and 7) premature birth (earlier than 34 weeks) or significant birth complications. Known genetic conditions were exclusionary for verbal ASD and TD groups but not for ASD-MVNV; however, no genetic conditions were reported for any ASD-MVNV individual. The study was approved by the CHOP Institutional Review Board and all participants' families gave written informed consent. As indicated by institutional policy, where competent to do so, children over the age of seven additionally gave verbal assent, in accordance with the principles of the Declaration of Helsinki.

Auditory stimuli. Auditory stimuli (/a/ and /u/) were presented using Eprime v1.1 experimental software (Psychology Software Tools Inc., Pittsburgh, PA). Auditory stimuli were delivered *via* a sound pressure transducer and sound conduction tubing to the subject's peripheral auditory canal *via* eartip inserts (ER3A, Etymotic Research, Illinois) or *via* a flat panel speaker (85 dB SPL). Vowel stimuli /a/ and /u/ of 300 ms duration were used with each token as the standard (85%) or deviant (15%) stimulus (standard: range 386–546 trials), deviant: range 87–101 trials)). Stimulus onset asynchrony was 700 ms [Roberts et al., 2012]. Two sessions with the vowels alternating as standard/deviant were conducted for matched token subtraction (i.e., deviant /u/−standard /u/ and deviant /a/−standard /a/).

MEG recording. MEG data were obtained in a magnetically shielded room using a 275-channel whole-cortex CTF magnetometer (CTF MEG, Coquitlam, Canada). At the start of the session, three head-position indicator coils were attached to the scalp to provide continuous specification of the position and orientation of the MEG sensors relative to the head [Roberts et al., 2011]. Foam wedges were inserted between the side of the subject's head and the inside of the MEG dewar to increase comfort and ensure that the head remained in the same place in the dewar across recording sessions. To minimize fatigue and encourage an awake state, subjects viewed a movie projected on to a screen positioned at a comfortable viewing distance. To aid in the identification of

eye-blink activity, the electro-oculogram (EOG, bipolar oblique, upper right and lower left sites) was collected. Electrodes were also attached to the left and right collarbone for electrocardiogram (ECG) recording.

For the ASD-MVNV children, MEG recording was supported by a clinical/behavioral and technical protocol developed by our team – the MEG Protocol for Low-language/cognitive Ability Neuroimaging (MEG-PLAN; Kuschner, 2019). Based on stakeholder feedback, MEG-PLAN was developed as an interdisciplinary protocol to be implemented by a team of clinicians, scientists, and MEG technicians in close consultation with participant families. Clinical and behavioral components focus on using parents as partners, with strategies based on the principles of applied behavior analysis, including systematic desensitization and habituation, differential reinforcement, visual supports, and individual tailoring. MEG-PLAN is implemented in three parts *via* (1) initial assessment, (2) plan and preparation for the family and team, and (3) *in vivo* support at the MEG Visit. MEG-PLAN made it feasible for the often excluded group of MVNV children on the spectrum to participate in this neuroimaging study.

Data Analysis

All analyses were performed blind to participant group. After a band-pass filter (0.03–150 Hz), EOG, ECG, and MEG signals were down sampled to 500 Hz. Third-order gradiometer environmental noise reduction was employed for the MEG data. Epochs 100 ms pre-stimulus to 498 ms post-stimulus were defined from the continuous recording. To correct for eye blinks, a typical eye blink was manually identified in the raw data (including EOG) for each participant. The pattern search function in BESA Research 6.1 (BESA GmbH, Germany) scanned the raw data to identify other blinks and an eye-blink average was computed. The eye-blink average was modeled using the first component topography from principal component analysis (PCA), with the 1st PCA component typically accounting for more than 99% of the variance in the eye-blink average. In addition to eye-blink activity, a heartbeat average was obtained and heartbeat activity was modeled by the first two PCA components topographies, typically accounting for more than 85% of the variance in the heartbeat average. Scanning the eye blink and heartbeat-corrected raw data, epochs with artifacts other than blinks and heartbeat were rejected by amplitude and gradient criteria (amplitude >300 fT, gradients >25 fT/cm).

