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Synchrony of auditory brain responses predicts behavioral ability to keep still in children with autism spectrum disorder
Auditory-evoked response in children with autism spectrum disorder

Yuko Yoshimura[a], Mitsuru Kikuchi[a,*], Hirotoshi Hiraishi[a], Chiaki Hasegawa[a], Tetsuya Takahashi[a], Gerard B. Remijn[b], Manabu Oi[a], Toshio Munesue[a], Haruhiro Higashida[a], Yoshio Minabe[a]

[a]Research Center for Child Mental Development, Kanazawa University, Kanazawa 920-8640, Japan
[b]International Education Center, Kyushu University, Fukuoka 819-0395, Japan,

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ABSTRACT

The auditory-evoked P1m, recorded by magnetoencephalography, reflects a central auditory processing ability in human children. One recent study revealed that asynchrony of P1m between the right and left hemispheres reflected a central auditory processing disorder (i.e., attention deficit hyperactivity disorder, ADHD) in children. However, to date, the relationship between auditory P1m right-left hemispheric synchronization and the comorbidity of hyperactivity in children with autism spectrum disorder (ASD) is unknown. In this study, based on a previous report of an asynchrony of P1m in children with ADHD, to clarify whether the P1m right-left hemispheric synchronization is related to the symptom of hyperactivity in children with ASD, we investigated the relationship between voice-evoked P1m right-left hemispheric synchronization and hyperactivity in children with ASD. In addition to synchronization, we investigated the right-left hemispheric lateralization. Our findings failed to demonstrate significant differences in these values between ASD children with and without the symptom of hyperactivity, which was evaluated using the Autism Diagnostic Observational Schedule, Generic (ADOS-G) subscale. However, there was a significant correlation between the degrees of hemispheric synchronization and the ability to keep still during 12-minute MEG recording periods. Our results also suggested that asynchrony in the bilateral brain auditory processing system is associated with ADHD-like symptoms in children with ASD.

1. Introduction

Auditory-evoked responses in children provide insight into the maturation of the human central auditory system (Seither-Preisler et al., 2014; Stefanics et al., 2011). In autism spectrum disorder (ASD), a number of previous studies have demonstrated alterations in cortical auditory processes (Edgar et al., 2014; Roberts et al., 2010; Yoshimura et al., 2016; Yoshimura et al., 2013) and increased rates of brainstem or peripheral hearing dysfunction (Demopoulos and Lewine, 2015; Hitoglou et al., 2010; Rosenhall et al., 2003; Roth et al., 2012). An auditory-evoked field (AEF) is a brain's response to auditory stimulation recorded by MEG and is the equivalent of the auditory-evoked potential recorded by electroencephalography (EEG). In studies using magnetoencephalography (MEG), the mid-latency AEF comprises the P50m (P1m), N100 m and P200m components. The P50m (P1m) is one of the mid-latency components and corresponds to the P50 (P1) in electroencephalography (EEG) studies (Gilley et al., 2005; Ponton et al., 2002). P1(m) is a prominent component in 1- to 10-year-old children (Gilley et al., 2005; Oram Cardy et al., 2004; Orekhova et al., 2013; Paetau et al., 1995; Ponton et al., 2002; Shafer et al., 2015; Sharma et al., 1997) in both hemispheres and provides insight into the development of auditory processing. To avoid confusion, we call this component P1m in the present study. P1m is thought to be a suitable metric for measuring changes in auditory input for speech-like signals (Chait et al., 2004 and Hertrich et al., 2000). Our recent studies using MEG in children have shown that P1m is associated with language development in typically developing (TD) children (Yoshimura et al., 2012; Yoshimura et al., 2014). Other previous studies have reported that P1m reflects cognitive development and developmental disorders in children, showing positive correlations with language impairments in children (Pihko et al., 2007), cognitive function in children born very prematurely (Hovel et al., 2015), ASD (Yoshimura et al., 2013) and attention deficit hyperactivity disorder (ADHD) (Seither-Preisler et al., 2014). Interestingly, Seither-Preisler et al. (2014) reported that musically trained children exhibited bilaterally more synchronized P1m components (i.e., latency),

Abbreviations: AEF, auditory-evoked field; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; MEG, magnetoencephalography; TD, typically developing; AEF, auditory-evoked field; ECD, equivalent current dipole; ISI, interstimulus interval.

