ORIGINAL RESEARCH

# Associations between the mismatch-negativity component and symptom severity in children and adolescents with attention deficit/hyperactivity disorder

Kazuhiko Yamamuro[1]
Toyosaku Ota[1]
Junzo Iida[2]
Yoko Nakanishi[1]
Naoko Kishimoto[1]
Toshifumi Kishimoto[1]

[1]Department of Psychiatry, [2]Faculty of Nursing, Nara Medical University School of Medicine, Kashihara, Japan

Correspondence: Kazuhiko Yamamuro
Department of Psychiatry, Nara Medical University School of Medicine, 840 Shijo-cho, Kashihara, Nara 634 8522, Japan
Tel +81 74 422 3051
Fax +81 74 422 3854
Email muro@naramed-u.ac.jp

**Aim:** Cognitive impairment is an important predictor of functional outcome in patients with attention deficit/hyperactivity disorder (ADHD). However, the neurophysiology of ADHD-related cognitive impairments remains unclear. Event-related potentials (ERPs) represent the noninvasive measurement of neural correlates of cognitive function. Mismatch negativity (MMN) is an ERP component that is presumed to index the preattentive monitoring of changes in the auditory environment.

**Materials and methods:** Previous studies have shown altered MMN amplitude and latency in patients with ADHD. However, little is known about the relationship between MMN and ADHD-symptom severity. To address this, we measured the amplitude and latency of MMN in ERPs and assessed correlations with the clinical severity of ADHD, as measured by the ADHD Rating Scale IV – Japanese version. Participants were 51 treatment-naïve children and adolescents with ADHD (mean age 10.42±3.35 years) and 15 normally developing age- and sex-matched children (mean age 11.8±3.36 years).

**Results:** In the ADHD group, MMN amplitudes were attenuated at the central electrode and MMN latencies prolonged at the parietal electrode (Pz) relative to those in the control group. Furthermore, MMN amplitudes at Pz were negatively correlated with ADHD full-scale and hyperactivity–impulsivity and inattention subscale scores, and MMN latency at Pz was positively correlated with ADHD hyperactivity–impulsivity subscale scores.

**Conclusion:** Our data suggest that MMN reflects the severity of ADHD symptoms in children and adolescents, and provides support for the use of ERPs in evaluating ADHD symptoms in patients.

**Keywords:** attention deficit/hyperactivity disorder, event-related potentials, mismatch negativity, symptom severity, relationship

## Introduction

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent condition in children and adolescents that is characterized by inattention, hyperactivity, impulsivity, and abnormalities in one or more cognitive processes. With regard to cognitive abnormalities, children with ADHD have difficulties inhibiting responses, and consequently tend to make more errors. These deficits are similar to those reported for patients with frontal lobe lesions.[1,2] Indeed, several neuroimaging studies have reported that deficits in inhibitory control are associated with structural and functional disorganization with respect to the connectivity between the basal ganglia and the prefrontal cortex (PFC) in individuals with ADHD.[3,4]

Event related potentials (ERPs) represent a sensitive, non-invasive reflection of covert brain activity. ERPs are obtained by measuring voltage fluctuations in electroencephalography (EEG) data, time-locked to an event of interest. The P300 is a well-characterized late-ERP component that has been implicated in various psychiatric disorders. It is thought to reflect executive and attentional function, including the updating of working memory, event categorization, and attentional reorientation.[5] Previous studies have reported that the P300 amplitude is lower in children with ADHD compared with control participants.[6–9] In addition, several studies have reported that the latency of the P300 is longer in children with ADHD compared with controls.[9,10] Previously, our group examined the P300 component in treatment-naïve children and adolescents with ADHD during an auditory oddball task, and found a positive correlation between ADHD-subscale rating and P300 amplitude at the central electrode (Cz), as well as P300 latency at the frontal electrode (Fz), Cz, and the parietal electrode (Pz).[11] These data suggest that the characteristics of P300 can be correlated with the severity of ADHD symptoms in patients. However, the P300 may reflect a late stage of the inhibitory process,[12] and is thus likely to be affected by preceding cognitive factors. For this reason, mismatch negativity (MMN), which is a pre-P300 component that provides an index of preattentive auditory sensory memory function, has become the focus of recent research. MMN is thought to reflect information processing more accurately than the P300, and is closely related to attention deficits. MMN is generated in response to occasional variations (eg, duration, frequency, intensity) in acoustic stimuli, and occurs about 100–200 ms after the onset of deviant stimulation, with peak amplitudes observed at the frontocentral leads.[13,14] Additionally, MMN reflects an automatic cerebral discrimination process that is not under attentional control.[15] Several studies have demonstrated that methylphenidate, an ADHD medication, normalizes decreased MMN amplitudes in children with ADHD.[16] Correspondingly, Sawada et al reported a correlation between ADHD severity and MMN components in children with pervasive developmental disorder with ADHD-like symptoms.[17] However, no studies have directly examined whether MMN amplitude and latency vary according to the severity of ADHD symptoms in ADHD-only patients.