Using all 275 channels of MEG data, determination of the strength and latency of auditory evoked field sources in the left and right STG was accomplished by applying a standard source model to transform each individual's raw MEG surface activity into brain space (MEG data coregistered to the Montreal Neurologic Institute (MNI) averaged brain) using a model with multiple sources [Scherg, 1990; Scherg & Berg, 1996; Scherg & Von Cramon, 1985]. In particular, the standard source model applied to each subject was constructed by including (1) left and right STG dipole sources (placed at Heschl's gyrus), and (2) nine fixed regional sources that modeled brain background activity and serve as probe sources for additional oscillatory activity. The eye-blink and heartbeat source vectors derived for each participant were also included in each participant's source model to account for eye-blink and heartbeat activity [Lins et al., 1993, Berg & Scherg, 1994]. The final source model served as a source montage for the raw MEG [Scherg & Ebersole, 1994; Scherg et al., 2002]. The MEG sensor data were transformed from sensor channel space into brain source space where the visualized waveforms represent the modeled source activities. This spatial filter disentangled the source activities of the different brain regions that overlapped at the sensor level. For the source analysis, a 1 Hz (12 dB/octave, zero phase) to 55 Hz (48 dB/octave, zero-phase) band-pass filter and powerline notch filter at 60 Hz (width 5 Hz) were applied.

MMF peaks were defined from the difference wave obtained by subtraction of the standard response from the deviant response for each token, with the MMF peak identified as the first peak following the residual 100 ms response in the subtracted waveform (and occurring ~150–350 ms post stimulus onset). It was computed separately for standard and deviant occurrences of each token from source-space waveforms. MMF responses were thus defined for each token and each hemisphere separately. To evaluate hemisphere laterality, LIs was computed using the formula, $LI = \frac{(LH-RH)}{(LH+RH)}$, where LH and RH represent MMF amplitude in the left and right STG, respectively.

Statistics

Effects of group (TD, ASD-V, ASD-LI, ASD-MVNV) on age and the neuropsychological assessments was evaluated with analysis of variance. Additionally, since there was considerable "missing" data in the ASD-MVNV sample, the effect of missingness (successful group including participants who complete scan and yield evaluable data vs. "missing" group including participants who did not attempt or did not complete MEG) was evaluated with independent samples t-tests for age, NVIQ, communication score and SCQ. Effects of group (TD, ASD-V, ASD-LI, ASD-MVNV), hemisphere (LH, RH) and token (/a/ and /u/) on the MMF responses (latency and amplitude) were evaluated with full factorial linear mixed models using these factors, with age as a covariate and subject as a random effect. Effect of group on the MMF LI was assessed using a linear mixed model with group and token as fixed effects, age as a covariate and subject as a random effect. Hierarchical regression assessed associations of language and cognitive ability above and beyond effects of age,

hemisphere and token on MMF latency and amplitude. For the LI, hierarchical regression assessed influence of language ability and cognitive ability above and beyond effects of age and token on the LI. Bonferroni correction were applied for multiple comparisons. We calculated (r) for effect size. All statistical analyses were performed with SPSS Statistics Version 25 (IBM, Armonk, USA).

