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ORIGINAL ARTICLE

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Reduced gamma oscillation during visual processing of the mother's face in children with autism spectrum disorder: A pilot study

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Abstract

Aim: This study aimed to investigate gamma oscillations related to face processing of children with autism spectrum disorders and typically developed children using magnetoencephalography.

Methods: We developed stimuli that included naturalistic real-time eye-gaze situations between participants and their mothers. Eighteen young children with autism spectrum

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disorders (62–97 months) and 24 typically developed children (61–79 months) were included. The magnetoencephalography data were analyzed in the bilateral banks of the superior temporal sulcus, fusiform gyrus, and pericalcarine cortex for frequency ranges 30–59 and 61–90 Hz. The gamma oscillation normalized values were calculated to compare the face condition (children gazing at mother's face) and control measurements (baseline) using the following formula: (face − control)/(face + control).

Results: The results revealed significant differences in gamma oscillation normalized values in the low gamma band (30–59 Hz) in the right banks of the superior temporal sulcus, right fusiform gyrus, and right pericalcarine cortex between children with autism spectrum disorders and typically developed children. Furthermore, there were significant differences in gamma oscillation normalized values in the high gamma band (61–90 Hz) in the right banks of the superior temporal sulcus, bilateral fusiform gyrus, and bilateral pericalcarine cortex between the groups.

Conclusion: This report is the first magnetoencephalography study revealing atypical face processing in young children with autism spectrum disorders using relevant stimuli between participants and their mothers. Our naturalistic paradigm provides a useful assessment of social communication traits and a valuable insight into the underlying neural mechanisms in children with autism spectrum disorders.

KEYWORDS

autism spectrum disorder, face recognition, gamma oscillation, magnetoencephalography, young children

INTRODUCTION

The human face is an important visual stimuli processed daily, giving clues regarding social behavior. Many researchers have explored the perception processing of social cues underlying interactive situations, especially face-to-face encounters. Autism spectrum disorder (ASD) is a developmental pathology characterized by impaired social communication accompanied by restricted and repetitive behavior or interests.[1] The first reported patient with autism was described as "never looked into anyone's face."[2] This unique gaze fixation pattern is a potential behavioral diagnostic marker for ASD.[1]

Atypical face recognition patterns and neural processing have been identified and reported in individuals with ASD.[3–6] Electroencephalography (EEG) studies suggest that gamma-band responses to faces reflect sequential processing of a multiple-level face-perception mechanism. Electrical event-related potentials revealed the presence of brain responses, termed "N170/M170," at a latency of approximately 170 ms from stimulus onset over the bilateral occipital scalp areas; they appear earlier in latency and larger in amplitude than responses elicited by nonface stimuli.[7,8] Functional magnetic resonance imaging (fMRI) has revealed cortical regions specialized for facial processing, including the occipital visual cortex, fusiform face area, and superior temporal sulcus (STS).[9] Pelphrey and Carter[10] reported that high-functioning adolescents and adults with autism have dysfunctional STS regions. This dysfunction was strongly and specifically correlated to the level of social impairment exhibited by participants, as assessed by the Autism Diagnostic Interview-Revised.[11] Furthermore, visual motion processing has been detected by gamma oscillations in the visual and motor areas.[12,13] Todorova et al.[14] reviewed biological motion perception in ASD and reported that the brain activation patterns show significant differences between ASD and control groups. This study showed that within the ASD population, there is a developmental delay in understanding biological motion, which improves with age.

