Auditory Magnetic Mismatch Field Latency: A Biomarker for Language Impairment in Autism

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Background: Auditory processing abnormalities are frequently observed in autism spectrum disorders (ASD), and these abnormalities may have sequelae in terms of clinical language impairment (LI). The present study assessed associations between language impairment and the amplitude and latency of the superior temporal gyrus magnetic mismatch field (MMF) in response to changes in an auditory stream of tones or vowels.

Methods: Fifty-one children with ASD, and 27 neurotypical control subjects, all aged 6 to 15 years, underwent neuropsychological evaluation, including tests of language function, as well as magnetoencephalographic recording during presentation of tones and vowels. The MMF was identified in the difference waveform obtained from subtraction of responses to standard from deviant stimuli.

Results: Magnetic mismatch field latency was significantly prolonged ($p < .001$) in children with ASD, compared with neurotypical control subjects. Furthermore, this delay was most pronounced (~50 msec) in children with concomitant LI, with significant differences in latency between children with ASD with LI and those without ($p < .01$). Receiver operator characteristic analysis indicated a sensitivity of 82.4% and specificity of 71.2% for diagnosing LI based on MMF latency.

Conclusions: Neural correlates of auditory change detection (the MMF) are significantly delayed in children with ASD, and especially those with concomitant LI, suggesting a neurobiological basis as well as a clinical biomarker for LI in ASD.

Key Words: Autism spectrum disorders, biomarker, electrophysiology, language impairment, magnetoencephalography, mismatch negativity

Autism spectrum disorders (ASD) are characterized by disabilities in social interactions, communication, and stereotypical behaviors, with prevalence ~1% in children in the United States (1). Language abilities in ASD are highly variable, with difficulties ranging from mild to severe impairments in pragmatics and/or social communication (2), with a subset of ASD individuals having language problems characteristic of those observed in developmental language impairment (LI) disorders. Mounting electrophysiological evidence suggests that deficits in discriminating rapid changes in sound may be associated with impaired speech processing in children suffering from developmental language disorders (3–5). Furthermore, electrophysiological evidence also indicates that a fundamental feature of ASD is abnormal cortical processing of auditory stimuli (6–10). Electrophysiological examination of speech sounds in individuals with autism may help identify the neural correlates of auditory deficits contributing to comorbid LI.

Given that language impairment in ASD may be associated with dysfunction in basic auditory sound processing, an assessment of mechanisms, such as sound discrimination, early in the auditory pathway could be used to address: 1) whether autistic children with and without LI exhibit a deficit in speech sound processing, and 2) whether the severity of the neuronal deficit correlates with the degree of LI. In the present study, magnetoencephalography (MEG) was used to record the auditory mismatch response to probe speech sound discrimination in children on the autism spectrum with and without concomitant LI. Magnetoencephalography is a noninvasive neuroimaging technique that provides measures of cortical neural activity on a millisecond time scale and with relatively good spatial resolution (11). Because of the nature of the responses generated by auditory neurons in the supratemporal plane, MEG is well suited for studying basic auditory activity, as cortical generators of evoked auditory responses are favorably positioned to produce strong currents for MEG recordings (12).

The mismatch negativity (MMN) (13) and its magnetic analogue, the mismatch field (MMF), are of particular interest in assessing auditory discrimination. The MMN/MMF is a neurophysiological index of auditory change detection that can be elicited in absence of focused attention (14). The response is typically elicited using an auditory oddball paradigm, where listeners are presented a series of stimuli, some frequently (standards) and others infrequently presented (deviants). Relative to the response evoked by standard stimuli, 100 to 300 milliseconds after stimulus onset deviant stimuli evoke a more pronounced response. In healthy populations, the time course of the MMN/MMF response is considered an indicator of change detection and has been used to probe speech discrimination (15–19). Atypical MMN responses have been reported, albeit inconsistently, in populations suffering from developmental language disorders (3). Thus, the MMN is considered a promising tool for investigating central auditory dysfunction.

Studies in children and adults on the autism spectrum show varied MMN/MMF findings. In Asperger's syndrome, reduced MMN amplitude and delayed latency were found during speech prosody discrimination in children and adults (20,21). In children with autism, Lepisto *et al.* (22,23) documented differential MMN amplitude in response to temporal cues in speech. The authors suggested that in autistic subjects, hypersensitivity to pitch changes adversely affects the ability to discriminate speech sounds, which requires abstracting invariant cue features from varying auditory input. Findings on MMN latency in autism are mixed, with some reports

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Table 1. Subject Demographics

	Age	Sex (M/F)	WISC-IV	CELF-4	ADOS	SCQ	SRS
ASD/+LI	8.47 ± .36	17/1	89.55 ± 3.33	68.16 ± 3.24	14.66 ± .99	20.33 ± 1.66	74.94 ± 2.41
ASD/−LI	9.846 ± .39	32/1	109.78 ± 2.55	99.85 ± 1.78	11.72 ± .67	21.28 ± .76	78.3 ± 1.91
TD	10.065 ± .47	12/15	109.25 ± 2.83	108.93 ± 2.05	1.96 ± .33	3.77 ± .87	45.65 ± 1.69

Characteristics of study sample including neuropsychological tests administered prior to MEG recordings. Battery of tests included Clinical Evaluation of Language Fundamentals-Fourth Edition, Wechsler Intelligence Scale for Children-Fourth Edition, Autism Diagnostic Observation Schedule, Social Communication Questionnaire, and Social Responsiveness Scale. Values are reported as mean ± standard error of the mean.