* Corresponding author at: Research Center for Child Mental Development, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8640, Japan.
E-mail address: mitsuruk@med.kanazawa-u.ac.jp (M. Kikuchi).

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whereas children with ADHD exhibited a distinct bilateral P1m asynchrony. Their study indicates that P1m asynchrony can be an index of central auditory processing disorder, which occurs in ~50% of individuals with ADHD (Riccio et al., 1994).

Autism spectrum disorder is a neurodevelopmental disorder characterized by restricted interests, repetitive behaviors, and deficits in communication and social interactions. ADHD is commonly comorbid with ASD, and a recent study reported that the prevalence was 59.1% in preschool and elementary school-aged children (Salazar et al., 2015) and approximately 30% in school-aged children with ASD (Simonoff et al., 2008). Although one recent study demonstrated that children with ADHD exhibited a distinct bilateral P1m asynchrony (Seither-Preisler et al., 2014), no reports to date have focused on the right-left hemispheric synchronization of P1m in children with ASD and the comorbidity of hyperactivity. Intriguingly, recent neuroimaging studies suggest aberrant interhemispheric connectivity in both ASD (Anderson et al., 2011; Dinstein et al., 2011; Kikuchi et al., 2015) and ADHD (Cao et al., 2010; Clarke et al., 2008; Onnink et al., 2015). Therefore, we hypothesized that symptoms of hyperactivity in children with ASD would correlate with a right-left hemispheric asynchrony of voice-evoked P1m latency. To test our hypothesis in children with ASD, we investigated the relationship between the voice-evoked P1m right-left hemispheric synchronization (i.e., latency) and hyperactivity in children with ASD.

Furthermore, ASD is often described as comprising an aberrant brain lateralization. Recent studies have reported that an atypical lateralization of the auditory-evoked response is one of the intriguing properties of human brain development and ASD (Flagg et al., 2005; Minagawa-Kawai et al., 2009; Seery et al., 2013). Therefore, we also investigated the relationship between right-left hemispheric lateralization in the voice-evoked P1m latency and hyperactivity in children with ASD.

2. Materials and methods

2.1. Participants

Thirty-five children with ASD (10 girls and 25 boys) aged 38–86 months were recruited from Kanazawa University and the prefectural hospitals in the Kanazawa and Toyama areas. The ASD diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) (the American Psychiatric Association, 1994), the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al., 2002), or the ADOS-G (Lord et al., 2000) and was conducted by a psychiatrist and a clinical speech therapist. The presence or absence of hyperactivity was classified using the item 'overactivity' in the ADOS. As a result, 17 children with ASD (3 girls and 14 boys) aged 48–79 months were classified as ASD with overactivity, and 18 children with ASD (7 girls and 11 boys) aged 38–86 months were classified as ASD without overactivity. Cognitive skills were assessed by the Japanese adaptation of the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman, 1983). This is typically used to assess the cognitive skills of 30- to 155-month-old children. To confirm the standardized scores on the mental processing scales in children, age-appropriate subtests from this battery were used. All participants had normal hearing according to their available medical records; i.e., they had never been noted to have a problem with hearing in a mass screening of 3-year-olds, and they displayed no problem with hearing in their daily lives. Left- or right-hand dominance was determined based on their preferences when handling objects, for both children with symptoms of hyperactivity (right = 14, left = 1, both = 2) and children without symptoms of hyperactivity (right = 16, both = 1). There were no significant differences in head circumference between the two groups.

The parents agreed to the participation of their child in the study with full knowledge of the experimental nature of the research. Written informed consent was obtained prior to participation in the study. The Ethics Committee of Kanazawa University Hospital approved the methods and procedures, all of which were performed in accordance with the Declaration of Helsinki. The demographic data for all participants are presented in Table 1.

2.2. Magnetoencephalography recordings

The conditions in the MEG recordings were identical to those detailed in our previous study (Yoshimura et al., 2012). MEG data were recorded using a 151-channel SQUID (Superconducting Quantum Interference Device), whole-head coaxial gradiometer MEG system for children (PQ 1151R; Yokogawa/KIT, Kanazawa, Japan) in a magnetically shielded room (Daido Steel, Nagoya, Japan) installed at the MEG Center of Ricoh Company, Ltd. (Kanazawa, Japan). The custom child-sized MEG system facilitates the measurement of brain responses in young children, which would otherwise be difficult using conventional adult-sized MEG systems. The child-sized MEG system ensures that the sensors are easily and effectively positioned for the child's brain and that head movements are constrained (Johnson et al., 2010). We determined the position of the head within the helmet by measuring the magnetic fields after passing currents through coils attached at 3 locations on the surface of the head, which served as fiduciary points relative to specific landmarks (the bilateral mastoid processes and nasion). An experimenter remained in the room to encourage the children and to prevent movement throughout the analysis. Stimuli were presented while the child was in a supine position on the bed and viewed video programs projected onto a screen.