Magnetoencephalography (MEG) and EEG has furthered our understanding and provided new insights with fine time resolution (e.g., gamma band analysis) for face processing. EEG and MEG detect the brain gamma activity during visual information processing,[12] although the parts of the cortex reflected in the signal are different between EEG and MEG. While MEG is insensitive to radially oriented sources, EEG is sensitive to radially and tangentially oriented sources. Gao et al.[15] estimated the M170 and gamma oscillations sources using the beamformer method. They showed that both the M170 and gamma were generated in a posterior-ventral network, including the fusiform, inferior-occipital, and lingual gyri, all in the right hemisphere.[15] Kovarski et al.[16] showed that individuals with ASD have stronger visual responses for emotional face stimuli in an early time window (105–135 ms) than controls, and the responses were reduced at longer latencies. This demonstrates that atypical facial processing in individuals with ASD is not only characterized by hypo-activation of the fusiform gyrus (FG), but by a broader atypical processing of the emotional face network. Safar et al.[17] showed

reduced gamma band (30–55 Hz) network connectivity in individuals with ASD when presented with angry faces.[17] Additionally, MEG provides noninvasive, silent, and capless experimental conditions that are feasible for young children and participants with hypersensitivity. He et al.[18] were the first to report face responses using MEG in young neuro-typically developing (TD) children (aged 4 years) with a custom child-sized MEG system. Compared to a conventional adult-sized MEG system, a child-sized MEG system is superior for measuring the face-sensitive M170 brain response in young children. Additionally, a face-sensitive M170 brain response in TD children (3–6 years old) has a longer latency and larger intensity than the adult M170.[19] These MEG studies provide support for further investigations in young children with ASD to reveal the face-processing mechanisms underlying autistic phenotypes.

However, much of the early research investigating face processing, including social eye gaze, was conducted using static images or schematic stimuli.[20] To elucidate neural mechanisms of social interaction, such as dynamic eye gaze, Redcay and Schilbach[21] suggested an experimental method in which a live social partner was presented through a real-time video link in the scanner room or a video recording of a person directing communicative gestures toward the participant.[21] Tanabe et al.[22] had demonstrated the neural correlates of direct, real-time interaction between individuals with ASD and normal participants; using two scanners, they simultaneously employed fMRI during the response to a joint attention task between paired participants. Their results suggest that the impairment of joint attention in patients with ASD is related to hypofunction of early visual processing and difficulty understanding shared intentions through eye contact. This was evidenced by reduced interparticipant synchronization of cortical regions, including the right inferior frontal gyrus. Reciprocal dynamic approaches revealed the neural mechanisms causing autistic behavioral characteristics in real-world interaction.

Many children with ASD show developmental differences, especially in social skills, from early infancy.[1] Considering that mother–infant interactive communication is the basis of social abilities,[23] brain responses characteristic of ASD may be reflected during mother–infant communication, therefore we focused on mother–child interactions in this study. In previous studies during noninteractive experimental conditions, gamma activity associated with human faces and gaze was reported in both adults[24] and infants,[25] and abnormalities in gamma activity were reported in children with ASD.[26] Such gamma activity abnormalities would also be expected during interactive experimental conditions in children with ASD; however, this has not yet been reported because of the difficulty in controlling the experimental conditions. The present study is the first report on gamma activity in children with ASD under interactive conditions. We hypothesized that children with ASD would have less of a difference in gamma activity between an interactive face-monitoring video condition (i.e., mother and child stare at each other in real time) and a nonface, noninteractive condition (i.e., child watches nonbiological motion) than would TD children. The aim of this study was to investigate whether normalized gamma oscillations were reduced in children with ASD as compared to TD children in an interactive condition. To test our hypothesis, using an interactive video camera monitoring system we conducted MEG measurements in children with ASD and TD children when the children and their mothers gazed into each other's eyes (gaze task). It was practical to use MEG because young children with ASD sometimes have difficulty wearing EEG electrodes owing to hyperesthesia. To target gamma oscillations related to visual processing, we examined 30–59 and 61–90 Hz frequency activity in the bilateral banks of the STS, FG, and pericalcarine cortex (PC). To improve the analytical accuracy for the child's brain, we used a child MEG system designed to fit a child's head and individual MRI scan imaging to reconstruct brain activity.

