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Original article

# Association of inattention with slow-spindle density in sleep EEG of children with attention deficit-hyperactivity disorder

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**Abstract**

*Objective:* We evaluated the power of slow sleep spindles during sleep stage 2 to clarify their relationship with executive function, especially with attention, in children with attention deficit-hyperactivity disorder (ADHD).

*Methods:* Subjects were 21 children with ADHD and 18 aged-matched, typically developing children (TDC). ADHD subjects were divided into groups of only ADHD and ADHD + autism spectrum disorder (ASD). We employed the Continuous Performance Test (CPT) to measure attention. We focused on sleep spindle frequencies (12–14 Hz) in sleep stage 2 and performed a power spectral analysis using fast Fourier transform techniques and compared sleep spindles with the variability of reaction time in CPT.

*Results:* In the CPT, reaction variabilities in ADHD and ADHD + ASD significantly differed from those in TDC. Twelve-hertz spindles were mainly distributed in the frontal pole and frontal area and 14-Hz spindles in the central area. The ratio of 12-Hz frontal spindle power was higher in ADHD than in TDC, especially in ADHD + ASD. Significant correlation between the ratio of 12-Hz spindles and reaction time variability was observed.

*Conclusions:* Twelve-hertz frontal spindle EEG activity may have positive associations with sustained attention function. Slow frontal spindles may be useful as a biomarker of inattention in children with ADHD.



*Keywords:* ADHD; Fast spindle; Inattention; Power spectrum; Electroencephalogram

## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders characterized by persistent patterns of inattention, hyperactivity, and/or impulsivity. The prevalence of ADHD in school-age children is approximately 5–10% [1]. According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), symptoms of ADHD must be observed in two different settings for 6 months or longer and to a degree that is greater than that observed in children of the same age. Additionally, ADHD often persists into adulthood, with resultant impairments in social, academic, and occupational functioning.

Moreover, the prevalence of sleep disturbances is reported to be 22 to 55% in patients with ADHD [2].

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In studies based on the perceptions of parents, children with ADHD are reported to be more prone to difficulties, such as in settling and going to sleep, sleep disruption, and tossing and moving during the night [3]. Studies using polysomnographic (PSG) recordings have revealed that patients with ADHD show a definite increase in nocturnal awakenings and reduced percentage of REM sleep in adulthood [4] and childhood [5]. In a study by Lecendreux et al, the subjects underwent PSG followed by the Multiple Sleep Latency Test (MSLT), and reaction times were measured during the day time. Children with ADHD were sleepier during the day, as shown by the MSLT, and they had longer reaction times [6]. Van der Heijden et al reported that ADHD-related sleep-onset insomnia was a circadian rhythm disorder with delayed sleep phase and delayed dim light melatonin onset [7]. These studies indicate that the patients with ADHD have poor sleep efficiency.

Sonuga-Barke et al. emphasized that the pathogenesis of ADHD may be elucidated by the triple pathway model, which involves executive dysfunction, delay aversion, and temporal processing deficits [8]. It is accepted that executive function is controlled by the prefrontal cortex. Recently, numerous studies have shown impairments across a wide range of frontal lobe functions in ADHD. For example, children with ADHD often have paroxysmal discharge at the frontal and Rolandic areas [9] and frontal paroxysmal discharge-related symptoms [10]. In studies with functional near infrared spectroscopy, hypo-oxygenation in children with ADHD has been reported during executive function tasks [11,12]. In a volumetric study, adults with ADHD had overall smaller cortical gray matter and prefrontal and anterior cingulate cortex volumes [13]. Thus, patients with ADHD may have both functional and structural abnormalities in the frontal cortex.

