Abnormal Cortical Activation During Silent Reading in Adolescents with Autism Spectrum Disorder

（自閉症スペクトラム児における黙読時の非定型な脳活動）

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Original article

Abnormal cortical activation during silent reading in adolescents with autism spectrum disorder

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Abstract

Objective: Autism spectrum disorder (ASD) is a developmental disorder characterized by communication deficits and social difficulties, and individuals with ASD frequently exhibit varied levels of language abilities. However, the neurophysiological mechanisms underlying their language deficits remain unclear. To gain insight into the neurophysiological mechanisms of receptive language deficits, we assessed cortical activation patterns in adolescents with ASD during silent word-reading.

Methods: We used magnetoencephalography to measure cortical activation during a silent word-reading task in 14 adolescent boys with high-functioning ASD and 17 adolescent boys with typical development (TD).

Results: Compared with participants with TD, those with ASD exhibited significantly decreased cortical activation in the left middle temporal gyrus, left temporoparietal junction, bilateral superior temporal gyrus, left posterior insula, and right occipitotemporal gyrus, and increased activation in the right anterior insula. Participants with ASD also exhibited a lack of left-lateralization in the central sulcus and abnormal right-lateralization in the anterior insula area. Furthermore, in participants with ASD, we found that abnormal activation of the right central sulcus correlated significantly with lower visual word comprehension scores, and that decreased activation of the right anterior insula correlated significantly with the severity of social interaction difficulties.

Conclusion: Our findings suggest that atypical cortical activation and lateralization in the temporal-frontal area, which is associated with higher-order language processing functions, such as semantic analysis, may play a crucial role in visual word comprehension and social interaction difficulties in adolescents with ASD.

Keywords: Autism spectrum disorder; Developmental disorders; Language; Lateralization; Magnetoencephalography; Temporal-frontal area; Visual word comprehension

1. Introduction

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that is defined by social communication impairment and restricted, repetitive patterns of behavior [1]. Although language impairment

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is not essential for an ASD diagnosis, receptive language disorders are observed in 61% of children with ASD [2]. A study of children with ASD reported that even those who read accurately exhibited impaired comprehension [3]. Latent growth curve modeling demonstrated that children with ASD performed at significantly lower levels than children with typical development (TD) on measures of linguistic and reading comprehension [4]. In addition, Ricketts et al., reported that word recognition and social impairments may constrain reading comprehension in adolescents with ASD [5].

Concerning the pathway for language cognition, several studies using functional magnetic resonance imaging (fMRI) have proposed a two-pathway model for the word-reading process in subjects with TD; this model involves a dorsal occipital–parietal–frontal stream and a ventral occipital-temporal stream [6]. The dorsal stream is thought to be involved in parietal cortex-based spatial perception and phonetic word decoding [7]. The ventral stream is thought to be involved in recalling familiar words and objects from temporal lobe lexical memory and to demonstrate anterior progression, especially of semantic processing activity.

A previous fMRI study suggested a qualitatively different strategy for lexicosemantic processing in ASD [8]. Harris et al. reported that semantic tasks elicited reduced activation in Broca's area, but increased activity in the left temporal cortex in individuals with ASD [9]. High-functioning adults with ASD also demonstrated atypical cortical activity associated with semantic category decision-making [10].

Furthermore, a number of studies have used magnetoencephalography (MEG) to investigate regional cortical activation and language processing [11] and have reported atypical cortical activity, such as delayed M100 latencies and abnormal lateralization, in response to auditory tasks, which correlated with language performance in children with ASD [12].

On the other hand, a few studies involving MEG and event-related potential (ERP) measurements have investigated this using visual language tasks in individuals with ASD. For example, MEG showed rightward lateralization in a visual reasoning task in children with ASD [13]. Cantiani et al. reported that non-verbal children with ASD showed significantly delayed basic perception and weakened higher-level language processing, including lexical-semantic functions, during picture-word matching tasks, based on ERP investigations [14]. However, the physiological characteristics of silent word-reading in adolescents with ASD remain unknown.

Thus, we here aimed to characterize the patterns of cortical activation related to language processing functions, such as lexical-semantic processing, using MEG in adolescent boys with high-functioning ASD. Based on previous reports, we hypothesized that 1) abnormal cortical activation and lateralization during a silent meaningful-word reading task would be observed in the temporal-frontal area, which is associated with lexicosemantic processing, in participants with ASD, and 2) abnormal cortical activation would correlate with visual word comprehension and social interaction in participants with ASD.

2. Methods

2.1. Participants

We recruited 15 boys with high-functioning ASD (mean age: 13.5 years, standard deviation: 1.1 years) and 17 age- and IQ-matched boys with TD (mean age: 12.4 years, standard deviation: 3.4 years, Table 1). All were native Japanese speakers. We excluded boys with hearing and/or visual impairments, dyslexia, or IQs lower than 80.

The boys with ASD were recruited from the Pediatrics Department at the Osaka University Hospital and were diagnosed with ASD by expert pediatric neurologists, based on the DSM-5 criteria [1]. The diagnoses were confirmed using the Autism Diagnostic Observation Schedule–Generic (ADOS-G) [15], which was administered to participants by research-accredited professionals, and the Japanese version of the Autism Spectrum Quotient (ASQ) [16]. The boys with TD were recruited via an advertisement in a public newsletter distributed throughout Osaka Prefecture. None of the TD participants reported any history of neurological, psychiatric, or developmental disorders, or received special education support, and all were confirmed to show no autistic traits on the ASQ.

