Differential responses of primary auditory cortex in autistic spectrum disorder with auditory hypersensitivity

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The aim of this study was to investigate the differential responses of the primary auditory cortex to auditory stimuli in autistic spectrum disorder with or without auditory hypersensitivity. Auditory-evoked field values were obtained from 18 boys (nine with and nine without auditory hypersensitivity) with autistic spectrum disorder and 12 age-matched controls. Autistic disorder with hypersensitivity showed significantly more delayed M50/M100 peak latencies than autistic disorder without hypersensitivity or the control. M50 dipole moments in the hypersensitivity group were statistically larger than those in the other two groups. M50/M100 peak latencies were correlated with the severity of auditory hypersensitivity; furthermore, severe hypersensitivity induced more behavioral problems. This study indicates auditory hypersensitivity in autistic spectrum disorder as a characteristic response of the primary auditory cortex, possibly resulting from neurological immaturity or functional abnormalities in it. *NeuroReport* **23:113–118**
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Introduction

Autistic spectrum disorder is a neurodevelopmental disorder characterized by qualitative impairments in social interactions and communication skills, along with a restricted repetitive and stereotyped pattern of behavior [1]. In addition to these core features, the coincidence of sensory processing abnormalities in autistic disorder has been reported at a frequency of 42–88% [2,3]. Especially, auditory hypersensitivity is the most common sensory impairment, interrupting behavioral adaptation [4]. In earlier studies, many researchers found different auditory processing in autistic disorder compared with that in typically developing controls: the III–V interpeak latency of the auditory brainstem response was longer in autistic disorder than in control patients [5]. Event-related potentials and magnetoencephalography (MEG) studies also showed delayed responses to auditory stimuli in autistic disorder [6,7]. These electrophysiological studies showed auditory processing differences between autism and control. However, the physiological mechanism underlying auditory hypersensitivity has not been previously investigated. Therefore, the purpose of this study was to investigate the characteristic electrophysiological features in autistic spectrum disorder with auditory hypersensitivity. To clarify the difference in the response of the primary auditory cortex to auditory stimuli, we examined the auditory-evoked field and analyzed it in association with the characteristic traits of auditory hypersensitivity.

Methods

Participants

Eighteen male children with high-functioning autistic spectrum disorder (9.52 ± 1.72 years) and 12 age-matched male controls (10.08 ± 1.73 years) were recruited at the Osaka University Hospital (Table 1). The diagnosis of autistic spectrum disorder was made with reference to the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition)-Text Revision [1]. Furthermore, the diagnosis was confirmed by the Japanese version of Autism Screening Questionnaire (ASQ-J) [8,9] and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) [10]. Intellectual quotient was assessed by using the *Wechsler Intelligence Scale for Children* (third version). In order to evaluate the characteristics of the auditory hypersensitivity and behavioral problems, we assessed the sensory profile (SP) [11] and used the Japanese version of the Child Behavior Checklist (CBCL) [12,13]. Children with autistic spectrum disorder were divided into two groups on the basis of the auditory item score of the SP: autistic disorder with auditory hypersensitivity and that without it. The cut-off value was set at 30. Controls were not only age-matched

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Table 1 Demographic information

	Autistic disorder with auditory hypersensitivity ($N=9$)	Autistic disorder without auditory hypersensitivity ($N=9$)	Controls ($N=12$)
Items	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	9.64 ± 1.89	9.40 ± 1.64	10.08 ± 1.73
FIQ	102.17 ± 22.71	96.13 ± 8.18	–
ADOS-G	12.33 ± 2.45	12.75 ± 3.66	–
ASQ	15.33 ± 5.85*1	15.11 ± 4.05*2	2.83 ± 3.29*1, *2
SP Auditory Item Score	20.33 ± 5.56**1	31.78 ± 2.44**1	39.00 ± 1.41**1
CBCL	75.43 ± 18.15	51.63 ± 13.93	–