METHODS

Participants

Twenty children with ASD, 25 age-matched TD children, and their respective parents participated in this study. A two-step diagnosis of the recruited children with ASD was performed. First, children were diagnosed with ASD by local psychiatrists based on the Diagnostic and statistical manual of mental disorders, fifth edition criteria.[1] Final diagnoses were made by psychologists who had experience working with children and adults with autism and who were trained on the reliable administration and scoring of the Diagnostic Interview for Social and Communication Disorders ver. 11[27,28] and the Autism Diagnostic Observational Schedule, Second Edition.[27,29] These diagnostic tools had been translated to Japanese and standardized in a Japanese population. An age-matched control group (TD) was recruited through the local community in the Ishikawa prefecture, Japan. TD children had no history of developmental problems. Three children (one from the TD group and two from the ASD group) participated with their fathers; we excluded those from this analysis. Finally, 18 children with ASD (seven girls aged 62–97 months, mean = 74.89, SD = 10.65), 24 TD children (11 girls aged 61–79 months, mean = 69.58, SD = 6.04), and their respective parents, were included in the analysis. All children and their mothers reported normal hearing and vision through self-administered reports. Mothers had no prior or current developmental, learning, or behavioral problems. All mothers agreed to their child's participation and to their own participation in the study with full knowledge of the experimental characteristics of the research. Written informed consent was obtained prior to participation. The study was approved by the Ethics Committee of Kanazawa University Hospital and performed in accordance with the Declaration of Helsinki.

Inclusion criteria

The participants fulfilled the inclusion criterion if the number of noise-free MEG segments (2.5 s) was >20 (i.e., longer than 50 s) for each condition (face and control conditions). Finally, we analyzed MEG data from 18 children with ASD and 24 TD children.

Experiment procedures

We developed a gaze task to assess neural activity during real-time face-to-face situations, as described in published studies.[30,31] We modified the task paradigm to acquire restricted experimental control.

In this study, the mother and child lay on a bed in a supine position, each facing a half-mirror screen. Two researchers remained in the shielded room to confirm that both participants were concentrating on the task and encourage the child to remain still when necessary. The task involved watching short (15 s) videos or images on the half-mirror screen. Nonbiological control videos were alternated with facial stimuli of the mother and child. There were two types of facial stimuli: real-time streaming video (dynamic) and still picture (static). The mother viewed an image/video of her child, while the child viewed an image/video of their mother. During the facial stimuli periods, they were instructed not to speak or move their head or body (e.g., "Look at each other's face. Do not move your head or body, as much as possible"). However, their facial expressions were not restricted, and interactions were neither encouraged nor restricted (i.e., we tried not to interfere with voluntary communication). Although the mother and child's brain activity were recorded simultaneously, we did not analyze the mother's data in the present study. Additionally, we did not analyze the responses to the static images due to the differences in visual stimulus types (i.e., dynamic vs. static). Both the mother and child viewed the same control videos, which were short clips called "Pythagorean device" (equivalent to the American "Rube Goldberg machine" and British "Heath Robinson contraption," presented on the famous TV program "PythagoraSwitch" broadcast by NHK E Tele, Japan). The participants were carefully monitored using a video monitoring system to assess instruction compliance (e.g., consistently attending to the visual display) and record any notable artifacts, such as head motion or inappropriate head position.

Data acquisition

Signals were recorded using our dual MEG setup in a magnetically shielded room (Daido Steel Co. Ltd) installed at the MEG Center of Ricoh Co. Ltd.[31] This study analyzed the data collected from children, which were recorded using a 151-channel superconducting quantum interference device whole-head coaxial gradiometer MEG system for children (PQ 1151 R; Yokogawa/KIT). To measure mother–child interactions in the face-to-face situation, we arranged a real-time dual video presentation to show the facial expressions of the mother and child, in addition to a standard auditory recording and stimulation system. This video presentation system allows the mother and her child to observe their mutual facial expressions in real-time. Hirata et al.[31] and Hasegawa et al.[30] provided full details of the visual presentation system with MEG. The experimental stimuli were projected on a half-mirror display in front of the child's face. The child's facial expressions were recorded simultaneously as video data, using a charge-coupled device camera (AS-808SP; MILS Systems Co. Ltd) placed behind the half-mirror.