To address this, we evaluated the relationship between changes in MMN and the severity of ADHD symptoms in treatment-naïve children and adolescent patients with ADHD. We hypothesized that more severe ADHD symptoms would be associated with lower MMN amplitude and longer MMN latency. To our knowledge, our study is the first to investigate direct correlations among MMN amplitude, latency, and symptom severity in children and adolescents with ADHD.

## Materials and methods
### Participants
We recruited 51 patients with ADHD (41 boys, mean age 9.74±3.08 years, and ten girls, mean age 13.2±3.5 years) from the outpatient clinic at the Department of Psychiatry at Nara Medical University, Japan (Table 1). We recruited 15 healthy individuals (eleven boys, mean age 11.8±2.77 years, and four girls, mean age 11.8±3.77 years) as controls. We confirmed the absence of psychiatric illness in the control group using a standard clinical assessment that included a psychiatric evaluation and a structured diagnostic interview (Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) Axis Disorders Nonpatient Edition). This study was approved by the Institutional Review Board at Nara Medical University and carried out in accordance with the Declaration of Helsinki. All study participants or their legal guardians provided written informed consent for participation prior to initiation of the study.

Patients were deemed eligible for inclusion if they had a diagnosis of ADHD according to the DSM-IV-Text Revision (DSM-IV-TR) as described in the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version,[18] as evaluated by one or more experienced psychiatrists. Exclusion criteria were as follows: presence of a neurological disorder, head injury, serious medical condition, or history of substance abuse/dependence. A trained psychologist assessed intelligence using the Wechsler Intelligence Scale for Children, fourth edition,

**Table 1** Participant characteristics

| | Controls | | Patients with ADHD | | t-value | P-value |
|---|---|---|---|---|---|---|
| | n=15 | | n=51 | | | |
| | Mean | SD | Mean | SD | | |
| Sex (boy/girl) | 11/4 | | 41/10 | | | 0.97 |
| Age (years) | 11.8 | 3.36 | 10.41 | 3.35 | −0.63 | 0.26 |
| FIQ (WISC-IV) | 100.07 | 10.67 | 92 | 12.57 | −0.68 | 0.25 |
| ARF | NA | NA | 27.37 | 14.35 | NA | NA |
| ARH | NA | NA | 11.57 | 8.13 | NA | NA |
| ARI | NA | NA | 15.8 | 7.59 | NA | NA |

**Abbreviations:** ADHD, attention deficit/hyperactivity disorder; SD, standard deviation; FIQ, full-scale intelligence quotient; WISC-IV, Wechsler Intelligence Scale for Children – fourth edition; ARF, ADHD Rating Scale IV – Japanese version full; ARI, ADHD Scale IV – Japanese version inattention subscale; ARH, ADHD Rating Scale IV – Japanese version hyperactivity–impulsivity subscale; NA, not applicable.

and participants with a full-scale intelligence quotient (FIQ) score below 70 were also excluded. None of the included participants had comorbid obsessive–compulsive disorder, major depressive disorder, schizophrenia, or epilepsy. Five patients had comorbid autism-spectrum disorder, one patient had comorbid tic disorder, and one patient had comorbid conduct disorder. All patients included were naïve to medical treatment.