Results

Demographics

As shown in Table 1, eighty-four participants (8–12 years) had evaluable MMF data (ASD-MVNV; n = 9, 9.67 ± 1.41 years, ASD; n = 48, (ASD-V: n = 27, 10.55 ± 1.21 years, ASD-LI: n = 21,10.67 ± 1.20 years), TD children, n = 27, 10.14 ± 1.38 years. An additional thirty-eight participants (n = 21 ASD-MVNV; n = 9 ASD; n = 8 TD) who did not complete scans or were screened out after neuropsychological assessments or who had non-analyzable MEG were not included in analysis. In the ASD-MVNV cohort, for these 21 participants who were excluded (n = 3, unable to complete neuropsychological assessment; n = 1, unable to complete MMF task, n = 17, withdrew participation or unable to attempt/complete scan) there are no group differences in age between ASD-MVNV who successfully completed the scan (n = 9; successful group) and those who did not have analyzable data (n = 18; "missing" group, but with complete neuropsychological data): successful group; 10.16 ± 1.39 years, "missing" group; 9.70 ± 1.21 years, t (28) = 0.95, p = 0.849, r = 0.18). The successful group tended to show higher NVIQ and Communication score compared to the "missing" group [NVIQ (successful group; 60.33 ± 10.44, "missing" group; 53.00 ± 15.15, t (25) = 1.30, p = 0.189, r = 0.25) and Communication Domain score (successful group; 46.33 ± 20.34, "missing" group; 41.00 ± 18.96, t (27) = 0.68, p = 0.134, r = 0.13)], however, p values did not reach statistically significance in this study. Additionally, the unsuccessful group tended to show more severe autistic features on SCQ (successful group; 22.78 ± 8.48, "missing" group; 27.00 ± 4.86, t (27) = −1.70, p = 0.849, r = 0.31), however, p values also did not reach statistically significance. There was a statistically significant main effect of group on SCQ with TD < ASD-V < ASD-LI < ASD-MVNV [F (3, 71) = 54.90, p < 0.001, r = 0.66], on NVIQ with TD > ASD-V > ASD-LI > ASD-MVNV [F (3, 70) = 45.84, p < 0.001, r = 0.63] and on the Vineland Communication Domain Standard Score with TD > ASD-V > ASD-LI > ASD-MVNV [F (3, 36) = 18.18, p < 0.001, r = 0.58]. For the *verbal* children, there was a main effect of group on CELF-5 core language [F (2, 48) = 47.88, p < 0.001, r = 0.71] with TD > ASD-V > ASD-LI and on GAI / FSIQ [F (2, 55) = 29.44, p < 0.001, r = 0.59] with TD > ASD-V > ASD-LI (See Table 1). There were no statistically significant group differences in age (p > 0.05).

MMFs Latencies and Amplitude

Example MMF waveforms are shown from representative individuals in each group in Figure 1. A fully factorial linear mixed model (LMM) with fixed effects of group, hemisphere and token and age (and with subject as a random effect) showed a significant effect of group on MMF latency [TD =170.09+/−2.35 ms; ASD-V = 213.01+/−2.35 ms; ASD-LI =239.28+/−2.73 ms; ASD-MVNV = 270.71+/−4.53 ms; F (3,76) = 195.04, p < 0.0001, r = 0.85], with a small, but significant effect of hemisphere [LH: 222.29+/−1.58 ms; RH: 224.26 +/− 1.58 ms; F (1,241) = 14.48, p < 0.001), r = 0.24] but not token [/a/: 223.01±1.58 ms; /u/: 223.53 +/−1.58 ms; F (1,241) =1.01, p = 0.316, r = 0.07] and no interactions [all p's > 0.05]. Across hemisphere and token, simple effect post-hoc tests indicated that all pairwise

Table 1. Characteristics of Study Participants

	TD	ASD-V	ASD-LI	ASD-MVNV
Number of participants	27	27	21	9
Gender (M:F)	25:2	24:3	18:3	8:1
Handedness (R:L:A)	22:5:0	22:5:0	17:3:1	6:1:2
Age	10.14 ± 1.38	10.55 ± 1.21	10.67 ± 1.21	9.67 ± 1.41
Social communication questionnaire	2.67 ± 2.37	17.44 ± 7.49	20.80 ± 5.74	22.78 ± 8.48
Communication skills (Vineland)	102.92 ± 11.22	90.30 ± 12.08	85.44 ± 20.40	52.13 ± 11.30
Nonverbal IQ	113.85 ± 13.35	109.64 ± 11.38	88.02 ± 13.68	60.25 ± 11.16
Full scale IQ [Estimated]	112.96 ± 13.96	111.94 ± 9.39	83.88 ± 13.55	-
CELF - 5 core language index	107.62 ± 12.27	102.07 ± 14.81	68.69 ± 10.56	-

Abbreviations: ASD-MVNV, minimally verbal/nonverbal children who have ASD; ASD-LI, ASD with language impairment; ASD-V, verbal children who have ASD without language impairment; TD, typically developing children.

Communication Skills: Communication Subscale from the Vineland-II/Vineland-III

Nonverbal IQ: Nonverbal IQ score from the WISC-IV/WISC-V/Leiter-3; Nonverbal Spatial Composite from the DAS-II

Full Scale IQ [Estimated]: General Ability Index or Estimated FSIQ score from the WISC-IV/WISC-V; General Conceptual Ability Score from the DAS-II; unavailable for ASD-MVNV group

CELF-5: Clinical Evaluation of Language Fundamentals - fifth edition.