None of the participants had received any medication on the day they underwent behavioral testing, and MEG and MRI measurements. All participants were right-handed, as confirmed with the Edinburgh Handedness Inventory [17]. One participant with ASD was excluded from the final analysis because of motion artefacts, leaving a final analysis pool of 31 participants (14 with ASD and 17 with TD).

2.2. Ethics statement

Written informed consent was obtained from all participants' parents, and verbal assent was obtained from all participants. All procedures were approved by the Osaka University Hospital's institutional review board and were performed in accordance with the relevant guidelines and regulations, including those of the Declaration of Helsinki.

2.3. Cognitive and language measures

IQ was measured using the Wechsler Intelligence Scale for Children, Third Edition (WISC-III). We

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Table 1
Participant demographics.

Measure	TD (n = 17)		ASD (n = 14)		
	Mean	SD	Mean	SD	*p*-value
Age (years)	12.4	3.4	13.5	1.1	0.492
Handedness[a]: right/left	17 / 0		14 / 0		
IQ[b]					
Full-scale IQ	119.4	15.2	115.5	10.0	0.301
Verbal IQ	119.2	15.9	115.1	9.0	0.240
Performance IQ	115.7	14.6	109	12.2	0.102
Verbal comprehension	119.4	16.3	116.5	10.5	0.257
PVT-R (SS)	14.1	2.2	14.6	1.7	0.690
SCTAW	29.5	1.8	29.0	1.9	0.455
ASQ	2.8	4.0	14.9	7.3	< 0.001

Abbreviations: ASD, autism spectrum disorder; ASQ, Autism Spectrum Quotient test; IQ, intelligence quotient; PVT-R, Picture Vocabulary Test–Revised; SCTAW, Standardized Comprehension Test of Abstract Words; SD, standard deviation; SS, scaled score; TD, typical development.
[a] Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971 [17]). All participants were right-handed.
[b] IQ and verbal comprehension were measured with the Wechsler Intelligence Scale for Children–Third Edition in all participants.

assessed language abilities with the WISC-III Verbal Comprehension component, the Picture Vocabulary Test–Revised (PVT-R) [18], and the Standardized Comprehension Test of Abstract Words (SCTAW) [19]. In the PVT-R, which assesses receptive vocabulary development, participants were presented with four pictures and asked to select the picture named by the experimenter. The SCTAW assesses visual word comprehension and involves presenting participants with six pictures and asking them to select the one that best represents an abstract word.

2.4. Silent reading task

We compiled a list of 106 meaningful visual nouns, each composed of three Japanese *hiragana* characters, that were drawn from a Japanese dictionary for elementary schools [20] and a Nippon Telegraph and Telephone Corporation database [21] to ensure that the words would be easily understandable for all participants [22,23]. The words were projected onto a screen located 325 mm from the participants' eyes, using Presentation software (Neurobehavioral Systems, Berkeley, CA) and a liquid-crystal projector (LVP-HC6800; Mitsubishi Electric, Tokyo, Japan). The stimulus duration was 3000-ms and the inter-stimulus interval was randomly 2700–3200 ms in length (Fig. 1). Participants were asked to read each word silently and press a button with their right forefingers if they saw the *hiragana* characters for *midori* (green) or *kiiro* (yellow) on the screen, to confirm that they were paying attention. Color stimuli were presented six times during MEG recording and excluded from the final analysis. To achieve accurate examinations, we explained the study protocol prior to the boys' participation and had them practice pushing the button.

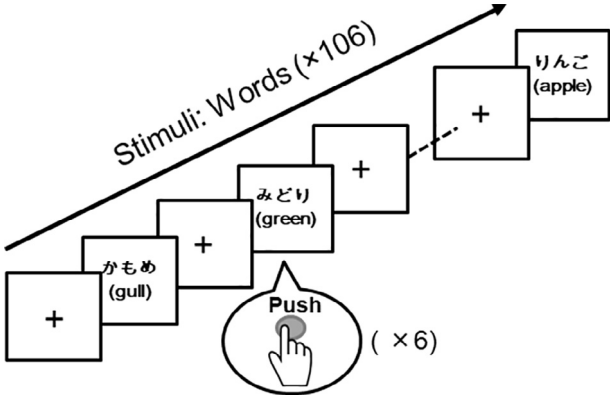

Fig. 1. Silent reading task. We used 106 meaningful nouns composed of three Japanese *hiragana* characters for the silent reading task. The stimulus duration was 3000 ms, and the inter-stimulus interval was 2700–3000 ms. Participants were asked to read each word silently and press a button with their right forefingers if they saw the *hiragana* characters for *midori* (green) or *kiiro* (yellow) on the screen. These color trials were excluded from the final analysis.

2.5. MEG recordings

Before MEG recordings, we scanned each participant's three-dimensional (3D) head surface with a FastSCAN Cobra device (Polhemus, Colchester, VT) with head-marker coils placed as fiduciary points on the external meatus of each ear, on two points on the forehead, and on the nasion. While lying on a bed in a magnetically shielded room, the participants underwent recordings with a 160-channel whole-head MEG system equipped with a superconducting quantum interference device gradiometer (PQ 1160C, Yokogawa Electric, Tokyo, Japan). The head-marker coil positions were recorded before and after each session to detect head movements. Data were acquired at a 1000-Hz sampling rate with a 0.03- to 200-Hz online band-pass filter and a

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60-Hz notch filter. During the recording, subjects were monitored from outside the magnetically shielded room by means of a video camera.