ADOS-G, Autism Diagnostic Observation Schedule-Generic (total score); ASQ, Autism Screening Questionnaire (cut-off ≥ 13) (*1, *2; $P<0.01$); CBCL, Child Behavior Checklist (total score); FIQ, full-scale intellectual quotient of *Wechsler Intelligence Scale for Children* (third version); SP, sensory profile, (**1; $P<0.01$).
*In ASQ, there are significant differences between autistic disorder with hypersensitivity and controls and also between autistic disorder without hypersensitivity and controls.
**In SP, there are significant differences between autistic disorder with hypersensitivity and autistic disorder without hypersensitivity and controls, and also between autistic disorder without hypersensitivity and controls.

children without a history of neurological diseases or developmental disorders, but also those who were not receiving special education services. In addition, all controls were assessed by the ASQ and SP, and showed no autism traits or sensory hypersensitivity. Written informed consent was obtained from the parents of all participants in the study, which was approved by the Institutional Review Board of Osaka University Hospital.

Auditory stimuli

Auditory stimuli, which were made by a presentation system (Yokogawa Electric Corporation, Kanazawa, Japan), were delivered through a sound pressure transducer and sound conduction tubing to the participant's auditory canal through ear tip inserts. A 1000-Hz sinusoidal tone pip of 200 ms duration was binaurally presented (with 10-ms rise and fall times). Stimuli were randomly presented with interstimulus intervals of 2700–3300 ms. The total number of stimuli was 100.

Measurements

Measurements by MEG were performed with the participants lying down on a bed in a magnetically shielded room using a 160-channel whole-head MEG system equipped with SQUID gradiometers (PQ1160C, Yokogawa Electric Corporation). Data were acquired at a sampling rate of 1000 Hz, with an online band-pass filter between 0.03 Hz and 200 Hz. The positions of five head marker coils were obtained before and after recording to evaluate head movement. Anatomical magnetic resonance imaging (MRI) data were obtained using a 3.0-T whole-body magnetic resonance scanner with a standard whole-head coil (Signa HDxt Excite 3.0 T, GE Healthcare UK Ltd, Buckinghamshire, UK).

In order to align MEG data with individual MRI data, we scanned the three-dimensional facial surface of each participant (FastSCAN Cobra, POLHEMUS, ARANZ Scanning Limited, Christchurch, New Zealand). Five head marker coils were attached to the scalp before recording the MEG, which provided the position and orientation of MEG sensors relative to the head. Three-dimensional facial surface data were superimposed on the anatomical facial surface provided by the MRI data.

Data analysis

The MEG data were analyzed at MEG Laboratory (Yokogawa Electric Corporation). The epochs were defined from 100 ms before stimulation to 1000 ms after stimulation. This prestimulus period of 100 ms was used as the baseline for the determination of ambient brain activity and noise of each epoch. Epochs containing artifacts such as eye blinks, head movements, and others were eliminated for each participant. The epochs were averaged for each condition [14], and averaged waveforms were high-pass filtered using a cut-off frequency of 3 Hz, low-pass filtered (cut-off frequency of 45 Hz), and band-pass filtered (cut-off frequency of 8–25 Hz). We evaluated the responses of each hemisphere by using half of all channels. To determine the M50/M100 peak, we calculated the root mean square of half of all channels. The M50/M100 peak was determined as the peak in the root mean square value in the intervals of 30–70 ms and 80–200 ms, respectively. The data were statistically examined by repeated-measures analysis of variance using PASW Statistics v. 18.0 (IBM, Tokyo, Japan), and the Pearson test was used to examine the correlation.

Results

Demography

The ASQ scores of autistic disorder with/without auditory hypersensitivity were significantly higher than those of the control (all Ps < 0.01). There was no significant group difference in age, scores of full intellectual quotient, ADOS-G, or CBCL between autistic disorder with auditory hypersensitivity and that without it (all Ps $>$ 0.15). However, there was a significant difference in the auditory score of the SP between these two groups, between autistic disorder with auditory hypersensitivity and control and between autistic disorder without auditory hypersensitivity and the control (all Ps < 0.01). Autistic disorder with hypersensitivity showed a significantly lower auditory item score of the SP (20.33 ± 5.56)

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than that without it (31.78 ± 2.44) or the control [39.00 ± 1.41; F (2, 27) = 76.34, $P < 0.01$; Table 1]. Furthermore, there was a statistically significant correlation between auditory item scores of the SP and the total scores of the CBCL ($r = -0.62$, $P < 0.05$; Fig. 1).