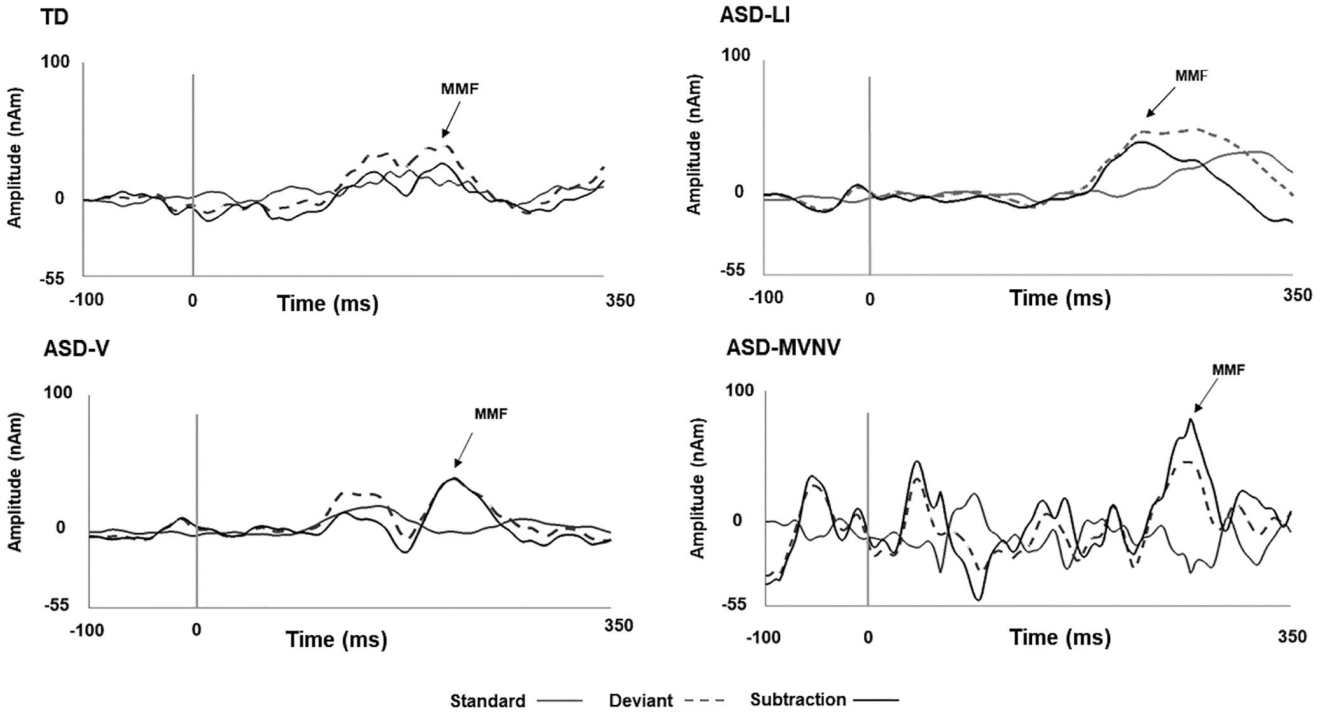

Figure 1. Source response waveforms from superior temporal gyrus in representative individuals from each group. Vertical lines on the waveform indicated stimulus onset (zero ms). Arrows indicate MMF latency in a representative TD child (182 ms), ASD-V (214 ms), ASD-LI (222 ms), and ASD-MVNV (270 ms). The solid gray line indicates the standard response, the dashed gray line indicates the deviant response, and the solid black line indicates their subtraction to yield the difference wave.

comparisons were significant (all p's < 0.001) with ASD-MVNV > ASD-LI > ASD-V > TD (Fig. 2A).

There was no significant main effect of group on MMF amplitude [TD = 13.53±1.73 nAm; ASD-V = 19.00±1.77 nAm; ASD-LI =17.23±1.97 nAm; ASD-MVNV = 17.53±3.32 nAm; F (3,72.8) = 1.72, p = 0.17, r = 0.15]. There was a main effect of hemisphere [LH: 15.13 ± 1.30 nAm; RH:18.52 ± 1.30 nAm; F (1,230.2) = 7.68, p < 0.01, r = 0.18] but not token [/a/: 16.43 ± 1.31 nAm; /u/: 17.22±1.30 nAm; F (1,234.0) = 0.41, p = 0.524, r = 0.04. Simple effect analyses of a significant hemisphere x Group interaction [p < 0.05], showed a significant right-hemisphere difference between TD (12.7±1.99nAm) and ASD-V (21.95±2.03nAm, p = 0.009). No other t-tests reached significance.