2.6. Magnetic resonance imaging

The anatomical magnetic resonance imaging (MRI) data were obtained with two systems, because our hospital replaced its device during our study. For 18 of 31 participants, we obtained MRI data with a 3-Tesla Signa Excite HDx system (GE Healthcare, Chicago, IL) using a 3D T1-weighted axial protocol (3D-spoiled gradient-recalled acquisition in steady-state sequence, repetition time = 10.1 ms, echo time = 3.0 ms, flip angle = 18°, field of view = 220 × 220 mm^2, matrix size = 320 × 256, slice thickness = 1.4 mm, number of slices = 128, and number of excitations = 1). For the other 13 participants, we used a 3-Tesla Discovery MR750w system (GE Healthcare) and a 3D silent T1-weighted sagittal protocol (repetition time = 10.1 ms, echo time = 16.0 ms, flip angle = 5°, field of view = 220 × 220 mm^2, matrix size = 320 × 256, slice thickness = 1 mm, number of slices = 480, and number of excitations = 1.5). We used the 3D head surface data and MEG fiduciary points to superimpose the MEG data onto the individual's MRI data, with an anatomical precision of a few millimeters.

2.7. MEG data analysis

To quantify the activity in each brain region, we used Brainstorm software (http://neuroimage.usc.edu/brainstorm; [24]. For spatial source analysis, we performed cortical reconstruction and parcellation of each subject's MRI data with FreeSurfer 5.3.0 image analysis software (http://surfer.nmr.mgh.harvard.edu/, [25]). We used FreeSurfer's watershed algorithm to generate individual inner-skull surface triangulations that were imported into Brainstorm and down-sampled to 15,000 vertices. The epochs were defined from 150 ms before stimulus onsets to 1500 ms after their onset. Heartbeat and eye movement artefacts were excluded using signal space projections [26], and all epochs with artefacts greater than 2000 ft/cm were excluded through visual inspections. In addition, we also removed the component when the signal was more than 12% and confirmed that all epochs were free of epileptiform discharges. The number of included epochs was 70 in both groups. After noise reduction, the remaining data were arithmetically averaged and z-score-normalized against baseline activity recording in the 150-ms before onset. We performed source estimation with weighted minimum-norm estimation, using an algorithm adapted from depth-weight minimum linear L2 norm estimators, in MNE software [27].

The grand-averaged data were projected onto the Colin 27 brain template from the Montreal Neurological Institute (MNI) (http://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27, [28]). We exported cortical activation data from each region of interest (ROI) as ASCII files for further analysis and calculated the time-course in each ROI (Fig. 3).

2.8. ROI determination

As shown in Table 2, we defined 20 ROIs in the left and right hemispheres according to cortical responses to silent reading and a previously published review [29] (Fig. 3). These ROIs included the bilateral middle occipital gyrus (MOG), occipitotemporal gyrus (OTG), inferior parietal lobe (IPL), middle temporal gyrus (MTG), temporoparietal junction (TPJ), superior temporal gyrus (STG), central sulcus (CS), posterior insula, inferior frontal gyrus (IFG), and anterior insula. Each ROI's MNI coordinates were identified with the WFU_PickAtlas_3.0.4 automated anatomical labelling toolbox (aal_MNI_V4.txt, https://github.com/ZhenYangCMI/microstate_code/tree/master/spm8/toolbox/WFU_PickAtlas_3.0.4/wfu_pickatlas/MNI_atlas_templates) for MATLAB R2012b (MathWorks, Natick, MA).

2.9. Statistical analyses

All statistical analyses were performed in SPSS version 22.0 (IBM, Tokyo, Japan). Unpaired t-tests were used to assess the group differences in age, and IQ, verbal comprehension, PVT-R, SCTAW, and ASQ scores. Kolmogorov–Smirnov tests showed that our data were not normally distributed; thus, we used Mann–Whitney U-tests to assess between-group differences in activation intensities and laterality indices (LIs), and calculated p-values. In addition, the sample size was small; therefore, we calculated effect sizes, obtained by standardizing the differences of median values between groups. We used r-values as effect sizes calculated with z-values, for non-parametric tests. We defined statistical significance and near-significance as $p < 0.05$ and $0.05 \leq p < 0.1$, respectively, unless otherwise noted. For between-group comparisons of cortical activation intensities in each ROI, we used mean activated intensities in 20-ms windows centered on the points of significant between-group differences.

For the activated intensities used to calculate LIs, we used only those points where significant between-group differences were detected in the left hemisphere, as this hemisphere is typically dominant in language functions. However, we used time windows described in a previous study [30] for the left MOG and OTG because we detected no significant between-group differences in their activated intensities. We calculated LIs in all ROIs using the following equation:

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Table 2
Region of interest coordinates.