M50/M100 group differences

Auditory-evoked field waveform, magnetic isofield maps, and dipole sources were superimposed on the MRI of individual participants selected as an example from each of the three groups (Fig. 2).

Peak amplitude

There was no significant difference in the M50 peak amplitude between autistic disorder with auditory hypersensitivity (41.37 ± 11.46 fT/cm) and that without it (74.67 ± 33.67 fT/cm) or the control (53.54 ± 16.34 fT/cm), or in the M100 peak amplitude between autistic disorder with auditory hypersensitivity (57.44 ± 17.85 fT/cm) and that without it (61.74 ± 33.67 fT/cm) or the control (83.08 ± 16.34 fT/cm). Furthermore, there was no statistically significant correlation between SP and M50/M100 peak amplitude (all Ps > 0.15).

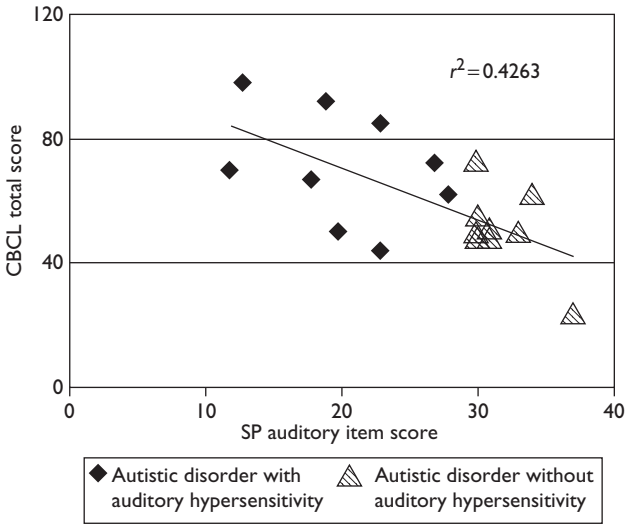
Peak latencies

M50 peak latencies were significantly longer in autistic disorder with auditory hypersensitivity than in the control [F (2, 27) = 4.35, $P < 0.05$; Fig. 3a]. However, autistic disorder with auditory hypersensitivity showed significantly longer M100 peak latencies than the other two groups [F (2, 27) = 12.59, $P < 0.01$; Fig. 3b]. There was a statistically significant negative correlation between auditory item scores of the sensory profile and M50 ($r = -0.52$, $P < 0.01$; Fig. 3c) or M100 latencies ($r = -0.69$, $P < 0.01$; Fig. 3d).

Dipole moments

The difference in dipole moments between autistic disorder with auditory hypersensitivity and the control was statistically significant [F (2, 24) = 3.75, $P < 0.05$], with the former showing larger M50 dipole moments (Fig. 3e). In addition, there was a statistically negative correlation between M50 dipole moment and auditory item scores of the SP ($r = -0.50$, $P < 0.05$; Fig. 3f). M100 dipole moments did not show any differences between groups (data not shown). There was no statistically significant correlation between the ASQ, CBCL or ADOS-G, and MEG measurements mentioned above (all Ps > 0.15).

Fig. 1



Scatter plot of the sensory profile (SP) auditory item scores and the child behavior checklist (CBCL). The total scores of the child behavior checklist were negatively correlated with auditory item scores of the SP (Pearson's test, $r = -0.62$, $P < 0.05$).

Discussion

Many autistic spectrum disorders with auditory hypersensitivity tend to have impaired adaptation in their daily lives. Actually, in our study, SP auditory scores were significantly correlated with behavioral problems, as revealed by the CBCL scores.