2.3. Auditory-evoked field stimuli and procedures

The stimuli and procedure were based on our previous study (Yoshimura et al., 2012). MEG recordings were obtained from all participants during auditory syllable sound stimulation that comprised the Japanese syllable /ne/ (Yoshimura et al., 2012). We used this syllable because /ne/ is one of the Japanese final sentence particles, which convey prosodic information (Anderson et al., 2007; Cook, 1990). The syllable /ne/ is often used in Japanese mother-child conversations and expresses a speaker's request for acknowledgement or empathy from the listener (Kajikawa et al., 2004; Squires, 2009). In the present study, we used typical oddball sequences consisting of standard stimuli (456 times, 83%) and deviant stimuli (90 times, 17%). In the standard stimulus, /ne/ was pronounced with a steady pitch contour, whereas in the deviant condition, /ne/ was pronounced with a falling pitch. Eventually, we adopted

Table 1
Demographic characteristics of the study participants.

Group	ASD children with hyperactivity	ASD children without hyperactivity	*P* value
Number of subjects	17	18	
Age (±SD)	67.2 (9.9)	59.6 (15.9)	n.s.
Gender (M/F)	14/3	11/7	
K-ABC mental processing scale (±SD)	100.0 (±19.7)	90.0 (±20.9)	n.s.
ADOS			
Module 1 (at most single words)	n = 0	n = 4	
Communication + social (range)		11.6 (7–14)	
Module 2 (phrase speech)	n = 16	n = 14	
Communication + social (range)	12.33 (8–17)	10.7 (2−23)	n.s.
Module3 (fluent speech)	n = 1	n = 0	
Communication + social (range)	15.0		

K-ABC, Kaufman Assessment Battery for Children; TD, typically developing; ASD, Autism Spectrum Disorder; n.s., no significant difference (i.e., unpaired *t*-test between two groups, $P > 0.05$).

only standard stimuli for subsequent ECD estimations because a sufficient number of periods to calculate ECD remained after artifact rejection in all children. A female native Japanese speaker produced the /ne/ sounds, which were recorded using a condenser microphone (NT1-A; Rode, Silverwater, NSW, Australia) and a personal computer. As shown in Fig. 1, the duration of the stimulus was 342 ms, and the duration of the consonant /n/ was 65 ms. In this study, the beginning of the vowel sound /e/ was defined as the onset time. The inter-stimulus interval (ISI) was 818 ms. Each stimulus had an intensity level of approximately 65 dB (A-weighted) at the head position against a background noise of 43 dB. Intensity was measured using an integrating sound level meter (LY20; Yokogawa, Tokyo, Japan). The stimulus was presented to participants binaurally through a hole in the MEG chamber using speakers (HK195 Speakers; Harman Kardon, Stamford, CT) placed outside the shielded room. The recording was 12 min long.

2.4. AEF acquisition and analysis

The procedures for the AEF acquisition and analysis were identical to those in our previous study (Yoshimura et al., 2012). The band-pass-filtered MEG data (0.16–200 Hz) were collected at a sampling rate of 1000 Hz. The time series from the onset of the syllable stimulus at −150 to 1000 ms and subsequent segments (at least 120 for standard stimuli) were averaged for each sensor after baseline correction (−50 to 0 ms). Segments contaminated with artifacts (eye-blink and eye and body movements, typically more than ±4 pT) were excluded from the analysis. A single ECD model was used to estimate current sources in the activated cerebral cortex using >30 sensors for each hemisphere (left and right) (Elberling et al., 1982). MegLaboratory 160 software (Yokogawa/KIT, Kanazawa, Japan) was used to estimate the localization of the current sources.