ROI	AAL	MNI coordinates			Scout size (cm^2)
		X	Y	Z	
MOG	Occipital_Mid (L)	−16.0	−92.5	14.0	9.95
	Occipital_Mid (R)	28.0	−98.5	14.0	10.03
OTG	Occipital_Inf (L)	−45.8	−76.7	−4.7	5.05
	Occipital_Inf (R)	42.1	−72.7	−7.3	5.05
IPL	Angular (L)	−42.0	−64.5	32.0	3.88
	Angular (R)	48.0	−58.5	28.0	3.88
MTG	Temporal_Mid (L)	−50.0	−55.5	6.0	3.06
	Temporal_Mid (R)	55.0	−53.5	14.0	3.18
TPJ	Temporal_Sup (L)	−45.0	−35.5	20.0	10.02
	Temporal_Sup (R)	46.0	−34.5	18.0	9.98
STG	Temporal_Sup (L)	−64.0	−13.5	5.0	10.01
	Temporal_Sup (R)	61.0	−7.5	6.0	9.95
CS	Precentral gyrus (L)	−55.6	−5.7	40.8	9.96
	Precentral gyrus (R)	53.6	−16.4	40.0	10.01
Posterior insula	Insula (L)	−38.0	−12.5	10.0	3.03
	Insula (R)	44.0	−7.5	7.0	2.96
IFG	Frontal_Inf_Oper (L)	−44.0	14.5	4.0	2.96
	Frontal_Inf_Oper (R)	49.0	17.5	3.0	3.06
Anterior insula	Insula (L)	−34.0	15.5	4.0	3.01
	Insula (R)	36.0	16.5	6.0	2.94

All ROIs were selected from grand-averaged cortical activation maps.
Abbreviations: AAL, automated anatomical labelling; CS, central sulcus; IFG, inferior frontal gyrus; Inf, inferior; IPL, inferior parietal lobe; L, left; Mid, middle; MNI, Montreal Neurological Institute; MOG, middle occipital gyrus; MTG, middle temporal gyrus; Oper, opercularis; OTG, occipitotemporal gyrus; R, right; ROI, region of interest; STG, superior temporal gyrus; Sup, superior; TPJ, temporoparietal junction.

$$LI = \frac{LH - RH}{LH + RH}$$

where LH and RH represent activation intensities in the left and right hemispheres, respectively [23]. We defined left- and right-lateralization as $LI > 0.10$ and $LI < -0.10$, respectively.

We calculated Pearson's r-values to test for correlations between SCTAW reading scores, ASQ or the ADOS-G social interaction scores, and activated intensities in the bilateral STG, posterior insula, CS, IFG, and anterior insula. We selected these ROIs because they exhibited significant between-group differences in LIs, which we here defined as $p < 0.1$. We performed multiple comparison corrections with the Benjamini–Hochberg method.

3. Results

3.1. Participant characteristics

Boys with ASD obtained significantly higher ASQ scores than the boys with TD ($p < 0.001$), but there were no significant between-group differences in Full IQ; Verbal IQ (VIQ), and verbal comprehension, which is a subtest of the VIQ; or in Performance IQ on the WISC-III; receptive vocabulary scores on the PVT-R; or reading scores on the SCTAW (Table 1).

3.2. Between-group differences in time-course and activation intensities

Both groups exhibited cortical activation that first appeared in the bilateral occipital lobe at 150 ms, shifted to the temporal and parietal lobes at 200 ms, and to the frontal lobe at 250 ms (Fig. 2).

Compared to the TD group, the ASD group exhibited statistically significantly weaker activated intensities in the right OTG (227–246 ms, TD: 4.64 (3.78–6.63), ASD: 2.86 (2.28–3.79), $p = 0.006$, $r = 0.46$), left MTG (346–365 ms, TD: 3.50 (1.60–6.05), ASD: 1.64 (1.09–3.75), $p = 0.048$, $r = 0.31$), left TPJ (464–483 ms, TD: 3.21 (2.58–4.85), ASD: 2.95 (1.11–3.58), $p = 0.041$, $r = 0.36$), left STG (466–485 ms, TD: 2.65(2.04–3.78), ASD: 1.45 (0.79–2.10), $p = 0.004$, $r = 0.51$), right STG (433–452 ms, TD: 3.35 (2.18–4.23), ASD: 1.43 (1.18–3.13), $p = 0.023$, $r = 0.36$), and left posterior insula (377–396 ms, TD: 3.61 (2.82–6.39), ASD: 2.06 (1.17–3.40), $p = 0.011$, $r = 0.46$). On the other hand, the ASD group showed significantly increased activated intensities in the right anterior insula (211–230 ms,

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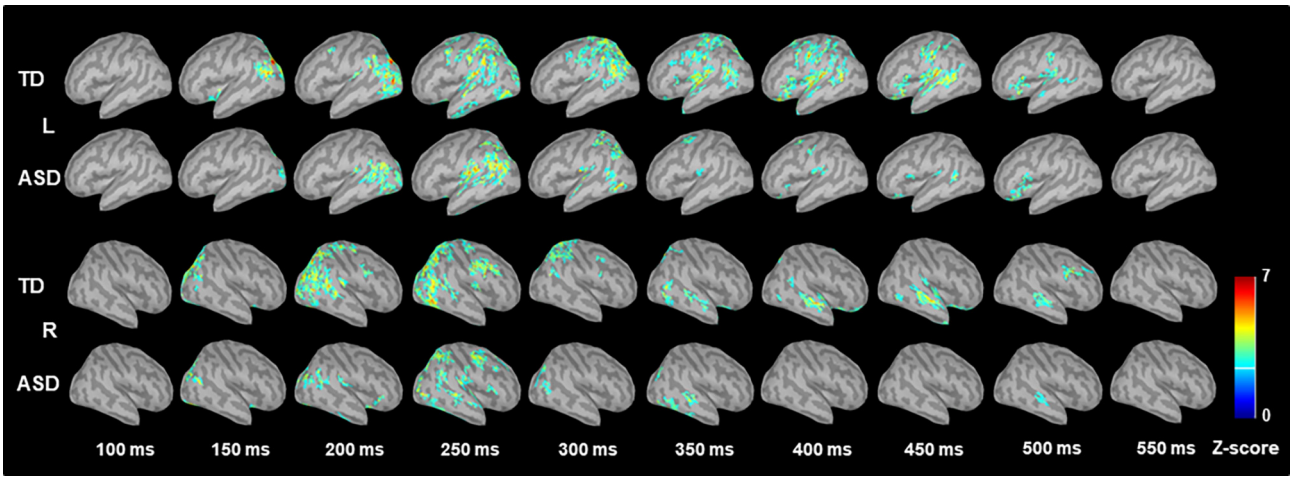