This study clearly demonstrated that M50/M100 latencies differed between autistic disorder with auditory hypersensitivity and that without it or the control group, and that auditory scores of the SP (i.e. severe hypersensitivity) were also significantly correlated with M50/M100 latencies (i.e. delayed latency) in autistic children. As there was no difference in the scores of the ASQ or the ADOS-G between autistic disorders with auditory hypersensitivity and that without it, auditory hypersensitivity might not be correlated with the severity of the core symptoms of autistic disorder, such as impaired social interaction.

Roberts *et al.* [7] reported that the peak latency of the primary auditory cortex is shortened with increasing age from 6 to 15 years in control, but not in autistic participants, and they speculated that the latter have maturational abnormalities in their auditory cortex. As the source of M50/M100 is generated from the primary auditory cortex, these findings suggest that a more severe auditory hypersensitivity corresponded to a more delayed response of the primary auditory cortex to auditory stimuli.

Gage *et al.* [15] and Bruneau *et al.* [16] reported longer latency in autistic children and hypothesized that this is due to abnormalities in myelination processes that would result in slower transmission rates in central auditory pathways.

Furthermore, in our study, the more severe auditory sensitivity was correlated with larger M50 dipole moments. The dipole moment has been used as a

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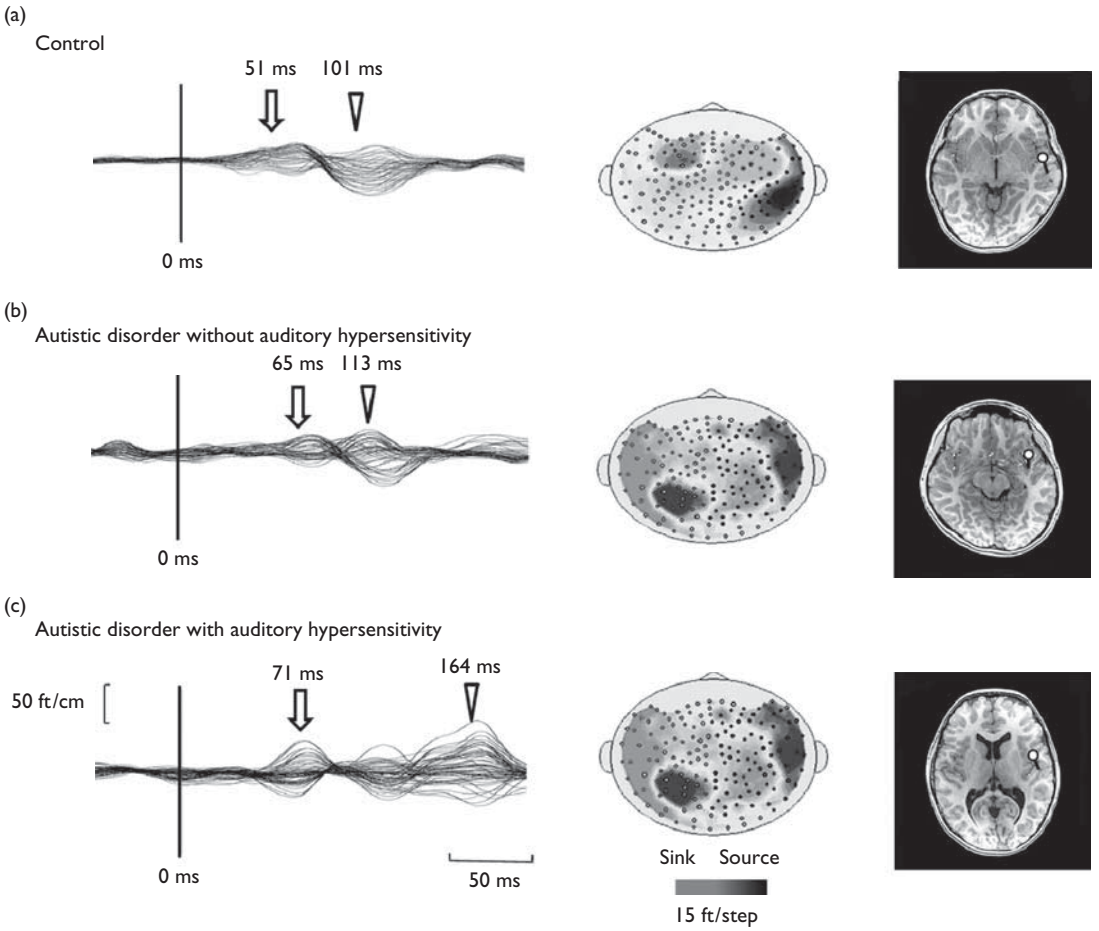
Fig. 2