## Assessment of ADHD symptoms

We evaluated ADHD symptoms and symptom severity in all patients using the ADHD Rating Scale IV – Japanese version (ADHD-RS-IV-J) of the ADHD-RS-IV – home version.[19] The ADHD-RS-IV-J is an 18-item scale based on the DSM-IV-TR, and is reliable and easy to administer for the assessment of ADHD symptoms. Each statement on the ADHD-RS-IV-J is rated on a 4-point Likert scale (never or rarely, sometimes, often, or very often), and the scale yields an ADHD-RS-IV-J full (ARF) score, an ADHD-RS-IV-J inattention subscale (ARI) score, and an ADHD-RS-IV-J hyperactivity–impulsivity subscale (ARH) score, where higher scores represent more severe ADHD symptoms.

## Measurement of ERPs

Based on guidelines for the measurement of evoked potentials, we elicited MMN components using an auditory oddball task.[20] We used a Multi Stim II auditory stimulus system (NEC, Tokyo, Japan) to present stimuli to both ears of the participants through headphones. Standard stimuli were 1,000 Hz tone bursts ($P=0.9$), and deviant stimuli were 1,100 Hz bursts ($P=0.1$). Stimuli were presented for 50 ms at 500 ms intervals and at 80 dB intensities. Frequent and infrequent stimuli were presented in a randomized fashion. MMN components were measured while participants read books or magazines of their choice. The participants were asked not to pay attention to the auditory stimuli.

## Recording and analyses

ERPs were recorded with an MEB 2200 evoked potential-measuring system (Nihon Kohden, Tokyo, Japan). EEG readings were recorded at the Fz, Cz, Pz, C3, and C4 positions on the scalp using disk electrodes. All electrodes were re-referenced off-line to the average of two mastoid electrodes. Electrode impedance was set to ≤5 kΩ. MMN was analyzed between the 50 ms prestimulus and the 360 ms poststimulus. Artifact-free responses to stimuli were summated and averaged for EEG-amplitude data ≥100 µV. To reduce high-frequency content irrelevant to the components of interest, a digital 0.5–70 Hz band-pass filter

(attenuation by 12 dB/octave) was applied to all data prior to analysis. Finally, data were corrected for eye-movement artifacts.[21]

The duration of each auditory oddball task was 250 seconds, and infrequent and frequent stimuli were presented 50 and 450 times, respectively. The sample rate was 5,000 Hz. The 450 responses to frequent standard stimuli and the 50 responses to infrequent deviant stimuli were averaged separately, and a waveform was calculated as the difference between the averaged waveforms (frequent minus infrequent). The MMN was identified from the difference waveform as a negative wave with a peak latency between 100 ms and 250 ms, and its latency and amplitude were recorded. To prevent participants from habituating to the stimuli, each trial was conducted only once.

## Statistical analyses

Statistical calculations were conducted with the assistance of PASW Statistics 18.0 J for Windows (SPSS, Chicago, IL, USA). Data are expressed as means ± standard deviation (SD). We calculated Spearman's correlation coefficient ($\rho$) for the relationships between ADHD-RS-IV-J scores (including ARF, ARI, and ARH subscale scores) and electrophysiological variables. Bonferroni-adjusted $P$-values are reported. $P$-values <0.05 were considered to be statistically significant.

# Results
## Demographic data

Age, sex, FIQ, and ADHD-RS-IV-J scores, including ARF, ARI, and ARH subscale scores, are shown in Table 1. The participant groups did not differ in terms of mean age ($t=-0.63$, $df=64$; $P=0.26$), sex ($\chi^2=0.01$, $df=1$; $P=0.97$), or FIQ ($t=-0.68$, $df=64$; $P=0.25$). The mean ARF, ARH, and ARI subscale scores of patients with ADHD were 27.37 (SD 14.35, range 6–51), 11.57 (SD 8.13, range 0–26), and 15.8 (SD 7.59, range 2–27), respectively.