Fig. 2. Cortical activity elicited by the silent reading task. The grand-averaged brain activity during the silent reading task is shown for participants with TD and those with ASD. Cortical activity in both groups started in the occipital lobe and then shifted to the temporal, parietal, and frontal lobes. The ASD group exhibited reduced activity in the primary visual cortex between 150 ms and 500 ms. Abbreviations: ASD, autism spectrum disorder; L, left hemisphere; R, right hemisphere; TD, typical development.

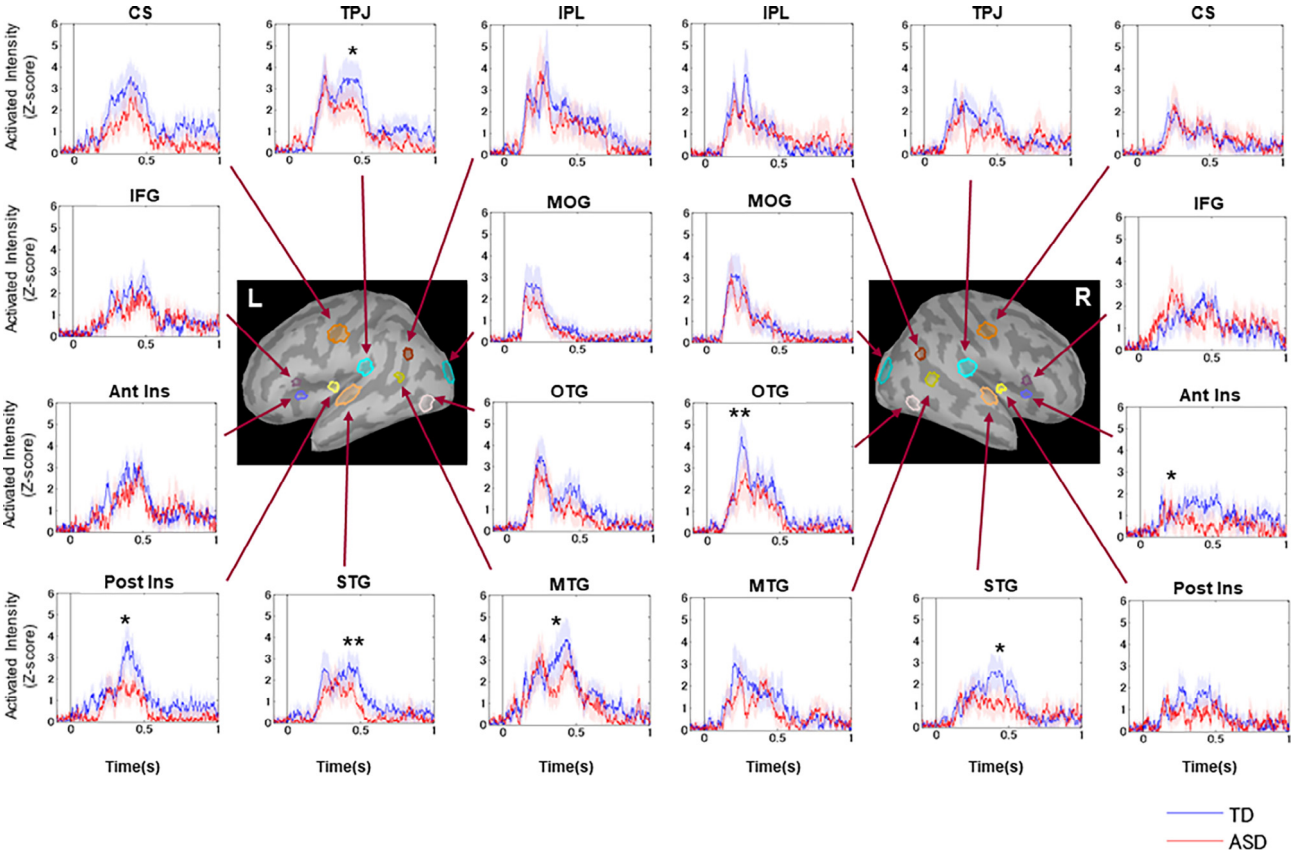

Fig. 3. Activity time-course in each region of interest. Asterisks indicate significant differences ($p < 0.05$) between the TD and ASD groups. Grand-averaged activity time-courses during the silent reading task are shown for each ROI. Abbreviations: ASD, autism spectrum disorder; Ant Ins, anterior insula; CS, central sulcus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; L, left hemisphere; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OTG, occipitotemporal gyrus; Post Ins, posterior insula; R, right hemisphere; ROI: region of interest; STG, superior temporal gyrus; TD, typical development; TPJ, temporoparietal junction.