Magnetic fields were sampled at 2000 Hz per channel (low-pass filtered at 500 Hz). The head location relative to the MEG device helmet was measured using four coils attached to the head surface as fiducial points with respect to the landmarks (bilateral preauricular points, Cz, and 5 cm anterior part from Cz) in children. Before the MEG session, a three-dimensional digitizer (FASTRAK Polhemus) was used to digitize the head surface points and fiducial landmarks of the participant. After the MEG recording, the positioning coils were replaced with MRI-visible markers.

Brain structure images were obtained from all participants using a 1.5 T MRI scanner (SIGNA Explorer; GE Healthcare) to compute the individual head models for source analyses. The T1-weighted gradient echo and Silenz pulse sequence images (TR = 435.68 ms, TE = 0.024 ms, 7° flip angle, 220 mm FOV, 256 × 256 pixel matrix size, 1.7 mm slice thickness, and 130 transaxial images) were used as anatomical references.

Preprocessing

Offline analysis of the MEG data was performed using Brainstorm[32] and MATLAB (The MathWorks Inc.). Throughout the experimental period, two sensors had technical trouble and were excluded from the analyses, resulting in 149 measurable channels. All participants completed the experiment. The total recording time was approximately 10 min. The MEG data were resampled at 500 Hz with 0.5–100 Hz bandpass and 60-Hz notch filters to exclude power-line noise and mechanical vibrations. Independent component analysis (ICA) using the Infomax algorithm was performed ("RunICA" implemented in Brainstorm; www.sccn.ucsd.edu/eeglab/) to remove contamination caused by eye movements, blinks, heartbeats, or similar. Other artifacts such as muscle activity were then visually identified and excluded from analyses. Applying the criteria used in a previous study,[33] data points with magnetic amplitudes exceeding a threshold of 4,000 fT were automatically rejected. Data were segmented into 2.5 s (1250 data points: 2.5 s × 500 Hz) blocks with nonoverlap in preprocessing. Each segment was bandpass-filtered as low gamma (30–59 Hz) and high gamma (61–90 Hz) based on commonly used frequency bands before calculating cortical activity. The cortical activity was calculated on all selected segments separately for each subject and averaged into a single value for each frequency band.

Source reconstruction

Source reconstruction was performed using Brainstorm. We estimated the signal source using the anatomical cortical surface data of each subject tessellated with 15,000 vertices, followed by spatial smoothing into 7500 vertices. The lead field was then computed using the overlapping sphere algorithm. The inverse solution was calculated using Tikhonov-regularized minimum-norm estimates with source orientation constraints,[34] chosen to compute the source

activity in the present study. The noise covariance matrix is the identity matrix.

Power spectrum analysis

Six regions of interest (ROIs: left/right [L/R] STS, L/R FG, and L/R PC) were determined based on the Desikan–Killiany atlas[35] implemented in FreeSurfer (Figure 1).

The MEG signals were grouped together into one unique signal that was subsequently used to represent the activity of the ROI. In this study, ROI values were obtained from the average signal values across all vertices within each ROI. We obtained the source estimated MEG amplitude values for each ROI in bandpass-filtered low gamma (30–59 Hz) and high gamma (61–90 Hz) frequency bands. We calculated the average amplitude value for each segment (time average) and the average across all these amplitude average values, and we calculated the normalized gamma oscillation value to compare the differences in gamma amplitude during the task condition (gazing at mother's face, face condition) and the control condition between the ASD and TD groups. This allowed us to compare the face condition to control measurements (as the baseline) using the following formula for each participant: (face−control)/(face + control).