## Comparison of MMN-component characteristics between patients with ADHD and control participants

Consistent with previous reports,[10,22,23] we found that the grand average of the MMN amplitude in the ADHD group was significantly smaller than that in the control group at Cz ($t=-1.97$, $df=64$; $P<0.05$). Also, we found that the grand average of the MMN latency in the ADHD group was significantly longer than that in the control group at Pz ($t=-2.33$, $df=64$; $P<0.05$) (Table 2 and Figure 1).

**Table 2** MMN amplitudes and latencies

| | Controls | | Patients with ADHD | | t-value | P-value |
|---|---|---|---|---|---|---|
| | n=15 | | n=51 | | | |
| | Mean | SE | Mean | SE | | |
| **MMN amplitude (μV)** | | | | | | |
| Fz | 7.57 | 4.58 | 6.73 | 5.98 | −1.38 | 0.09 |
| Cz | 6.3 | 4.08 | 5.23 | 5.57 | −1.97 | <0.05 |
| Pz | 5.25 | 3.81 | 3.94 | 3.86 | −1.65 | 0.05 |
| **MMN latency (ms)** | | | | | | |
| Fz | 174.67 | 23.16 | 192.32 | 33.26 | −0.36 | 0.36 |
| Cz | 172.49 | 20.22 | 194.69 | 34.60 | −1.24 | 0.11 |
| Pz | 173.91 | 23.05 | 193.52 | 34.83 | −2.33 | <0.05 |

**Abbreviations:** MMN, mismatch negativity; ADHD, attention deficit/hyperactivity disorder; SE, standard error; Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode.

## Correlation between MMN-component characteristics and ADHD-RS-IV-J subscale scores

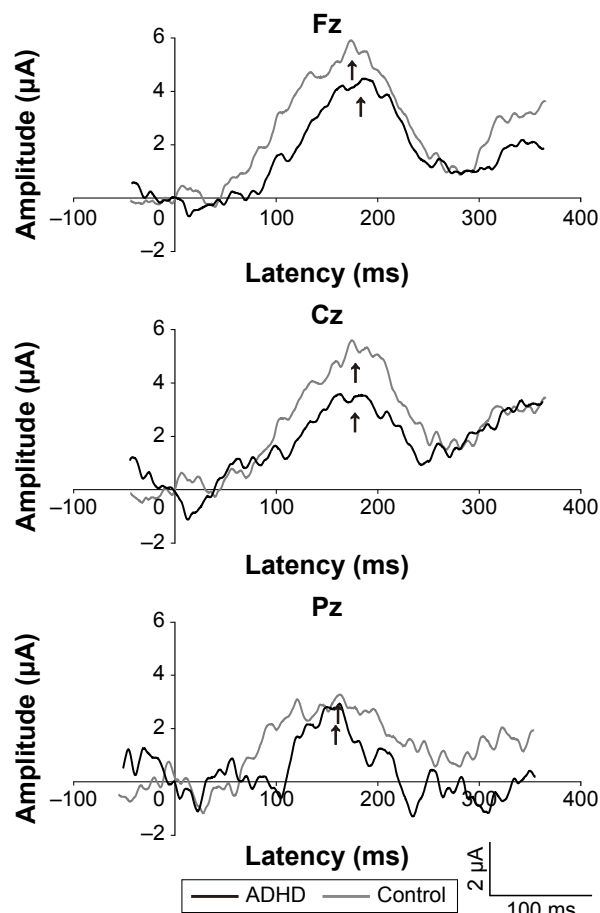We calculated Spearman correlation coefficients (with Bonferroni-adjusted P-values) for MMN amplitude and



**Figure 1** Mismatch negativity (MMN) grand-average waveforms from children and adolescents with attention deficit/hyperactivity disorder (ADHD) and healthy controls.
**Notes:** Black lines represent the ADHD group, gray lines represent the control group, and MMN amplitudes are indicated by arrows.
**Abbreviations:** Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode.

latency, as well as ADHD-RS-IV-J subscale scores (Table 3 and Figures 2–4). We identified negative correlations between the amplitude of MMN at Pz and ARF ($\rho=-0.32$, Bonferroni-corrected $P<0.05$), ARH ($\rho=-0.322$, Bonferroni-corrected $P<0.05$), and ARI ($\rho=-0.295$, Bonferroni-corrected $P<0.05$) scores. Furthermore, we found positive correlations between ARH scores and MMN latency at Pz ($\rho=0.33$, Bonferroni-corrected $P<0.05$).