TD: 1.58 (1.32–2.70), ASD: 2.29 (1.73–4.21), $p = 0.029$, $r = 0.39$). In addition, the ASD group exhibited a tendency toward weaker activated intensities in the left IPL (336–355 ms, TD: 3.35 (1.65–4.78), ASD: 1.43 (0.84–3.27), $p = 0.074$, $r = 0.38$), left CS (292–311 ms, TD: 3.24 (1.84–4.87), ASD: 2.36 (1.14–2.83),

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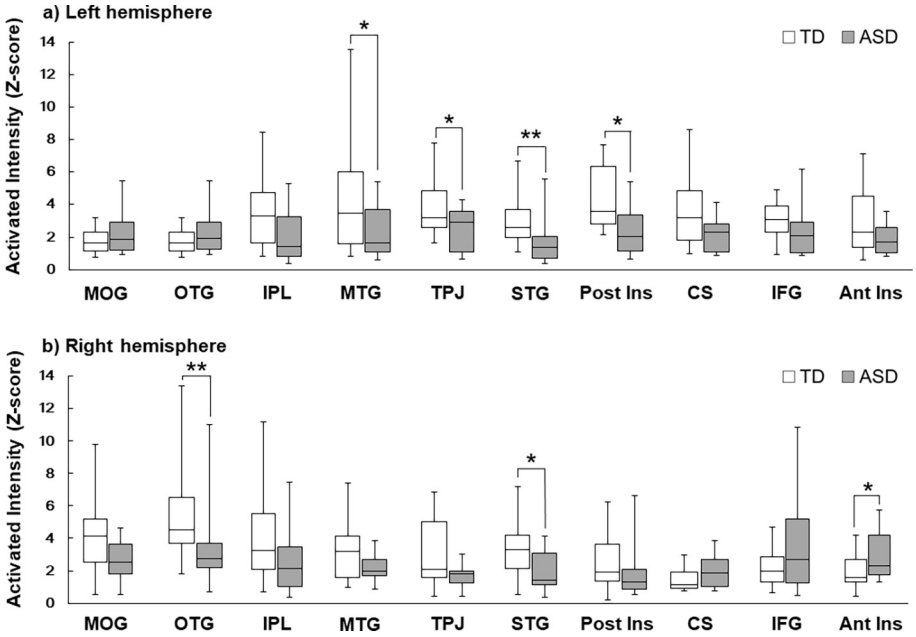

Fig. 4. Activated intensities in each region of interest for each group. Median values of activated intensities are presented for each ROI of each group in (a) the left hemisphere and (b) the right hemisphere. Asterisks indicate significant differences ($^{*}p < 0.05$, $^{**}p < 0.01$) between the TD and ASD groups. Abbreviations: ASD, autism spectrum disorder; Ant Ins, anterior insula; CS, central sulcus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; L, left hemisphere; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OTG, occipitotemporal gyrus; Post Ins, posterior insula; R, right hemisphere; ROI: region of interest; STG, superior temporal gyrus; TD, typical development; TPJ, temporoparietal junction.

$p = 0.054$, $r = 0.37$), left IFG (373–392 ms, TD: 3.12 (2.36–3.96), ASD: 2.09 (1.07–2.97), $p = 0.062$, $r = 0.34$) and left anterior insula (245–264 ms, TD: 2.33 (1.39–4.57), ASD: 1.73 (1.08–2.62), $p = 0.091$, $r = 0.25$). There were no significant between-group differences in the left or right MOG, left OTG, right IPL, right MTG, right TPJ, right posterior insula, right CS, or right IFG (Figs. 3 and 4).

3.3. ROI-specific LIs

The TD group exhibited left-lateralization in the IPL, MTG, TPJ, STG, posterior insula, and CS, whereas the ASD group exhibited left-lateralization only in the TPJ and right-lateralization in the STG and anterior insula. We observed significant between-group LI differences in the CS ($p = 0.035$, $r = 0.38$), and nearly significant between-group LI differences in the STG ($p = 0.081$, $r = 0.31$) and anterior insula ($p = 0.095$, $r = 0.30$) (Fig. 5).

3.4. Relationships between cortical activated intensities and scores for reading and social interaction

Although the TD group exhibited positive correlations between SCTAW reading scores and activated intensities in the left STG ($r = 0.44$, $p = 0.092$) and left IFG ($r = 0.50$, $p = 0.050$), the ASD group showed no such correlations. However, the ASD group demonstrated negative correlations between SCTAW reading scores and activated intensities in the right CS ($r = -0.79$, $p = 0.001$) and right IFG ($r = -0.53$, $p = 0.049$), whereas the TD group did not. Additionally, the TD group exhibited a positive correlation between ASQ and activated intensities in the left STG ($r = 0.577$, $p = 0.019$), whereas the ASD group did not. Additionally, the ASD group showed a negative correlation between ASQ and activated intensities in the left posterior insula ($r = -0.537$, $p = 0.048$), whereas the TD group did not. Furthermore, the ASD group exhibited negative correlations between ADOS-G social interaction scores and activated intensities in the left CS ($r = -0.49$, $p = 0.073$) and right anterior insula ($r = -0.72$, $p = 0.004$). There were no correlations between ADOS-G social interaction scores and activated intensities in any other ROI (Fig. 6).