To identify P1m, we accepted estimated ECDs when (i) the goodness of fit (GOF) exceeded 80%; (ii) the location of estimated dipoles using a single ECD model was stabilized within ±5 mm of each coordinate for at least 6 ms during the P1m response; (iii) the dipole amplitudes were ≤80 nAm; and (iv) ECDs predominantly had an anterosuperior direction. The latency time point was defined as the maximum estimated dipole amplitude value obtained in accordance with the above criteria within a time window of 20 to 150 ms. Regarding the P1m component coordinates, the center of a sphere as a spherical model of the volume conductor for the ECD estimation was defined as the origin, and the x-, y-, and z-coordinates represented the leftward direction, occipital direction, and vertex, respectively.

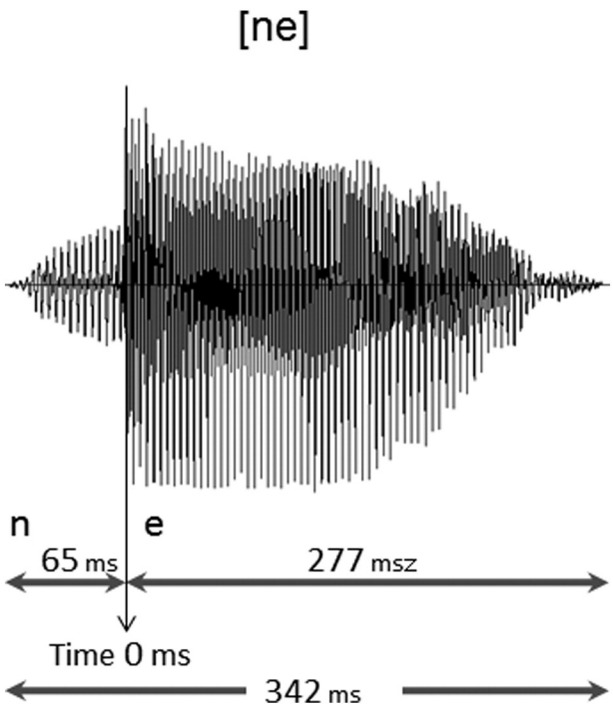

Fig. 1. Waveform of the /ne/ speech stimulus. The total duration was 342 ms, with 65 ms for the consonant /n/ and 277 ms for the post-consonantal vowel sound /e/. The onset time for MEG averaging was set at the start of the vowel.

2.5. Statistical analysis

Statistical analyses were conducted using SPSS for Windows statistical software, version 20.0 (IBM, Tokyo, Japan). As an indicator of the functional synchronization (i.e., the difference in P1m peak latency) between the right and left auditory responses, the following formula was used:

$$\text{Synchronization index} = 1 - |(\text{left} - \text{right}/\text{left} + \text{right})|$$

A value of 1 (maximum value) in the synchronization index indicates complete interhemispheric synchronization in P1m peak latency.

As an indicator of the functional lateralization (i.e., the difference of P1m peak latency) between the right and left hemispheres, the following formula was used:

$$\text{Laterality index} = (\text{left} - \text{right}/\text{left} + \text{right})$$

To test for differences between groups, unpaired *t*-tests were used. Because of the significant effect of age on the AEF latencies in young children (Edgar et al., 2015), we also performed analysis of covariance (i.e., ANCOVA) to include clinical variables (i.e., age, gender and cognitive skills as assessed by the K-ABC) as covariants.

Apart from the classification using the item 'overactivity' in the ADOS, we quantified the ability to keep still during a 12-min MEG recording session. We calculated a ratio (i.e., the number of the MEG segments during which children could keep still divided by the number of all MEG segments during 12 min of recording), and we used this ratio as an index of stillness. For all children with ASD, Pearson's correlation was used to find significant correlations between P1m synchronization index or laterality index and index of stillness. In addition, we evaluated the existence of a possible age, gender or cognitive skills effect via multiple linear regressions to predict the P1m synchronization index or laterality index (i.e., dependent variable), using the index of stillness, age, gender and cognitive skills as predictors (i.e., three independent variables). The significance level was set at $P < 0.05$.

In the present study, if there were significant findings in these analyses, as a complementary analysis, further analysis were performed using the data from 34 TD children (Table S1).

3. Results

3.1. P1m component (Fig. 2)

For the ASD group with symptoms of hyperactivity, we were able to detect the P1m component in the left hemisphere in all children (n = 17), in the right hemisphere in 15 out of 17 children, and in both hemispheres in 15 out of 17 children. For the ASD group without symptoms of hyperactivity, we were able to detect the P1m component in the left hemisphere in 17 out of 18 children, in the right hemisphere in 17 out of 18 children, and in both hemispheres in 16 out of 18 children. In ASD children with hyperactivity, 332 ± 93 (mean ± SD) segments were used for analysis. In ASD children without hyperactivity, 353 ± 67 (mean ± SD) segments were used for analysis. There was no significant difference in the number of segments between the two groups.