## Discussion

To the best of our knowledge, this is the first study to investigate the relationship between MMN characteristics and the clinical severity of ADHD in treatment-naïve children and adolescents. As mentioned, MMN is produced in the frontal cortex in association with shifts in attention following the automatic detection of changes in stimuli by the auditory cortex.[24,25] Accordingly, MMN is a preattentive ERP component. Indeed, MMN amplitudes have been suggested to reflect preattentive cognitive operations.[26] Previous studies have indicated that MMN has reduced amplitude and prolonged latency in children with ADHD relative to control participants.[10,22,23] MMN abnormalities have also been reported in several psychiatric disorders, including schizophrenia,[27] bipolar affective disorder,[28] and major depression.[29] Furthermore, MMN has been posited as an index of general cognitive decline in a broad spectrum of clinical disorders.[13] Our data are in agreement with these findings: in the present study, we observed that reductions in the MNN amplitude at Pz correlated with ADHD-symptom severity, as measured by the scores for all subscales of the ADHD-RS-IV-J. Additionally, the MMN latency at Pz was positively correlated with the severity of hyperactivity–impulsivity symptoms, suggesting that MMN latency may

**Table 3** Correlations between ERP components and ADHD-RS-IV-J scores

| | Spearman's correlation | | |
|---|---|---|---|
| | **ARF** | **ARH** | **ARI** |
| **MMN amplitude (μV)** | | | |
| Fz (n=51) | −0.019 | 0.059 | −0.001 |
| Cz (n=51) | −0.017 | 0.04 | 0.016 |
| Pz (n=45) | −0.320* | −0.322* | −0.295* |
| **MMN latency (ms)** | | | |
| Fz (n=51) | 0.122 | 0.235 | 0.001 |
| Cz (n=51) | 0.059 | 0.208 | −0.068 |
| Pz (n=45) | 0.184 | 0.330* | 0.123 |