ADOS, Autism Diagnostic Observation Schedule; ASD/+LI, autism spectrum disorder with language impairment; ASD/−LI, autism spectrum disorder without language impairment; CELF-4, Clinical Evaluation of Language Fundamentals-Fourth Edition; F, female; M, male; MEG, magnetoencephalography; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale; TD, typically developing; WISC-IV, Wechsler Intelligence Scale for Children-Fourth Edition.

suggesting an intact MMN response in ASD. In high-functioning autistic children, Čeponienė *et al.* (24) reported no difference in MMN latency when varying the complexity of tonal and vowel stimuli. Kemner *et al.* (25) also reported an absence of abnormalities in speech-sound-elicited MMN in children with autism. However, evidence for an abnormal MMN response in ASD was demonstrated by Jansson-Verkasalo *et al.* (26), who found bilaterally delayed MMN following tones in ASD, as well as a right hemisphere delay following consonant changes in syllabic stimuli. Oram-Cardy (27) reported delayed MMF responses in autism with LI. These delays were not specific to speech, being equivalent for vowel contrasts and acoustically matched tone contrasts. Differences in methods and population characteristics as well as small sample size likely contribute to discrepant findings in the literature; it remains to be determined whether MMN/MMF time course is predictive of LI in autism.

In the present study, the MMF to tone and speech sounds was examined in a large cohort of children with ASD with language impairment (ASD/+LI), children with ASD without language impairment (ASD/−LI), and in age-matched typically developing (TD) control subjects. Magnetoencephalography measurements probed superior temporal gyrus (STG) auditory MMF brain functioning in two conditions. First, standard and deviant stimuli were sinusoidal tones with carrier frequencies identical to the first formant of the vowel stimuli used in the second condition (300 Hz and 700 Hz). English vowel-like sounds /u/ and /a/ were presented in the second condition. It was hypothesized that delays in MMF latency in children with ASD/+LI would be observed, indicating an impairment in acoustic/vowel change detection at an early perceptual level.

Methods and Materials

Participants

Subjects with ASD were recruited from the Regional Autism Center of the Children's Hospital of Philadelphia, the Neuropsychiatry program of the Department of Psychiatry of the University of Pennsylvania School of Medicine, and from local and regional parent support groups, such as the Asperger Syndrome Information Alliance for Greater Philadelphia, Autism Society of America, and Autism Speaks. All children screened for inclusion in the ASD sample had a prior ASD diagnosis made by an expert clinician, typically a developmental pediatrician in the Regional Autism Center. The original diagnosis was made after extensive clinical interview, documentation of DSM-IV criteria for ASD, and use of various ASD diagnostic tools, such as the Childhood Autism Rating Scale and the Autism Diagnostic Observation Schedule (ADOS). Typically developing subjects were recruited through newspaper advertisements and from pediatric practices of the Children's Hospital of Philadelphia primary care network.

Research participants made two visits. During the first visit, clinical and diagnostic testing were performed to confirm referral diagnosis, to administer neuropsychological tests, and to ensure that TD children met inclusion criteria. Assessments were performed by licensed child psychologists with expertise in autism. Given the extensive clinical evaluations upon which the original diagnosis was made, an abbreviated diagnostic battery was used to confirm diagnosis. Specifically, the ASD diagnosis was confirmed with gold standard diagnostic tools, including direct observation with the ADOS (28) and parent report on the Social Communication Questionnaire (SCQ) (29). Dimensional symptom severity ratings were also obtained by parent report on the Social Responsiveness Scale (30). Asperger's disorder symptomatology was measured with the Krug Asperger's Disorder Index (31). For final inclusion in the ASD group (including children with diagnosis of Asperger's syndrome), children were required to exceed established cutoffs on both the ADOS and SCQ. An SCQ cutoff score of 12 in conjunction with an ADOS autism spectrum cutoff score (of 7) was adopted to maximize the likelihood of correctly classifying children as ASD. In prior studies, combining the ADOS with an SCQ cutoff score of 12 resulted in specificity that is comparable with that of the combination of the ADOS and Autism Diagnostic Interview, Revised (.86), although sensitivity is modestly low (.76). To confirm presence of LI, all subjects were evaluated with the Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4) (32). The ASD group with language impairment (ASD/+LI) was comprised of subjects with a CELF-4 core language score below the 16th percentile. The ASD group without LI (ASD/–LI) performed at or above the 16th percentile on the CELF-4. To rule out global cognitive delay, all subjects were required to score at or above the fifth percentile (standardized score $>$ 75) on the perceptual reasoning index (PRI) of the Wechsler Intelligence Scale for Children-Fourth Edition (33).

Inclusion criteria for the TD children included scoring below the cutoff for ASD on all domains of the ADOS and on parent questionnaires and performance above the 16th percentile on the CELF-4. In addition to the above inclusion criteria, subjects were native English speakers and had no known genetic syndromes or neurological (e.g., cerebral palsy) or sensory impairments. The study was approved by the Children's Hospital of Philadelphia Institutional Review Board and all participants' legal guardian(s) gave informed written consent. Where competent to do so, children over 7 years gave verbal assent.

Seventy-eight participants between the ages of 6 and 15 years were recruited (51 ASD, 49 male participants, 2 female participants; 27 TD, 12 male participants, 15 female participants). Within the ASD group, 33 were classified as ASD/−LI and 18 as ASD/+LI. The ASD and TD groups did not differ in age (9.4 ± 2.1 vs. 10.1 ± 2.4 years, mean ± SD, $p = .19$). Demographics are shown in Table 1.