4. Discussion

In this study, we found decreased cortical activation in the left MTG, left TPJ, bilateral STG, left posterior insula, and right OTG and increased activation in the right anterior insula during a silent word-reading task in adolescents with ASD. These adolescents also exhibited a lack of left-lateralization in the CS and abnormal right-lateralization in the anterior insula area. Furthermore, in participants with ASD, the abnormal activation levels in the right CS

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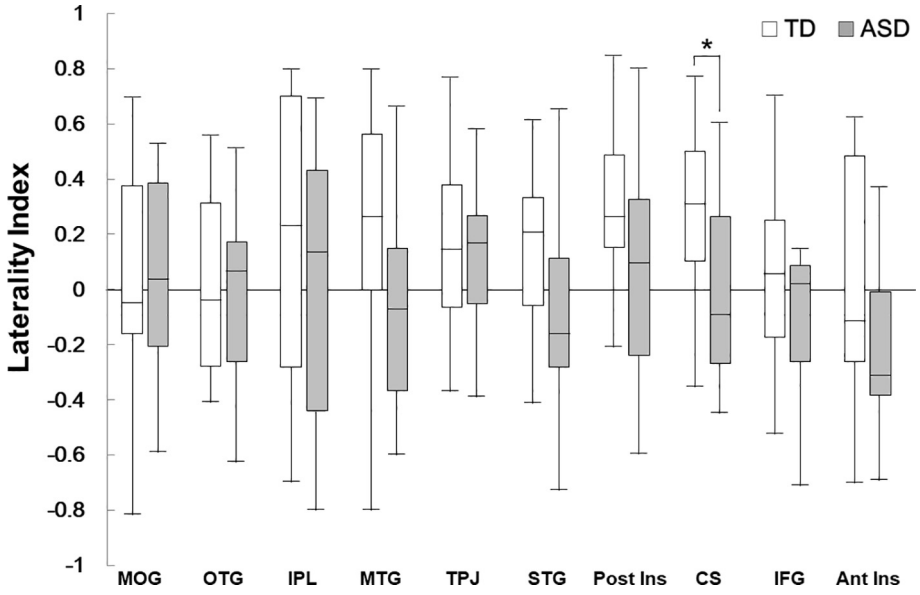

Fig. 5. Laterality indices in each region of interest of each group. The median LIs for all ROIs are presented for each group. Asterisks indicate significant differences ($p < 0.05$) between the TD and ASD groups. Abbreviations: Ant Ins, anterior insula; ASD, autism spectrum disorder; CS, central sulcus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; L, left hemisphere; LI, laterality index; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OTG, occipitotemporal gyrus; Post Ins, posterior insula; R, right hemisphere; ROI: region of interest; STG, superior temporal gyrus; TD, typical development; TPJ, temporoparietal junction.

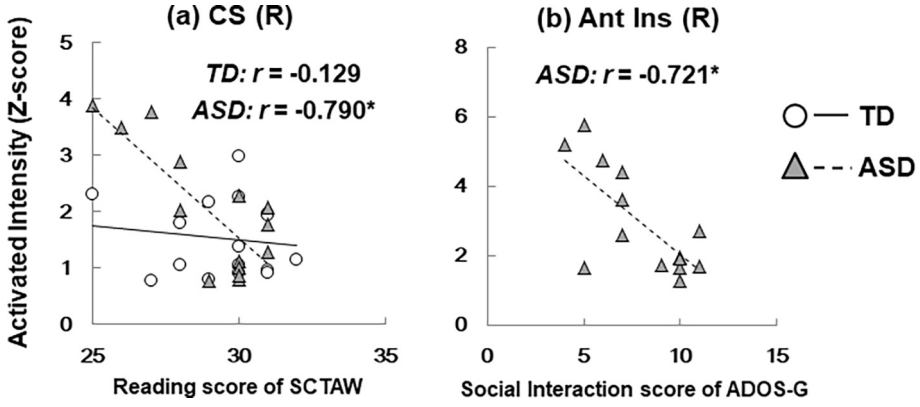

Fig. 6. Correlations between cortical activated intensities and SCTAW reading scores or ADOS-G social interaction scores. The scatter plots present cortical activated intensities and SCTAW reading scores for both groups in the right CS (a) and cortical activated intensities and ADOS-G social interaction scores for the ASD group in the right Ant Ins (b). Asterisks indicate significant differences ($p < 0.05$) between the TD and ASD groups. Abbreviations: ADOS-G, Autism Diagnostic Observational Schedule–Generic; ASD, autism spectrum disorder; Ant Ins, anterior insula; CS, central sulcus; SCTAW, Standardized Comprehension Test of Abstract Words; TD, typical development.

significantly correlated with lower visual word comprehension scores, and the decreased right activation levels in the anterior insula significantly correlated with the severity of social interaction deficits. In addition, the decreased left activation levels in the posterior insula significantly correlated with the severity of ASD. Our findings suggest that atypical neural networks in the temporal-frontal area, which manages higher-order language processing functions, such as phonological and semantic analysis, may play crucial roles in visual word comprehension and social interaction abilities in individuals with ASD.

The Japanese language uses multiple character systems, including syllabographic *hiragana* and *katakana* and morphometric *kanji*. A previous study using *hiragana* and *katakana* reported ERPs similar to those observed in subjects reading alphabetic scripts [31]. In our study with a *hiragana*-reading task, we observed that cortical activity during the task progressed spatially from the occipital lobe to the temporal, parietal, and frontal lobes, which is in turn consistent with the results of a previous study of *hiragana*-reading [32].

During word-reading in normal adults, visual information flows through the MOG, OTG language

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domain, and the left MTG, constituting the "ventral stream" [7]. This stream contributes to semantic analysis during reading. On the other hand, visual information in the MOG also flows through the left IPL, including its angular and supramarginal portions, and the left TPJ, constituting the "dorsal stream" [7]. This stream contributes to orthography-to-phonology conversion and phonological transformation to motor representations for articulation. In addition, the left STG, CS, and IFG are involved in both streams, which supports acoustic and phonological representations, processes phonological or syllabic information, and is responsible for semantic unification, respectively [33,34].