**Notes:** *$P<0.05$. Spearman's correlation coefficients (with Bonferroni-adjusted P-values) were obtained separately for ERP components and ADHD-RS-IV-J scores.
**Abbreviations:** ERP, event-related potential; ADHD, attention deficit/hyperactivity disorder; ADHD-RS-IV-J, ADHD Rating Scale IV – Japanese version; ARF, ADHD Rating Scale IV-Japanese Version full; ARH, ADHD-RS-IV-J hyperactivity–impulsivity subscale; ARI, ADHD-RS-IV-J inattention subscale; MMN, mismatch negativity; Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode.
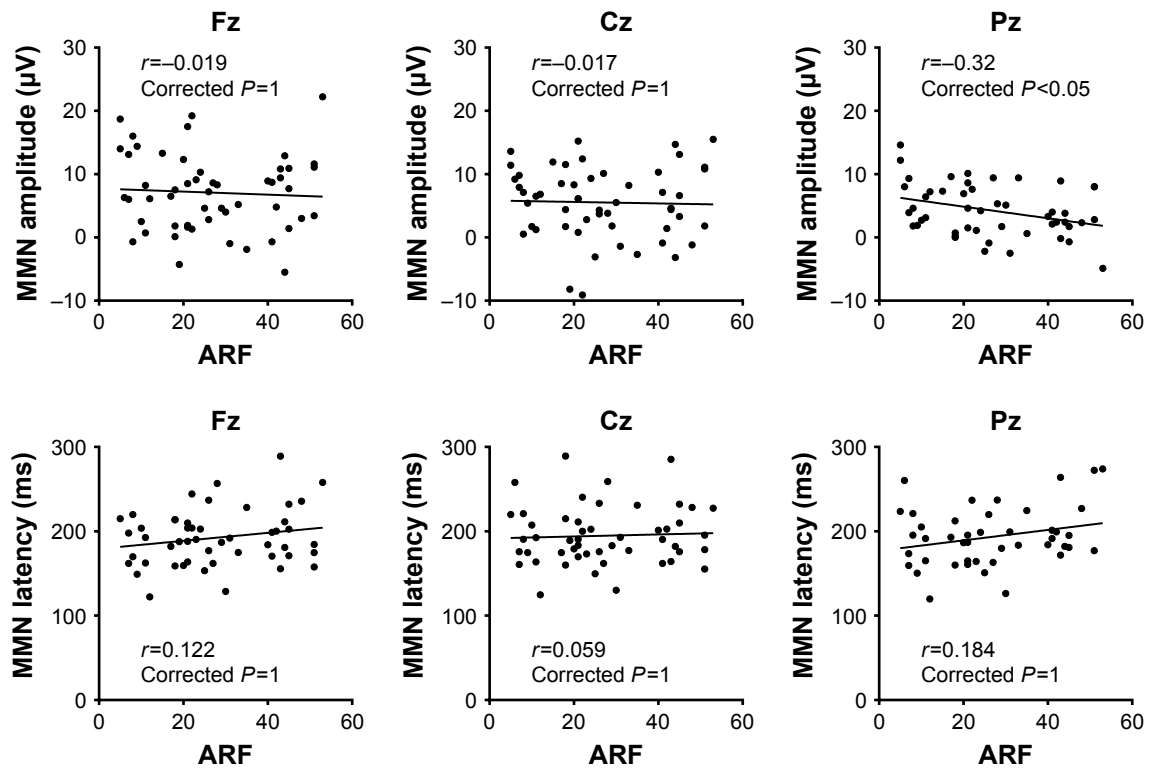
**Figure 2** Correlations between the mismatch negativity (MMN) component and ADHD Rating Scale IV – Japanese version full (ARF) scores.
**Note:** Spearman's correlation coefficient and the corresponding Bonferroni-adjusted *P*-value are indicated for each panel.
**Abbreviations:** ADHD, attention deficit/hyperactivity disorder; Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode; MMN, mismatch negativity; ARF, ADHD Rating Scale IV – Japanese version full.
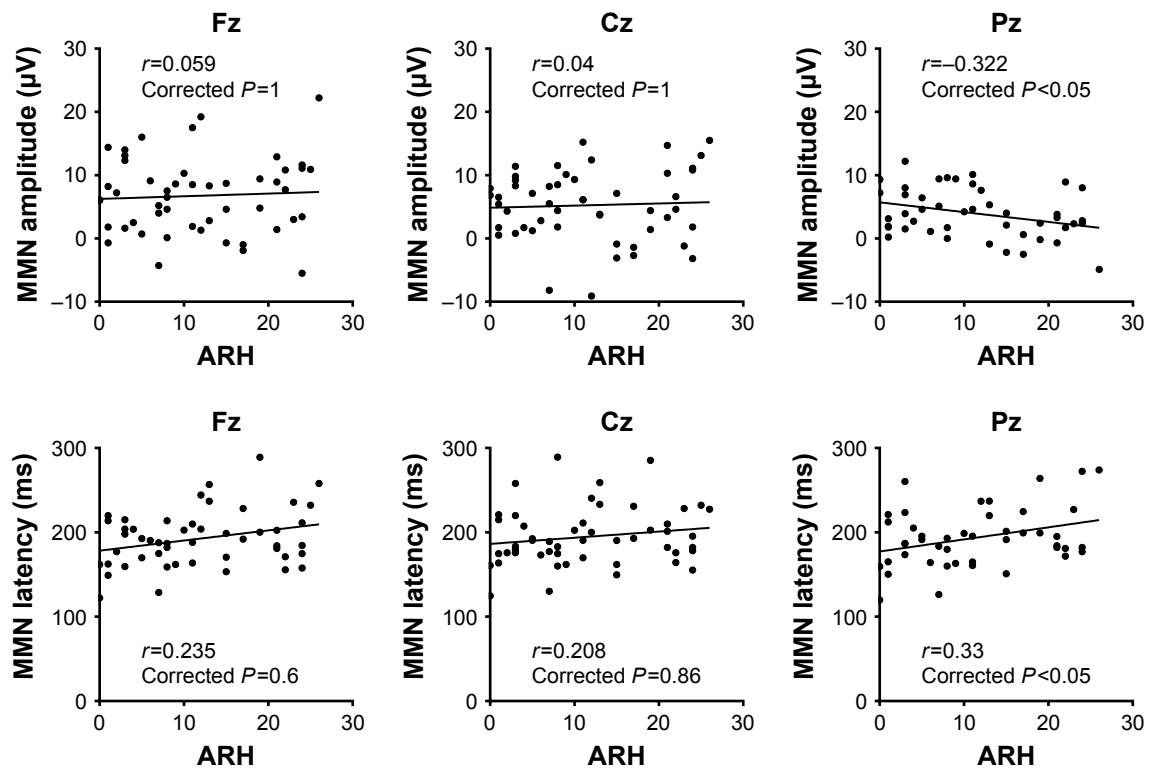