Representative figures of auditory-evoked field waveforms (left), magnetic isofield maps (middle), and dipole sources (right) superimposed on the individual brain magnetic resonance imaging of participants selected from each of the three groups. The magnetoisofield map shows the latency of M100 peak; and the dipole sources were estimated at the same time. (a) Controls, (b) autistic disorder without auditory hypersensitivity, and (c) autistic disorder with auditory hypersensitivity. Vertical lines in the left figures indicate stimulus onset (0 ms). Arrows and arrowheads indicate the M50 peak and the M100 peak, respectively. Both M50 and M100 latencies are longer in autistic disorder with auditory hypersensitivity than in the other two groups.

potential determinant of the absolute magnitude of neuronal activity [17,18]. Therefore, the increase in the M50 dipole moment may be explained by hyperactivity of the corresponding region of the primary auditory cortex.

In recent years, there have been findings of abnormal brain connectivity in autistic disorder [19], and additionally, autistic disorders from postmortem brains show disrupted minicolumns and decreased inhibitory interneurons [20]. Thus, abnormal brain connectivity resulting from reduced interneuron activity might induce cortical hypersensitivity in the primary auditory cortex. Various degrees of hypersensitivity could stem from interindividual heterogeneity in brain connectivity.

As another possibility, Guiraud *et al.* [21] reported that infants at high risk for autism show less habituation to repeated sounds than those at low risk. We speculated that this difference might be associated with auditory hypersensitivity in autism. In our study, we did not directly analyze this hypothesis. In a future study, the oddball paradigm of MEG may enable us to investigate whether the reduced habituation is associated with thalamic sensory gating.

These lines of evidence suggest that measurement of the auditory-evoked field could be an objective marker of auditory hypersensitivity as one of the autistic characteristics. This measurement would be especially useful for assessment of infants and nonverbal autistic disorder. As auditory hypersensitivity causes incomprehensible behavioral problems in daily life, earmuff usage or avoidance of noisy environments may be recommended for relief from discomforting sounds.