Statistical analysis

Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS ver. 25; IBM Corp). Furthermore, we applied Mann–Whitney *U* tests (two-tailed) to compare the differences in normalized gamma oscillation values between the ASD and TD groups. Furthermore, Spearman's rank correlation coefficients were calculated to explore the correlation between gamma oscillations and psychological scales (Social Responsiveness Scale [SRS] total *T*-score and mental processing scale [MPS] of the Kaufman Assessment Battery for Children [K-ABC]). Benjamini–Hochberg false discovery rate (FDR) correction was applied for group comparisons and the correlations between normalized gamma oscillation values ($q < 0.05$ was applied for 12 variables: six ROIs × two frequency bands).

RESULTS

Demographic and clinical data

The MEG recordings were completed for all 42 participants assessed for intelligence using the K-ABC.[36] Significant differences were found in the MPS scores between the two groups ($z = 3.168$, $r = 0.489$, $P = 0.002$). The autistic traits of 41 participants were evaluated by their parents based on the SRS.[37] We could not acquire the SRS questionnaire from one TD participant. A significant difference in the total SRS *T*-scores was observed between the TD and ASD groups ($z = -5.023$, $r = 0.784$, $P < 0.0001$). Data for all participants are presented in Table 1.

After artifact rejection, the average number of artifact-free segments in the ASD and TD groups was 47.50 and 47.63, respectively, in the face condition and 105.56 and 109.71, respectively, in the control condition. No significant difference was found between the number of segments in the ASD and TD groups (face condition: $z = -0.267$, $r = 0.041$, $P = 0.789$; control

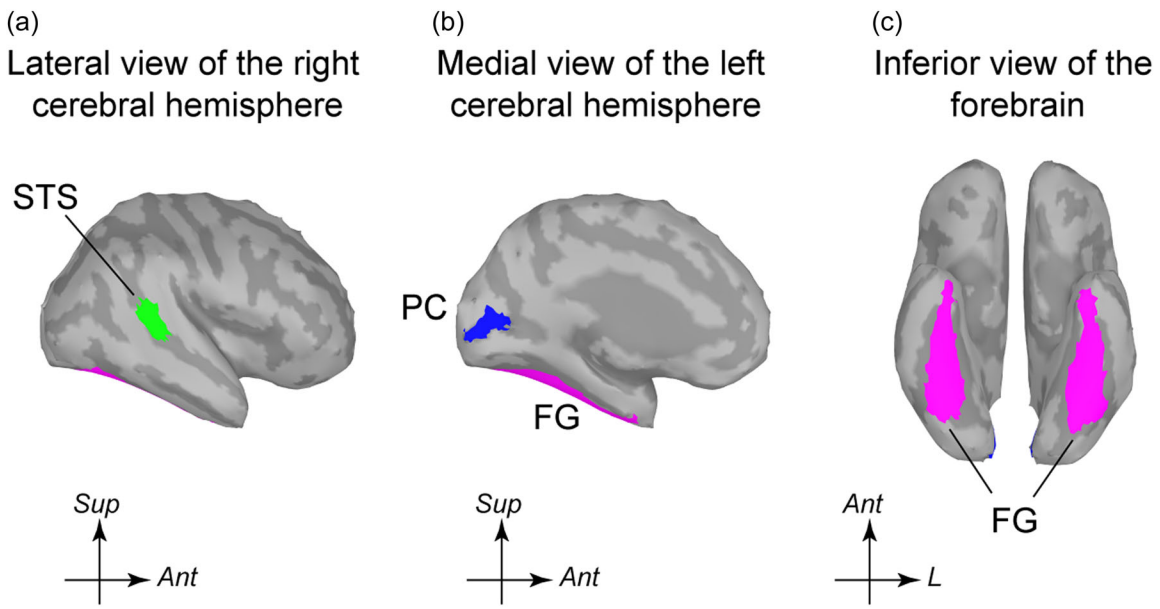

FIGURE 1 Regions of interest in the present study. (a) Lateral view of the right cerebral hemisphere. (b) Medial view of the left cerebral hemisphere. (c) Inferior view of the forebrain. Green indicates the location of the STS, pink indicates the location of the FG, and blue indicates the location of the PC. Ant, anterior; FG, fusiform gyrus; L, left; PC, pericalcarine cortex; STS, banks of the superior temporal sulcus; Sup, superior.