**Figure 3** Correlations between the mismatch negativity (MMN) component and ADHD Rating Scale IV – Japanese version hyperactivity–impulsivity subscale scores.
**Note:** Spearman's correlation coefficient and the corresponding Bonferroni-adjusted *P*-value are indicated for each panel.
**Abbreviations:** ADHD, attention deficit/hyperactivity disorder; ARH, ADHD Rating Scale IV – Japanese version hyperactivity–impulsivity subscale; Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode; MMN, mismatch negativity.
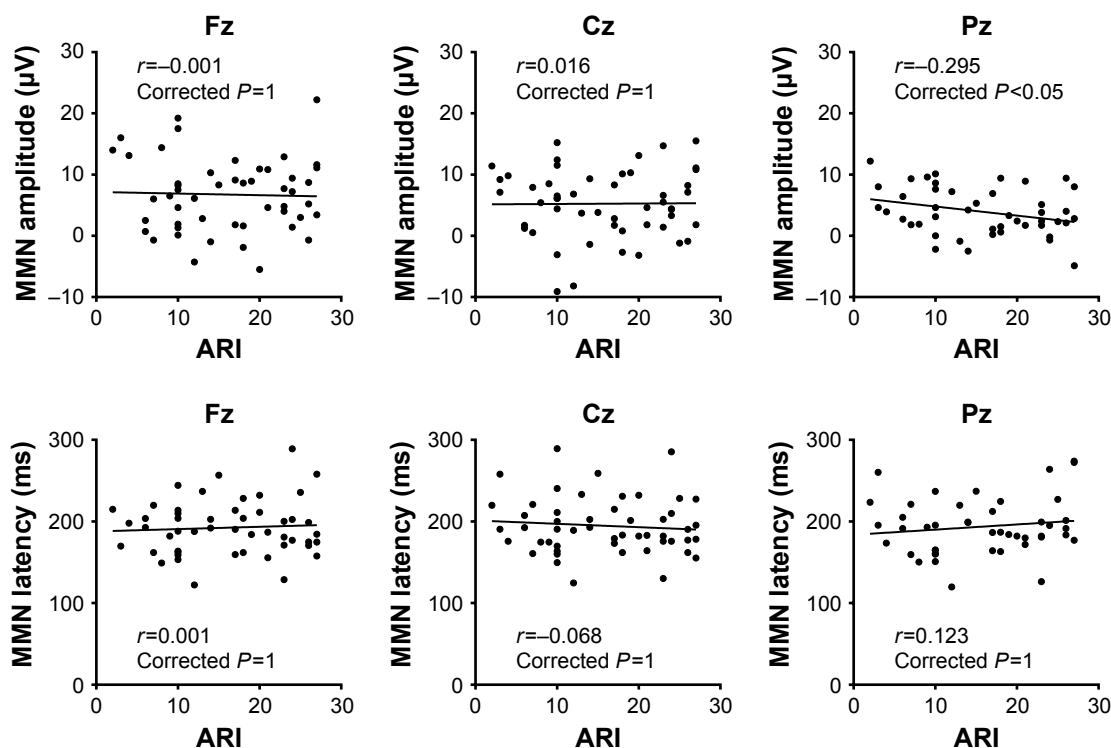
**Figure 4** Correlations between the mismatch negativity (MMN) component and ADHD Rating Scale IV – Japanese version inattention subscale scores.
**Note:** Spearman's correlation coefficient and the corresponding Bonferroni-adjusted *P*-value are indicated for each panel.
**Abbreviations:** ADHD, attention deficit/hyperactivity disorder; ARI, ADHD Rating Scale IV – Japanese version inattention-subscale; Fz, frontal electrode; Cz, central electrode; Pz, parietal electrode; MMN, mismatch negativity.