A prior electroencephalography/MEG study of reading processing in adults with ASD reported reduced ventral stream activity, increased dorsal pathway activity, and no differences depending on the word categories [35]. We observed that both the TD and ASD groups exhibited clear activation in both the ventral and dorsal stream. In this study, we did not examine cortical activation intensities between the temporal and dorsal stream in the two groups. As our participants were adolescents, there may not be marked differences between these two lexicosemantic pathways.

However, in our study, atypical cortical activation patterns were noted in areas from the temporal to the frontal lobes in the ASD group and may be related to abnormalities of phonological and linguistic semantic processing in persons with ASD.

A recent anatomical covariance network study of children with ASD reported that the disruption of intrahemispheric covariance, especially in the left frontotemporal network, correlated with these individuals' verbal abilities [36]. A diffusion tractography study also reported that children with high-functioning ASD exhibited reduced connectivity between the inferior frontal region and temporal areas [37]. Based on our results, we speculate that abnormal connectivity between the temporo-frontal areas may be related to word-reading comprehension in participants with ASD.

In our LI analysis, the ASD group showed markedly weaker left-lateralization and atypical right-lateralization in word perception. Functional lateralization is thought to be an evolutionary adaptation that improves processing efficiency, and age-related lateralization changes are associated with language skill acquisition, rather than with general brain maturation [38]. The right hemisphere generally develops faster than the left hemisphere and remains dominant until approximately 3 years of age [39]. A structural study in children with TD reported that the left-hemisphere language areas, including Broca's area, do not become dominant until 11 years of age and that microstructural maturation and language acquisition may be reciprocal [40]. Furthermore, interhemispheric inhibition is essential for smooth information processing [41].

Brain growth and maturation in children with ASD is quite atypical, especially during early infancy. For example, autistic brains grow faster and generate redundant neurons in the first years of life [42]. Many studies have reported atypical lateralization in ASD. In 3- to 7-year-old children with ASD, Kikuchi et al. reported atypical right-lateralized functional connectivity in the parietal and temporal regions during video-viewing [43]. Additionally, functional magnetic resonance imaging studies show that subjects with ASD exhibit reduced left-lateralization and alternatively increased activation in the right IFG, STG, and MTG during linguistic tasks [44].

In our study, adolescents with TD exhibited clear left-lateralization, resulting in efficient processing. However, our participants with ASD showed a lack of left-lateralization from the temporal areas to the frontal areas and exhibited abnormal right-lateralization in STG and anterior insula area. This might have resulted from early arrest of brain maturation and dysfunctional interhemispheric inhibition in ASD.

Furthermore, in a study in adults, the anterior insula was associated with semantic functions and pronunciation [45]. However, in individuals with ASD, cortical activation in the insula during sensory processing showed atypical properties, with decreases on the left and increases on the right [46]. Moreover, in adolescents with high-functioning ASD, right anterior insula and left posterior insula volumes negatively correlated with the severity of insight deficits, and left posterior insula volume negatively correlated with the severity of "autistic-like" symptoms [47]. In our study, the abnormal cortical activation in the right anterior and left posterior insula may be related to atypical semantic function and could lead to atypical social interaction in adolescents with ASD.

Neither the TD nor the ASD groups exhibited any specific language impairment, but even "average readers" with ASD can still exhibit impaired comprehension during conversations [48]. These findings suggest that the physiological mechanisms underlying abnormal visual word-reading may involve several neural mechanisms, such as atypical maturation, abnormal connectivity, and dysfunctional interhemispheric inhibition. Our results may also facilitate the development of novel clinical interventions, such as neurofeedback training, which enables self-regulation of brain functions through real-time neural signal feedback, and repetitive transcranial stimulation in cortical areas associated with language.

This study has several limitations that require consideration. First, in this study, all participants were boys, because ASD is more common in boys than girls, and we wanted to exclude the effect of sex differences in brain maturation during early adolescence. Second, our ASD group was exclusively composed of boys with high-

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functioning ASD. Since boys with ASD tend to exhibit hyperactivity and poor adherence to task instructions, we had to exclude boys who were pre-adolescent or had low-functioning ASD. To elucidate the relationship between evoked cortical activity and language abilities, it is necessary to replicate our experiments with participants of more diverse ages and IQs. Third, as early adolescence is a developmental stage characterized by marked maturational differences, it will also be necessary to consider the effects of delayed cortical maturation and examine changes over time. Fourth, to avoid the task execution time being intolerably long for boys with ASD, we included no pseudo-words in the silent *hiragana* word-reading task. We therefore could not determine whether the cortical activation was evoked by word comprehension or by reading the letters. In future studies, we would like to conduct experiments in which pseudo-words are presented in several blocks separated by breaks.

In conclusion, the present study of adolescents with ASD who performed a silent word-reading task revealed that abnormal cortical activation levels in the right CS significantly correlated with the severity of visual word comprehension deficits and that abnormal cortical activation levels in the right anterior insula significantly correlated with the severity of social interaction deficits. Participants with ASD also exhibited abnormal right-lateralization in the anterior insula and a lack of left-lateralization in the CS. We suggest that atypical maturational processes, abnormal connectivity, and dysfunctional interhemispheric inhibition in the temporal-frontal area may play crucial roles in visual word comprehension and social interaction difficulties experienced by individuals with ASD.

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Competing interests

The authors declare no competing financial interests.

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