Regarding associations between MMF latency and communication ability, when entered after age, hemisphere

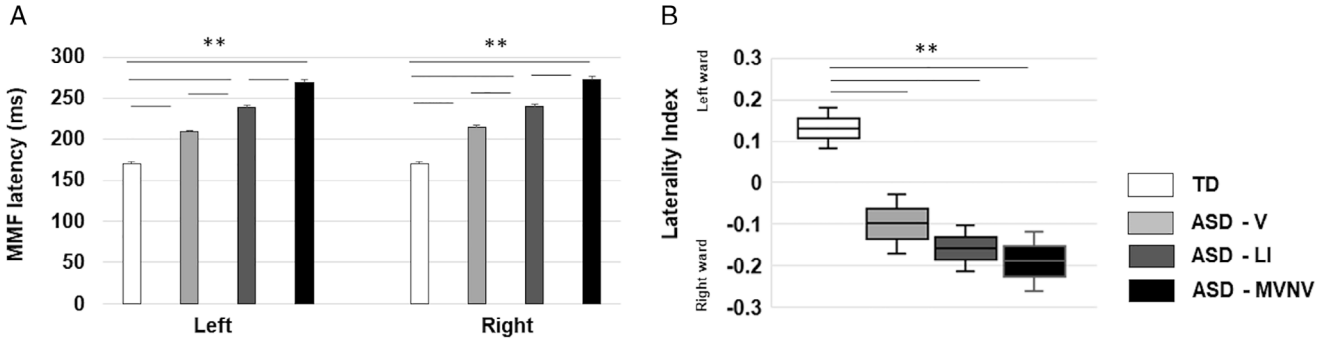

Figure 2. A. Estimated marginal mean MMF latencies by group and hemisphere. Error bars represent one standard error of the marginal means. There was a significant main effect of group on MMF latency (p < 0.0001), which was evidenced in both hemispheres. Post-hoc t-tests revealed significant differences between all pairwise comparisons of ASD-MVNV, ASD-LI, ASD-V, and TD in both hemispheres (all p's < 0.001), with ASD-MVNV>ASD-LI > ASD-V > TD. B. Estimated marginal means of LI by group. Error bars represent one standard error of the marginal means. There was a significant main effect of group on LI (p < 0.0001). ASD-MVNV (as well as ASD-LI and ASD-V) showed a rightward LI derived from hemispheric MMF amplitudes, which was significantly different from the leftward LI observed in TD (all p's < 0.01).

and token (together $R^2 = 0.002$ $p > 0.50$), NVIQ accounted for significant additional variance in MMF latency ($R^2 = 0.55$, $\Delta R^2 = 0.54$, $p < 0.001$), and Vineland Communication Domain Standard Score entered next accounted for further additional significant variance in MMF latency ($R^2 = 0.58$, $\Delta R^2 = 0.029$, $p < 0.01$). When the order of entry for NVIQ and Vineland was reversed, Vineland continued to account for significant variance in MMF latency ($R^2 = 0.43$, $\Delta R^2 = 0.43$, $p < 0.001$) as did NVIQ ($R^2 = 0.58$, $\Delta R^2 = 0.14$, $p < 0.001$), suggesting that the associations with MMF latency held for NVIQ and Vineland (themselves correlated $r = 0.72$, $p < 0.001$). The above pattern of findings held for the whole cohort as well as when restricted to just the ASD cohort. There were no associations between MMF amplitude and communication ability.