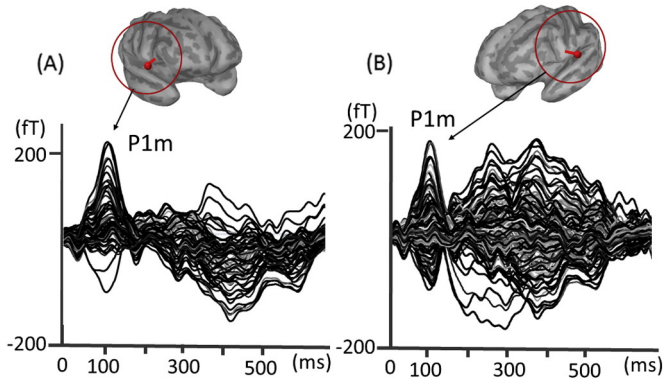

Fig. 2. Waveform of P1m (a) and dipole source in auditory cortex (b). The red sphere indicates the dipole source, and the red bar indicates the direction of the current source. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

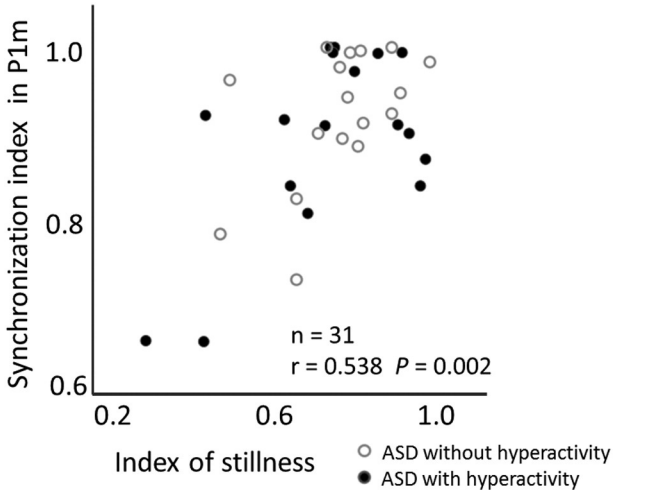

Fig. 3. Scatter plot showing strong positive linear correlation between the synchronization index in P1m and the index of stillness during MEG recording in 31 children with ASD. Children with ASD who were able to keep still during 12 min of MEG recording showed higher interhemispheric synchronization in the P1m peak latency.

3.2. P1m latency

For the ASD group with symptoms of hyperactivity, the P1m dipole latency was 80 ± 16 and 71 ± 24 (mean ± SD) in the left and right hemispheres, respectively. For the ASD group without symptoms of hyperactivity, the dipole latency was 81 ± 24 and 84 ± 20 (mean ± SD) in the left and right hemispheres, respectively. There is no significant difference for either hemisphere between ASD groups with and without symptoms of hyperactivity (left: $t = -0.195$, $P = 0.849$; right: $t = -1.562$, $P = 0.128$). According to the analysis of covariance (i.e., ANCOVA), which included age, gender and cognitive skills, the difference between the two groups did not reach statistical significance either for the left P1m latency ($F = 0.127$, $P = 0.724$) or for the right P1m latency ($F = 1.174$, $P = 0.288$).

3.3. Comparison of right-left hemispheric synchronization of P1m latency

There was no significant difference between the ASD group with symptoms of hyperactivity and the ASD group without symptoms of hyperactivity in P1m right-left hemispheric synchronization ($t = 0.799$, $P = 0.430$). ANCOVA addressing age, gender and cognitive skills revealed no significant difference between these two groups ($F = 0.226$, $P = 0.638$).