be a specific indicator of cognitive abnormality in children and adolescents with ADHD.

Neuropsychological theories of ADHD highlight the role of impaired frontal lobe function, especially in the PFC. Functional magnetic resonance imaging studies of patients with ADHD have indicated abnormal activity in the dorsolateral and ventrolateral PFC.[30,31] These findings are consistent with the observation that working memory, which is thought to primarily involve the PFC, is a core cognitive function that is affected in individuals with ADHD.[32] On the other hand, patients with ADHD have been found to have increased activity in the parietal lobe,[33,34] an area that plays a role in attention.[35] Our findings of significant correlations among MMN-component characteristics over the PFC and the clinical severity of ADHD symptoms emphasize the relevance of the PFC in ADHD.

In patients with schizophrenia, reports about a negative correlation between MMN amplitude and symptom severity have been inconsistent. However, MMN has been consistently associated with scores on the Global Assessment of Functioning scale[25,36,37] and other measurements of social and occupational status.[38,39] Sawada et al examined MMN components during an auditory oddball task in ten individuals with pervasive developmental disorder with

ADHD symptoms.[17] They found that scores on the ADHD-RS-IV-J tended to be positively associated with MMN latency and were significantly and strongly negatively correlated with MMN amplitude. We found that lower MMN amplitude and prolonged MMN latency were correlated with the severity of subdomains of the ADHD-RS-IV-J (ie, the ARH). These findings indicate that MMN may be a common index of preattentive auditory sensory memory function in several psychiatric disorders, including ADHD.

There are some limitations that should be taken into consideration when interpreting our findings. First, our sample size was relatively small, and six patients with ADHD had comorbid psychiatric illnesses, including autism-spectrum disorder (n=4), tic disorder (n=1), and conduct disorder (n=1). Future studies using a larger cohort are needed to validate our findings and to determine whether MMN-component characteristics can distinguish patients with ADHD from those with other neurodevelopmental disorders. Second, since our study evaluated ADHD symptoms using only the ADHD-RS-IV-J, future studies employing other neuropsychological tests would be helpful in increasing the strength of our hypothesis. Third, the methods employed in our study did not allow a focus on altered patterns of connectivity. Recently, functional magnetic resonance imaging studies have produced evidence supporting

the necessity of network integration during response inhibition, and have confirmed altered functional connectivity in individuals with ADHD.[40–42] Fourth, the MMN baseline interval used in our study was short, which might have reduced the reliability of the signal. However, our group has taken ERP measurements using this method during several investigations of psychiatric disorders,[17,43,44] and these findings were consistent with those of our previous studies. Given these limitations, future studies should be conducted to determine whether abnormalities in the frontal lobe are resultant from or causative of altered functional connectivity.

## Conclusion

The present study demonstrates that changes in MMN amplitude and latency can predict the severity of ADHD symptoms, and thus indicates that these may be important signals for the neurophysiological mechanisms underlying ADHD. Furthermore, our findings support the notion that ERPs represent a clinically useful and noninvasive method for estimating disease severity in children and adolescents with ADHD.

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## Author contributions

KY, TO, JI, YN, NK, and TK were involved in data collection and wrote the first draft of the manuscript. JI and TK supervised the entire project, were critically involved in study design, and contributed to the editing of the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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