condition: $z = -0.547$, $r = 0.084$, $P = 0.584$). The data availability was 79.17% and 79.38% for the face condition and 83.77% and 79.17% for the control condition in the ASD and TD groups, respectively.

Gamma oscillation in the visual area related to face recognition

We calculated normalized gamma values to estimate the differences in gamma oscillations between the face and control conditions in bilateral STS, FG, and PC in TD children and children with ASD. A two-tailed Mann–Whitney *U* test with FDR correction demonstrated significant group differences in the gamma oscillation normalized value between the TD and ASD groups. For low-gamma oscillations (30–59 Hz), there were significantly higher values in the right STS ($z = 2.618$, $r = 0.404$, $P = 0.009$), right FG ($z = 3.075$, $r = 0.475$, $P = 0.002$), and right PC ($z = 2.237$, $r = 0.345$, $P = 0.025$) in the TD group than in the ASD group. For high-gamma oscillations (61–90 Hz), there were significantly higher values in the right STS ($z = 3.101$, $r = 0.478$, $P = 0.002$), bilateral FG (left: $z = 2.186$, $r = 0.337$, $P = 0.029$; right: $z = 2.745$, $r = 0.424$, $P = 0.006$), and bilateral PC (left: $z = 2.160$, $r = 0.333$, $P = 0.031$; right: $z = 2.669$, $r = 0.412$, $P = 0.008$) in the TD group than in the ASD group. No significant diffrences were obtained in left STS in low gamma band ($z = 1.195$, $r = 0.184$, $P = 0.232$) and high gamma band ($z = .718$, $df = 43$, $P = 0.007$), left FG in low gamma band ($z = 1.779$, $r = 0.275$, $P = 0.075$), and left PC in low gamma band ($z = 1.932$, $r = 0.298$, $P = 0.053$). Figure 2 shows group differences for the normalized values in the bilateral STS, FG, and PC for low gamma (30–59 Hz) and high gamma (61–90 Hz) frequencies. The results demonstrated that the group average of gamma oscillation normalized values in response to face stimuli was

TABLE 1 Demographic details of the participants included in the MEG analyses

	TD (*N* = 24)			ASD (*N* = 18)				
	Mean	SD	Range	Mean	SD	Range	z	*P*
Number of girls (*N*)*	11			7			0.203	0.653
Age (months)	69.58	6.043	61–79	74.89	10.654	62–97	−1.604	0.109
Age (year: month)	5:9		5:1–6:7	6:2		5:2–8:1		
K-ABC MPS score	108.38	13.048	80–132	92.56	17.870	71–146	3.168	0.002
SRS total *T*-score	46.61	6.556	36–63	70.78	12.754	48–98	−5.023	<0.0001

Abbreviations: K-ABC, Kaufman Assessment Battery for Children; MPS, mental processing scale; SD, standard deviation; SRS, Social Responsiveness Scale.
*P value was calculated using χ^2 test.