Pearson's correlation revealed significant correlations between the synchronization index in the P1m latency and the index of stillness ($n = 31$ $r = 0.538$, $P = 0.002$) (Fig. 3). In the multiple regression model to predict the synchronization index (i.e., dependent variable) using the index of stillness, age, gender and cognitive skills as predictors (i.e., four independent variables), the index of stillness was the significant predictor of the synchronization index ($\beta = 0.542$, $P = 0.003$), whereas age ($\beta = -0.156$, $P > 0.05$), gender ($\beta = -0.008$, $P > 0.05$) and cognitive skills ($\beta = 0.062$, $P > 0.05$) did not reach statistical significance. As a complementary analysis, we excluded 4 subjects with ambidexterity or left-handedness from the analysis. Analysis of only the right-handed participants showed no significant difference between the ASD groups with and without symptoms of hyperactivity in P1m right-left hemispheric synchronization ($t = 0.844$, $P = 0.407$). Pearson's correlation revealed significant correlations between the synchronization index and the index of stillness ($n = 27$ $r = 0.553$, $P = 0.003$). In the multiple regression model used to predict the synchronization index (i.e., dependent variable), with the index of stillness, age, gender and cognitive skills as predictors (i.e., four independent variables), the index of stillness was the only significant predictor of the synchronization index ($\beta = 0.562$, $P = 0.005$); age ($\beta = -0.158$, $P \geq 0.05$), gender ($\beta = 0.038$, $P \geq 0.05$) and cognitive skills ($\beta = 0.016$, $P \geq 0.05$) did not reach statistical significance. As a further complementary analysis, if we included the data from TD children (Table S1), within all participants (i.e., 34 TD and 31 ASD children), Pearson's correlation revealed significant correlations between the synchronization index in P1m latency and the index of stillness ($r = 0.340$, $P = 0.006$) (Fig. S1). In the multiple regression model to predict the synchronization index (i.e., dependent variable) using the index of stillness, age, gender and cognitive skills as predictors (i.e., four independent variables), the index of stillness was the significant predictor of the synchronization index ($\beta = 0.352$ $P = 0.005$), whereas age ($\beta = -0.082$, $P > 0.05$), gender ($\beta = -0.095$, $P > 0.05$) and cognitive skills ($\beta = -0.011$, $P > 0.05$) did not reach statistical significance.

3.4. Comparison of right-left functional lateralization of P1m latency

We compared the P1m functional laterality index (i.e., latency) between the ASD children with symptoms of hyperactivity and the ASD children without symptoms of hyperactivity. An unpaired *t*-test showed a significant difference between the ASD groups with and without symptoms of hyperactivity ($t = 2.151$, $P = 0.040$); i.e., the P1m latency in the right hemisphere was significantly shorter than that in the left hemisphere in the ASD group with a symptom of hyperactivity. However, if we included clinical variables (i.e., age, gender and cognitive skills as assessed by the K-ABC) as covariance in the analysis of covariance (i.e., ANCOVA), the difference between the two groups did not reach statistical significance ($F = 3.664$, $P = 0.067$). Pearson's correlation revealed no significant correlations between the laterality index in the P1m latency and the index of stillness ($r = -0.229$, $P > 0.05$). In the multiple regression model used to predict the lateralization index (i.e., dependent variable) based on the index of stillness, age, gender and cognitive skills as predictors (i.e., four independent variables), the index of stillness was not a significant predictor of the lateralization index ($\beta = -0.233$ $P = 0.231$). Notably, age ($\beta = 0.211$, $P \geq 0.05$), gender ($\beta = 0.028$, $P \geq 0.05$), and cognitive skills ($\beta = -0.494$, $P \geq 0.05$) also did not reach statistical significance.

As a complementary analysis, if we included the data from TD children (Table S1), within all participants (i.e., 34 TD children, 15 ASD children with hyperactivity and 16 without hyperactivity), one-way ANOVA of the laterality index failed to demonstrate significant differences between the three groups ($F = 2.952$, $P = 0.059$). ASD children with hyperactivity tended to show shorter P1m latency in the right hemisphere compared with TD and ASD children without hyperactivity (Fig. S2).

4. Discussion

The present study is the first study to demonstrate that interhemispheric synchronization (i.e., latency) of the voice-evoked P1m is related to the ability of ASD children to keep still in an experimental environment. Our custom-sized MEG system for children enables us to analyze bilateral AEFs simultaneously, which would be difficult to perform using conventional adult-sized MEG systems. Based on the result of a previous study (Seither-Preisler et al., 2014), we hypothesized that ASD children with symptoms of hyperactivity would show a right-left hemispheric asynchrony of voice-evoked P1m latency compared with ASD children without symptoms of hyperactivity. Although we failed to demonstrate a significant difference in the P1m right-left hemispheric synchronization between ASD children with and without symptoms of hyperactivity as evaluated by the ADOS subscale, we did uncover new findings that higher interhemispheric synchronization of the P1m is related to the ability of ASD children to keep still. Although the index of stillness is not an index of ADHD, as shown in Table 2, all 3 children who scored in the lowest 10% of the index of stillness were classified as showing hyperactivity as when evaluated using the ADOS subscale. Therefore, it is thought that the index of stillness during MEG measurement may be a suitable behavioral index for measuring overactivity during other conditions for young children with ASD.