Laterality Indices (LI)

A linear mixed model (LMM) with fixed effects of group, token and age (and with subject as a random effect) showed a significant main effect of group [TD = 0.129 ± 0.05 nAm; ASD-V = –0.102 ± 0.05 nAm; ASD-LI = –0.168 ± 0.06 nAm; ASD-MVNV = –0.197 ± 0.09 nAm; F (3,73) = 7.18, $p < 0.0001$, $r = 0.30$, Fig. 2B], with no effect of token [/a/: –0.088±0.04, /u/: –0.081±0.04, F (1,73) = 0.013, $p > 0.05$, $r = 0.01$], or any interactions [$p > 0.05$] on the LI. All three ASD groups showed a rightward LI, significantly different from a leftward LI in TD (all p's < 0.01). There were no LI differences between ASD-MVNV and ASD-LI or ASD-V.

Regarding associations between LI, and communication skills, when entered after age and token (together accounting for $\Delta R^2 = 0.006$, $p > 0.50$), NVIQ accounted for significant variance in LI ($R^2 = 0.099$, $\Delta R^2 = 0.093$, $p < 0.01$). Entered next, the Vineland Communication Domain Standard Score accounted for only a non-significant additional 4% of variance in LI ($R^2 = 0.137$, $\Delta R^2 = 0.038$, $p = 0.074$). When the order was reversed, however, Vineland Communication Domain Standard Score accounted for significant variance in LI ($R^2 = 0.133$, $\Delta R^2 = 0.127$, $p < 0.001$) and NVIQ did not account for significant additional variance ($R^2 = 0.137$, $\Delta R^2 = 0.004$, $p > 0.05$). The above findings suggested that although LIs are associated with functional ability it was not possible to readily disambiguate communication ability from general cognitive ability.

Discussion

Findings showed abnormal vowel contrast MMF responses in all ASD groups, both verbal and minimally-verbal/non-verbal. The main findings were: 1) delayed MMF latencies in ASD-MVNV compared with ASD-LI, ASD-V or TD, 2) MMF latencies were associated with communication skills as well as general cognitive ability, and 3) a lack of neurotypical left-hemisphere lateralization of MMF amplitude in all ASD groups, with LI abnormalities associated with both communication skill and general cognitive ability. Previous studies have reported prolonged MMF latencies in children who have ASD [Roberts et al., 2011, 2012]. While, consistent with the present findings, the MMF latency delay was most pronounced in children with more severe language impairment [Roberts et al., 2011], the above previous studies focused on *verbal* children who had ASD and with no intellectual disability. In contrast to the present findings, Gomot et al., [2011] reported shorter MMN latencies in children who have ASD with developmental and language delay and they suggested that children with ASD detect acoustic changes in their surroundings more rapidly than normally developing children because of a hyper reactivity to the deviancy. As auditory sensitivity was not assessed in the present study beyond simple thresholding, further investigation is needed to examine relationships between MMF latency, severity of language and communication ability, and sensory abnormalities in both verbal ASD and ASD-MVNV.

The mechanism underlying the MMF findings observed in the present study remain unknown. In general, MMF/MMN peak latency decreases throughout childhood [Glass et al., 2008, Morr et al., 2002], with present findings potentially favoring a maturational delay hypothesis in ASD as previously reported that brain becomes tuned (related to synaptic pruning) and speeding up of transmission as pathways become more efficient (related to myelination) throughout brain development [Picton et al., 2007]. This is consistent with structural studies that have reported that bilateral temporal-frontal white-matter connections develop more slowly than other regions, especially for the language-relevant inferior longitudinal fasciculus, the superior longitudinal fasciculus - arcuate fasciculus and inferior fronto-occipital fasciculus pathways [Brauer et al., 2013, Menjot de Champfleur et al., 2013]. Furthermore, abnormalities in glutamate and gamma- aminobutyric acid (GABA) neurotransmitter levels have been reported in ASD, and GABA dysfunction may account for the MMF abnormalities observed in the present study [Rojas et al., 2008, Gaetz et al., 2014, Port et al., 2017]. An alternative possibility relates to β - Amyloid (1–42), the 42 - amino acid fragment of the amyloid precursor protein [Haass, 2004, Liu et al., 2018]. In particular, lower β-Amyloid levels and delayed latency to auditory stimuli have been observed in patients with cognitive impairment stemming from Alzheimer disease (AD) [Papaliagkas et al., 2009]. Although ASD and AD are different disorders, there is emerging support for similar β-Amyloid biochemical abnormalities (1–42) as well as Tau Protein or Apolipoprotein E4 abnormalities [Omura et al., 2015]. Future studies examining associations between MMF activity and brain structure and brain chemistry are needed.