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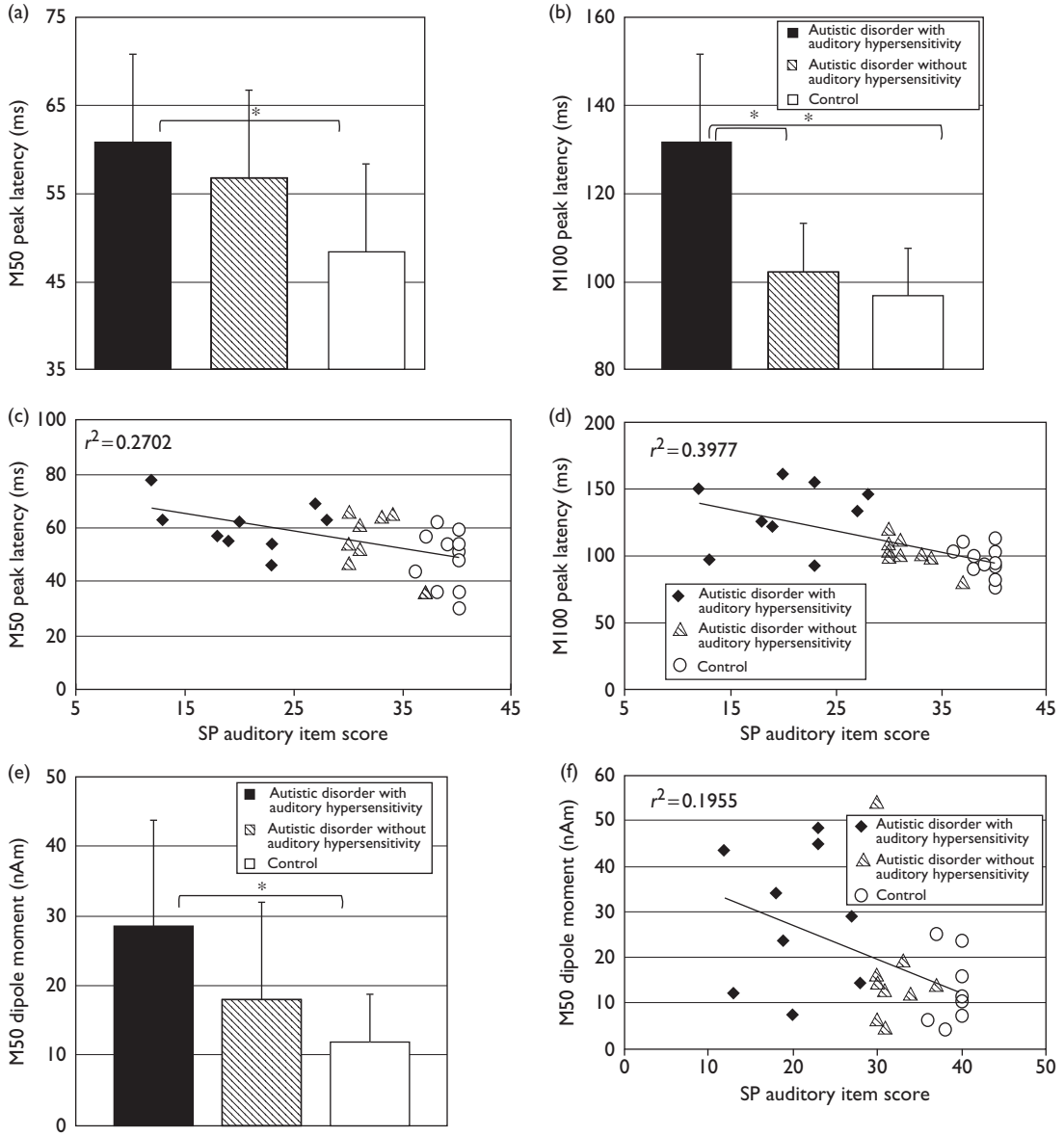
Fig. 3



(a and b) Mean M50 and M100 peak latencies. Error bars represent one standard error of the mean. Both latencies in autistic disorder with auditory hypersensitivity are significantly longer than those in the control (*$P<0.05$). (c and d) Scatter plot of M50 peak latencies or M100 peak latencies and auditory item scores of sensory profile (SP). Both M50 and M100 peak latencies correlate negatively with auditory item scores of the SP ($r=-0.52$, $P<0.01$; $r=-0.69$, $P<0.01$). (e) Mean M50 dipole moment. Error bars represent one standard error of the mean. The M50 dipole moment in autistic disorder with auditory hypersensitivity is significantly larger than that in the control (*$P<0.05$). (f) Scatter plot of the M50 dipole moment and auditory item scores of the SP. There is a negative correlation between the two parameters ($r=-0.50$, $P<0.05$).

Conclusion

This study shows that M50/M100 responses generated by the primary auditory cortex were correlated with the severity of auditory hypersensitivity in children with autistic spectrum disorder. Understanding of the neurological basis of auditory hypersensitivity could have clinical benefits by providing an objective assessment of the severity of auditory hypersensitivity and by validating effective treatment for it in the future.

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Conflicts of interest

There are no conflicts of interest.

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