During sleep stage 2, sleep spindles are observed at the fronto-centro-parietal region from 12 Hz to 14 Hz. Sleep spindles play an important role in cognitive function in children because basal sleep spindle activity is associated with aspects of cognitive performance, such as narrative memory, sensorimotor functioning, planning abilities, and working memory [14]. Sleep spindles appear in two types of EEG frequency, i.e., the frontal-dominant 12-Hz slow spindles and the parietal-dominant 14-Hz fast spindles [15]. The sources of slow spindles were considered to be preferentially concentrated over the frontal cortices in low-resolution brain electromagnetic tomography (LORETA) analysis [16]. In a study of developmental change with slow and fast spindles, while centroparietal spindles showed little change in power from 4 to 24 years of age, frontal spindles remarkably decreased in power and became stable at approximately 13 years of age; this led the authors to conclude that frontal spindle activity could be a good indicator of central nervous system maturation [17]. The maturation period of frontal slow spindles is similar to that of frontal structural and functional development. Therefore, we hypothesized that frontal slow spindles could be used as an indicator to evaluate cognitive function, especially attention and/or executive function. Furthermore, we evaluated whether fontal spindles are biomarkers of inattention and executive dysfunction in children with ADHD.

## 2. Subjects

A total of 21 children with a primary clinical DSM-5 diagnosis of ADHD (mean age $9.07 \pm 1.79$ years) and 18 age-matched typically developing children (TDC) (nine boys and nine girls, mean age $9.55 \pm 1.58$ years) were recruited from the Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP) between April 2015 and September 2017. Children with ADHD and autism spectrum disorders (ASD) were diagnosed by pediatric neurologists based on the DSM-5 criteria. Among the children with ADHD, seven had comorbid ASD. Hence, the children with ADHD were separated into two groups, one with only ADHD (11 boys, mean age $8.82 \pm 1.48$ years) and the other with ADHD + ASD (eight boys and two girls, mean age $9.34 \pm 2.04$ years). All children with ADHD were naive for medical treatment and had neither neurological abnormal findings nor previous seizure history. Four children with only ADHD, four children with ADHD + ASD, and two TDC had epileptic discharges on their sleep EEG. To quantify the ADHD symptom presentations, we interviewed their parents using the Japanese version of Swanson, Nolan, and Pelham IV scale (SNAP-IV) [18]. To measure ASD symptoms, we employed the Parent-interview ASD Rating Scale (PARS-TR) (Table 1). The procedures for informed consent and the study design were approved by the Medical Ethical Committee of the NCNP (#A2014-114), and informed assent and consent were obtained from each participant and from the children's parents after full explanation of the procedures involved.

## 3. Methods

### 3.1. Neuropsychological tasks

Neuropsychological tasks included Raven's Colored Progressive Matrices (RCPM) as a measure of nonverbal intelligence, the Das-Naglieri Cognitive Assessment System (DN-CAS) as a measure of executive function, and the Mogras test (NoruPro Light Systems, Inc., Tokyo, Japan) with the Continuous Performance Test (CPT) as a measure of attention function. This test is a whack-a-mole type of game utilizing a PC monitor. We calculated the standard deviation (SD) from the

Table 1
Characteristics of subjects.

| | TDC | ADHD | ADHD + ASD | *p*-value | | |
|---|---|---|---|---|---|---|
| | | | | ADHD vs TDC | ADHD + ASD vs TDC | ADHD + ASD vs ADHD |
| Gender (M/F) | (9/9) | (11/0) | (8/2) | | | |
| Age (SD) | 9.6 (1.6) | 8.8 (1.5) | 9.3 (2.0) | 0.521 | 0.949 | 0.774 |
| *SNAP* | | | | | | |
| Inattention | 4.5 (2.9) | 16.1 (5.7) | 18.5 (5.7) | 0.001*** | 0.001*** | 0.495 |
| Hyperactivity/impulsivity | 2.1 (2.2) | 2.8 (5.9) | 8.9 (3.7) | 0.001*** | 0.001*** | 0.866 |
| Oppositional defiant | 2.9 (2.5) | 7.5 (5.4) | 10.0 (5.9) | 0.04* | 0.001*** | 0.429 |
| *PARS* | | | | | | |
| Retrospection | 1.3 (1.6) | 3.2 (4.4) | 9.7 (6.6) | 0.496 | 0.001*** | 0.004** |
| Present | 1.4 (1.5) | 6.1 (3.5) | 13.1 (5.0) | 0.003** | 0.001*** | 0.001*** |

TDC; typical development children, ADHD; attention deficit hyperactivity disorder, ASD; autism spectrum disorders, SNAP; Japanese version of Swanson, Nolan, and Pelham IV scale, PARS; Pervasive Developmental Disorders Autism Society Japan Rating Scale, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

mean age-specific RCPM scores as calculated by Uno A et al. (2005) and the mean age-specific error rates, reaction times, and variability of reaction times in the CPT as calculated by Inoue et al. [19].