The non-significant tendency towards MMF amplitude group differences is consistent with previous reports. In particular, Lepistö et al., (2008) reported that discrimination of spectral auditory information (pitch and phoneme change), indexed by MMF amplitude, was enhanced in children with ASD who had severe language deficits (mean verbal IQ 54), and they suggested that this enhanced low-level perceptual skill in children with ASD might hamper processing speech sounds at a higher level.

Findings of an association between atypical rightward lateralization with language and communication skills may be interpreted in light of differences in the developmental of the right and left hemispheres. In particular, the right hemisphere generally develops earlier than the left hemisphere, with Broca's area left- lateralized by middle childhood [Amunts et al., 2003]. Atypical MMF lateralization is ASD is also possibly associated with dysfunction of interhemispheric inhibition and/or connectivity. A meta-analysis of functional magnetic resonance imaging studies noted more right hemispheric language processing activity in core language areas (i.e., STG and inferior frontal gyrus) in ASD [Herringshaw et al., 2016], and a MEG study also reported greater right hemispheric activation in children with ASD [Flagg et al., 2005].

Supporting the concept of atypical MMF lateralization arising from atypical interhemispheric inhibition, it should be noted that the corpus callosum (CC), a major pathway connecting homologous cortical areas of the two hemispheres, has been proposed as a mechanism of interhemispheric inhibition that allows language dominance to develop [Bloom & Hynd, 2005, Alsaadi & Shahrour, 2014]. In previous reports, individuals with ASD tended to have decreased fractional anisotropy and increased mean diffusivity in white-matter tracts spanning many regions such as CC [Travers et al., 2012, Giuliano et al., 2018]. These findings may reflect atypical maturation of interhemispheric connectivity. The present MMF findings suggest that this abnormal between-hemisphere connectivity may contribute to atypical MMF activity and laterality as well as downstream language and communication ability in ASD and ASD-MVNV.

Study limitations include the fact that there was no clinical control group of children with intellectual disability but without ASD. As such, the relative relation between MMF abnormalities and general cognitive abilities vs. language impairment cannot be elucidated. Additionally, despite the successes of the MEG-PLAN approach our evaluable participant pool was nonetheless limited because of the problems of incomplete recording and assessment in the ASD-MVNV population. Of note, however, this MMF paradigm was performed as a part of a battery of tests and subjects had already undergone approximately 30 min of scanning prior to commencement of this protocol. Successful scan rates were considerably higher (up to 75%) for the earlier paradigms, pointing towards a total scan duration limit of the order of 30 min for future studies, necessitating fewer paradigms, shorter paradigms or more efficient (compact) paradigm design.

The associations between MMF latency and language and communication skills as well as general cognitive ability observed in the present study suggest that auditory vowel discrimination may be attributed to sensory function or to higher-level language processing (or both). To examine dependencies between lower-order sensory perception and higher-order linguistic skills, other tasks using stimuli such as words and pseudowords, or involving, for example, sentence listening tasks are needed to establish more fine-grained information regarding MMF and language impairment in ASD (although extrapolation to MVNV remains to be verified). Another limitation is that brain imaging measures derived from other modalities were not assessed (for example, cortical myelin content, diffusion tensor imaging and/or GABA magnetic resonance spectroscopy). Further studies are needed presenting other tasks and combining other modalities to develop appropriate objective markers associated with auditory language discrimination processing in both verbal and indeed MVNV children who have ASD. This may likely require extension of the MEG-PLAN approach to MRI.

Conclusion

This study demonstrated profoundly delayed MMF responses and atypical rightward MMF lateralization in ASD-MVNV. MMF activity was associated with communication skills as well as general cognitive ability. MMF delays in ASD-MVNV were more pronounced than MMF delays also observed in *verbal* children with ASD, consistent with the relationship between increasingly-prolonged MMF latency and increasing functional impairment.

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Competing financial interests

Dr Roberts declares consulting/advisory board relationships with Prism Clinical Imaging, CTF, Ricoh, Spago Nanomedical, Avexis Inc. and Acadia Pharmaceuticals. Additionally, he and Dr Edgar disclose intellectual property related to MEG as a biomarker for pharmaceutical therapy.

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