Lower interhemispheric functional synchronization observed in the present study might be due to two possible neurophysiological mechanisms in ADHD. One is that lower interhemispheric functional connectivity, which has been reported in ADHD subjects (Cao et al., 2010; Clarke et al., 2008; Onnink et al., 2015), might contribute to the aberrant interhemispheric synchronization in our study. The other is that unbalanced lateralized maturation of the brain might contributed to the aberrant interhemispheric synchronization in our study. We investigated the relationship between the P1m functional lateralization (i.e., latency) and hyperactivity in children with ASD. If we did not consider the confounding factors (i.e., age, gender and cognitive skills as assessed by the K-ABC), the shorter P1m latency in the right hemisphere relative to that in the left hemisphere is associated with comorbidity of hyperactivity in children with ASD. Our current finding is consistent with the result of the previous study (Seither-Preisler et al., 2014), which showed that the low synchronization group (i.e., the low musical practice group and the ADHD group) showed an earlier P1m latency in the right hemisphere than in the left hemisphere. Given that the decreasing latency of the P1m to auditory stimuli is a result of brain maturation (i.e., myelination) (Ponton et al., 2002), the right hemispheric dominance (or the left hemispheric recessiveness) in the brain's maturity might be associated with the comorbidity of hyperactivity in children with ASD. However, after the consideration of the confounding factors (i.e., age, gender and cognitive skills as assessed by the K-ABC), our result did not quite reach statistical significance in the P1m laterality index.

Recent studies have reported the atypical lateralization of auditory evoked response magnitude to speech in children with ASD (Eyler et al., 2012; Seery et al., 2013; Stroganova et al., 2013; Yoshimura et al., 2013). Seery et al. (2013) showed that at 6–12 months, children with a low risk for ASD displayed a lateralized response to speech sounds, whereas the children at risk for ASD failed to display this lateralized response. These results suggested that atypical lateralization to speech may be an ASD endophenotype. Our findings also suggested that, as shown in Fig. S2, the comorbidity of hyperactivity is one of the factors that contributes to the diversified brain lateralization in children with ASD.

The present study had some general limitations. First, we investigated the P1m using only one type of auditory stimulus (a human voice saying "/ne/"). Therefore, we cannot generalize our findings to any other type of auditory stimulation, and we cannot conclude whether the hemispheric asymmetry reflected the "acoustic salience", "phonological salience" and/or "semantic salience" of 'ne'. Second, only a weak significant difference was found in the results from laterality analysis. In addition, when we considered covariance (i.e., age, gender and cognitive scale), the difference between the two groups did not quite reach statistical significance. Further studies with larger sample sizes are necessary. Third, previous reports have indicated that in addition to alterations in cortical auditory processes, the ASD population exhibits increased rates of brainstem or peripheral hearing dysfunction (Demopoulos and Lewine, 2015; Hitoglou et al., 2010; Rosenhall et al., 2003; Roth et al., 2012). Dysfunctions in both peripheral and central auditory processing also distort the cortical AEF components. Therefore, further studies, including analyses of brainstem function and fine peripheral hearing function, are necessary. Fourth, we cannot compare the anatomical characteristics of the auditory cortex (i.e., Heschl's gyri) between ASD children with and without symptoms of hyperactivity because it was difficult to perform the MRI measurement in preschool-aged children. Finally, replication of these findings is necessary to validate the robustness of this novel index (i.e., the index of stillness). Despite these limitations, this is the first study to suggest that asynchrony in the bilateral brain auditory processing system is associated with ADHD-like symptoms in children with ASD.

Table 2
The presence or absence of hyperactivity in the ADOS classification in three thresholds of the "index of stillness".

	Hyperactive (number of participants)	Non-hyperactive (number of participants)
Index of stillness (lowest 10%)	3	0
Index of stillness (lowest 20%)	5	2
Index of stillness (lowest 30%)	6	4

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.07.009.

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