### 3.2. Electroencephalography (EEG) recording and power spectrum analyses

For each subject, scalp EEG was recorded according to the international 10–20 system with a 19-electrodes montage (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz). An ear electrode linked to a 10-kΩ register was used as the reference lead. EEG channels were sampled at 500 Hz using Neurofax (Nihon Kohden Co, Tokyo, Japan). At least 3 child neurologists (YS, YK, MO, KK, MI) determined the sleep staging and sleep spindles in EEG. We extracted 5 min of EEG data starting 3 min after the first spindle was recorded in sleep stage 2 and analyzed the power spectrum with fast Fourier transform using EEG analytic software (EMSE Suite, Cortech Solutions Inc., Wilmington, NC). For the analysis of slow and fast spindles, the relative power (divided by all spectrum power) at both 12 Hz and 14 Hz was calculated. Patients who had difficulty sleeping were administered pentobarbital (1.25–2.5 mg/kg wt, Ravona tablets) or triclofos sodium (50–70 mg/kg wt, Tricroryl syrup). Medication to induce sleep was administered to all patients and two TDC.

### 3.3. Statistical analyses

We compared the neuropsychological and behavioral data among the three groups using one-way analysis of variance (ANOVA). Post-hoc analyses were then performed between each two groups using Tukey's method. EEG power spectrum analysis employed two-way ANOVA (EEG electrode, subjects), and used Turkey's method for comparing between each two groups. Pearson's correlation coefficients were determined to examine the associations between the neuropsychological tasks and the 12-Hz power spectrum analysis. All statistical analyses were conducted using SPSS version 19 (SPSS Japan, Tokyo, Japan). Significance was set at $p < 0.05$, $p < 0.01$, and $p < 0.001$.

## 4. Results

### 4.1. ADHD and ASD rating scales (Table 1)

Both ADHD behaviors in the SNAP-IV and ASD behaviors in the PARS-TR were significantly different among the three groups based on the ANOVA analysis. In the SNAP-IV, the scores of inattention, hyperactivity/impulsivity, and oppositional defiant disorder in the ADHD and ADHD + ASD groups were significantly higher than those in the TDC group as shown in Table 1. In the PARS-TR, the ADHD + ASD group showed significantly higher scores compared to the other groups (Table 1).

### 4.2. Neuropsychological testing

We used RCPM to ascertain that all subjects had normal intelligence. We calculated the standard deviation (SD) from the normal range for each age bracket [20]. The SD scores of all subjects were within a range of mean and mean minus 2.0 SD. In the DN-CAS, the scores of the ADHD and ADHD + ASD groups tended to be lower than those of the TDC group but there was no significant difference (Table 2). In the CPT, the variability of reaction times in the ADHD and ADHD + ASD groups were significantly different from those in the TDC group (ADHD, ADHD + ASD; $p < 0.05$, Table 2). Reaction times in the ADHD + ASD group were significantly longer than those in the TDC group

Table 2
Results of neuropsychological tests.

| | TDC | ADHD | ADHD + ASD | *p*-value | | |
|---|---|---|---|---|---|---|
| | | | | ADHD vs TDC | ADHD + ASD vs TDC | ADHD + ASD vs ADHD |
| RCPM (SD) | −0.38 (0.6) | −1.0 (1.2) | −1.5 (1.8) | 0.362 | 0.071 | 0.671 |
| DN-CAS Stroop (rate of score) | 50.2 (19.6) | 33.6 (19.0) | 36.3 (24.6) | 0.060 | 0.250 | 0.817 |
| *CPT* | | | | | | |
| Reaction time (SD) | −0.7 (0.9) | −0.4 (0.8) | 1.2 (2.2) | 0.839 | 0.006** | 0.048* |
| Variability of reaction (SD) | −0.3 (1.7) | 2.3 (2.6) | 2.4 (2.8) | 0.017* | 0.032* | 0.985 |
| Commission error (SD) | −0.3 (1.5) | 0.9 (1.2) | 1.2 (1.3) | 0.104 | 0.067 | 0.967 |
| Omission error (SD) | 0.03 (1.9) | 3.1 (3.8) | 3.7 (3.6) | 0.040* | 0.030* | 0.982 |

