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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

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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.

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## 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, inter-stimulus interval.

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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, $P > 0.05$).

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