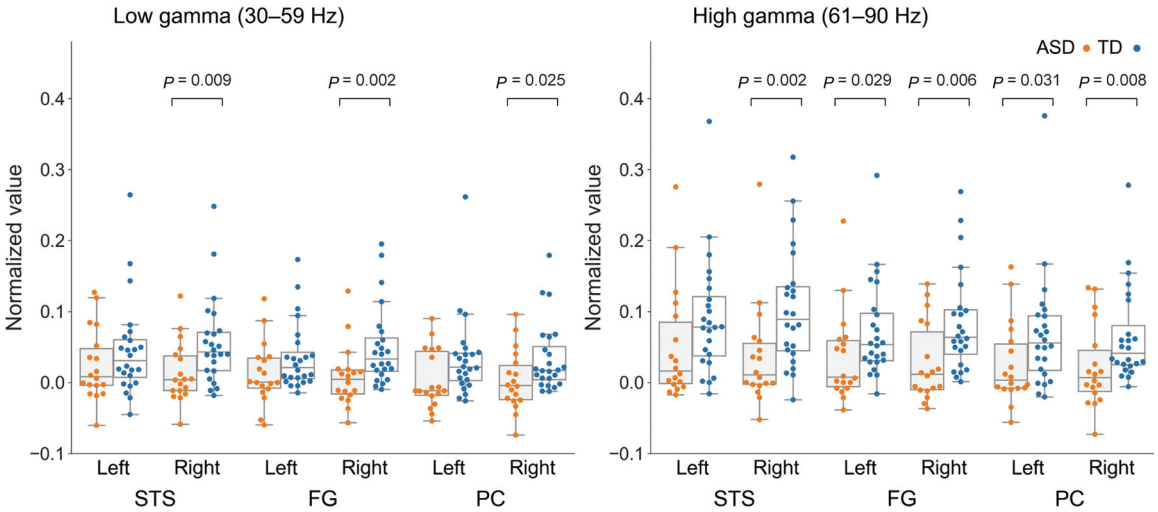

FIGURE 2 Box plots of normalized gamma oscillation values in response to face stimuli. Left: the normalized values of low gamma frequency (30–59 Hz) in the bilateral STS, FG, and PC for children with ASD or TD children. Right: the normalized values of high-gamma frequency (61–90 Hz) in the bilateral STS, FG, and PC for children with ASD and TD children. The normalized values were calculated using the following formula: (face condition − control)/(face condition + control). The horizontal lines denote median group values, whiskers represent 1.5 times the interquartile range, and dot plot indicates value from each participants. The *P* value represents a statistically significant difference between the groups which passed FDR correction ($q = 0.05$). ASD, autism spectrum disorders; FDR, false discovery rate; FG, fusiform gyrus; PC, pericalcarine cortex; STS, banks of the superior temporal sulcus; TD, typically developed

greater in the TD group than in the ASD group in the STS, FG, and PC of the right hemisphere.

DISCUSSION

This MEG study examined differences in neural responses to human face stimuli between children with ASD and TD children. We used face movies recorded during real-time face-to-face eye-gaze situations between young children and their mothers and nonface (nonbiological) movies as controls. We estimated the electrical source using MEG signals and then projected the source to a cortical map. We calculated differences in task conditions with baseline correction to investigate differences in neural activity between groups, that is, face condition − control condition/face condition + control condition, and then conducted statistical tests between the ASD and TD groups. Our results revealed that children with ASD showed lower gamma oscillation in the right hemisphere STS, FG, and PC in the low gamma oscillation normalized values and in the right hemisphere STS, bilateral FG, and bilateral PC in the high gamma oscillation normalized values.

Studies in behavioral and cognitive neuroscience have recently investigated the processing of face recognition and eye gaze during various tasks and social situations. Functional neuroimaging studies using fMRI and PET (positron emission tomography) have assessed face perception in patients with ASD and reported structural abnormalities in several brain regions such as the FG, amygdala, and STS.[10,38–41] Of note, MEG has advantages in measuring cortical neural activity with high temporal resolution and moderate spatial resolution. MEG gamma oscillations are especially difficult to detect because of potential contamination by artifacts due to their extremely small oscillation cycle. However, the gamma-band neural oscillation contains an important bottom-up component of visual information processing.[42]

Atypical face processing in young adults and preadolescent children with ASD was revealed using MEG.[5,16,26,43–47] Contrarily, the present study investigated young children with ASD (5–6 years old). Results have demonstrated a reduction of high-gamma oscillation-related face-perception processes in young children with ASD. This study supports previous findings and might provide valuable evidence of atypical facial processing in ASD.