TDC; typical development children, ADHD; attention deficit hyperactivity disorder, ASD; autism spectrum, disorders, RCPM; Neuropsychological tasks included Raven's Colored Progressive Materices, DN-CAS; Das-Naglieri Cognitive Assessment System, CPT; continuous performance test, *$p < 0.05$, **$p < 0.01$.

($p < 0.01$) and in the ADHD group ($p < 0.05$). There were no significant differences in commission errors, but omission errors were more prevalent in the ADHD and ADHD + ASD groups than in the TDC group ($p < 0.05$).

### 4.3. Analysis of EEG frequency during sleep stage 2

We detected high voltage spindles in most children with ADHD, dominant at the frontal pole (Fp) and frontal (F) regions, as shown in Fig. 1. Therefore, at first, we analyzed each EEG band frequency during sleep stage 2 and compared the relative power in each band frequency in the whole brain among the three groups, as shown in Table 3. Although the relative power in the α and β band frequencies was not significantly different between the TDC and ADHD groups, that of the θ band frequency was significantly lower in the ADHD than in the TDC group. We further analyzed the relative power in each band frequency in each group

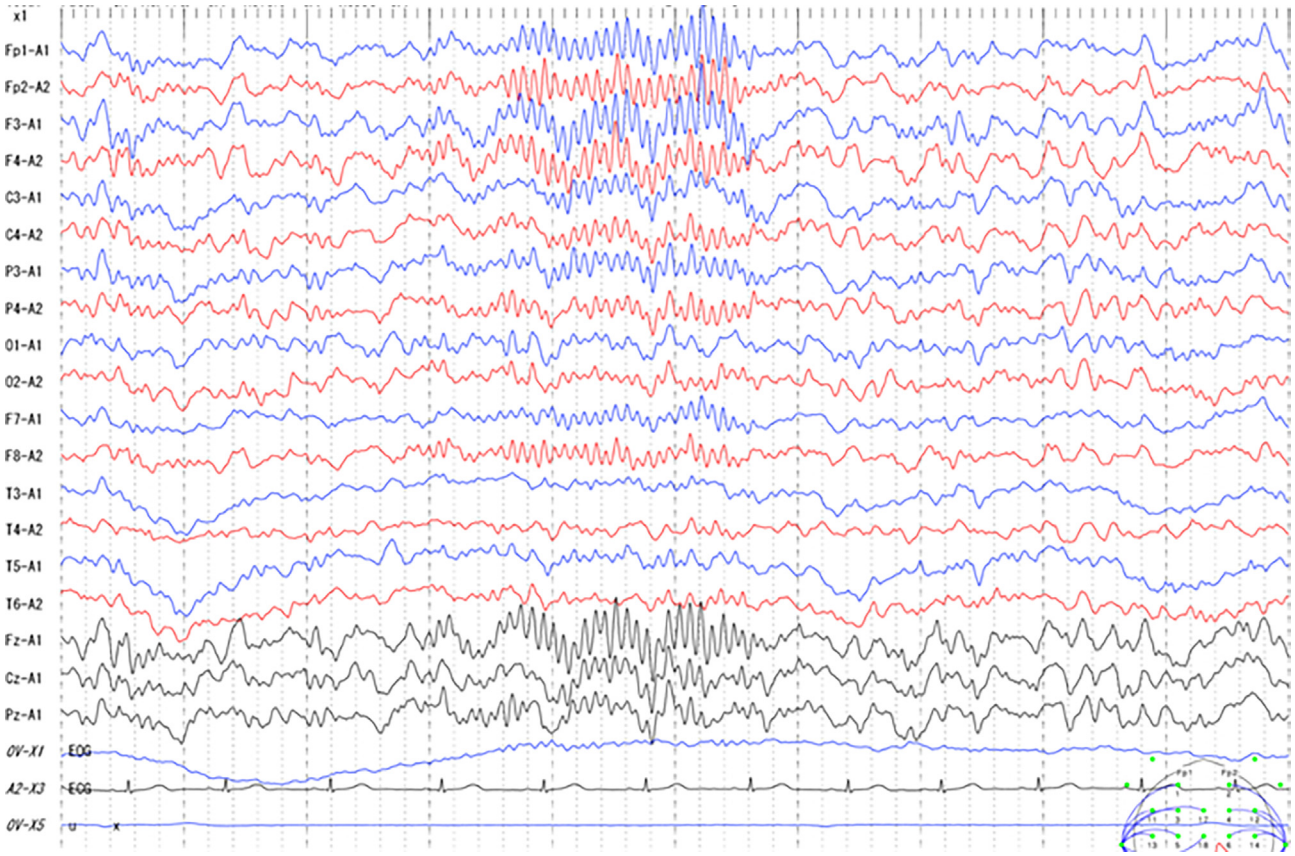


Fig. 1. Electroencephalography (EEG) findings during sleep stage 2 in a case of attention deficit-hyperactivity disorder (ADHD). Scalp 10–20 system EEG on a 7-year-old child with ADHD shows spindles with high amplitude at the frontal pole and frontal regions in sleep stage 2.

Table 3
The analysis of EEG frequency during sleep stage 2.

| Rerative power (%SD) | | TDC | ADHD | ADHD + ASD | *p*-value |
|---|---|---|---|---|---|