Moreover, a unique feature of this study is that we used face stimuli that included a naturalistic real-time eye-gaze situation between a mother and child. Newer neuroimaging approaches allow for examining neural mechanisms in social interactions within the context of real-time reciprocal face-to-face interactions.[21] Our experimental design offers a useful approach for revealing neural traits related to social communication deficits in ASD. Regarding mother–child relationships, an EEG study has investigated whether mothers showed differential neural responses to the eye gaze of their child compared with that of an unfamiliar child.[48] Future studies must be conducted to evaluate alternative social contexts and compare the effects of personal familiarity and novel interaction using this approach.

This study has several limitations. First, we failed to measure eye-gaze during the experiment. Eye-gaze measurement during MEG experiment provides evidence of whether or not the children were looking properly at the mother's face. Second, we could not avoid the brain magnetic field evoked by facial expressions and noise contamination from muscle movements, facial expressions, and talking. With full attention, we reduced artifacts during data preprocessing. However, it was difficult to eliminate contamination of the data. Regrettably, we could not rate the amount of talking and body movement owing to the lack of voice recording and video recording of the whole body. The collection of electrooculography, especially for frontal and temporal sources, is highly desirable for MEG.[49] This study used an unrestricted task to measure neural networks during daily interaction behaviors to examine natural communication situations. Third, the sample size was small. Considering that ASD has a broad phenotype, there might be a variety of neural and behavioral responses to the mother's face. Future studies with larger sample sizes, including several autistic trait subgroups or sex differences, must be conducted to assess clinical and subclinical traits using this paradigm.

Future studies using time course analysis will be critical to optimize the excellent combination of temporal and spatial resolution that MEG offers. Furthermore, it is necessary to quantify facial expressions through video analysis and to consider facial expressions as a confounding factor. Additionally, we suggest that future studies should improve the control baseline correction for both experimental and control stimuli, such as using the same blank block before task periods.

CONCLUSION

This study demonstrated a reduction in low and high-gamma oscillations related to face-perception processes in young children with ASD. This report is the first MEG study revealing atypical face processing in young children with ASD, using real-time eye-gaze stimuli between participants and their mothers. Additionally, our task paradigm suggests an important application to provide valuable insight into the underlying neural mechanisms in individuals with ASD. In the future, a naturalistic experimental approach might be useful in developing a biological marker or clinical assessment for ASD.

AUTHOR CONTRIBUTIONS

Takashi Ikeda, Masayuki Hirata, Minoru Asada, and Mitsuru Kikuchi designed the study. Chiaki Hasegawa, Tetsuya Takahashi, Takashi Ikeda, Yuko Yoshimura, Hirokazu Kumazaki, Daisuke N. Saito, Kyung-Min An, and Mitsuru Kikuchi performed the experiments. Chiaki Hasegawa, Tetsuya Takahashi, Takashi Ikeda, Yuko Yoshimura, Hirokazu Kumazaki, Daisuke N. Saito, Ken Yaoi, Kyung-Min An, and Mitsuru Kikuchi performed the MEG analysis and interpretation of the data. Chiaki Hasegawa and Mitsuru Kikuchi drafted the

manuscript. All authors contributed to drafting the final manuscript and approved its submission.

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CONFLICT OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential competing or conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets collected during or analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The Ethics Committee of Kanazawa University Hospital approved all the methods and all procedures were performed in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Providing full knowledge of the experimental characteristics of the research, the parent (mother) agreed to their child's participation and to their own participation in the study. Written informed consent was obtained prior to participation.

CLINICAL TRIAL REGISTRATION

N/A.

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