| δ | 1–3 Hz | 57.1 (6.0) | 62.3 (6.0) | 56.1 (7.6) | ADHD/TDC** |
| θ | 4–7 Hz | 27.8 (3.5) | 23.2 (3.0) | 25.3 (4.1) | |
| α | 8–12 Hz | 9.2 (2.7) | 8.7(2.3) | 10.4 (2.5) | |
| β | 13–29 Hz | 5.0 (2.2) | 4.8 (2.2) | 7.2 (2.7) | |
| γ | 30–44 Hz | 0.3 (0.1) | 0.4 (0.2) | 0.5 (0.2) | |
| θ/β | | 21.7 (10.5) | 18.0 (6.9) | 13.3 (6.2) | ADHD/TDC* |
| δ/θ | | 2.1 (0.5) | 2.8 (0.6) | 2.3 (0.7) | |
| δ/β | | 45.5 (24.4) | 51.7 (29.5) | 32.7 (24.7) | |

TDC; typical development children, ADHD; attention deficit hyperactivity disorder.
* $p < 0.05$.
** $p < 0.001$.

(Fig. 2a). We found a high relative power at 11–13 Hz at the frontal region in all groups (Fig. 2a). Second, we analyzed the relative power at 12 Hz and 14 Hz because these frequency bands contain slow spindles at 12 Hz (Figs. 2b, 3) and fast spindles at 14 Hz (data not shown). In the relative power at 12 Hz, the interaction between EEG regions and groups was significant (EEG regions × groups; $F(36, 648) = 4.387$, $p < 0.001$); however, in the relative power at 14 Hz, the interaction was not significant. Interestingly, for each region, only the relative power at 12 Hz was significantly higher in the ADHD + ASD compared to the TDC group at Fp1, Fp2, and F8 ($p < 0.001$); F7 ($p < 0.01$), and F4, C4, and T4 ($p < 0.05$); additionally, the relative power at 12 Hz was significantly higher in the ADHD + ASD compared to the ADHD group at F8 and T4 ($p < 0.01$) (Figs. 2b, 3). These relative powers at 12 Hz tended to be higher in the order of TDC, ADHD, and ADHD + ASD in the frontal regions (Figs. 2b, 3). However, the relative power at 14 Hz was not significantly different among groups (data not shown). There was no significant difference in the relative power at 12 Hz

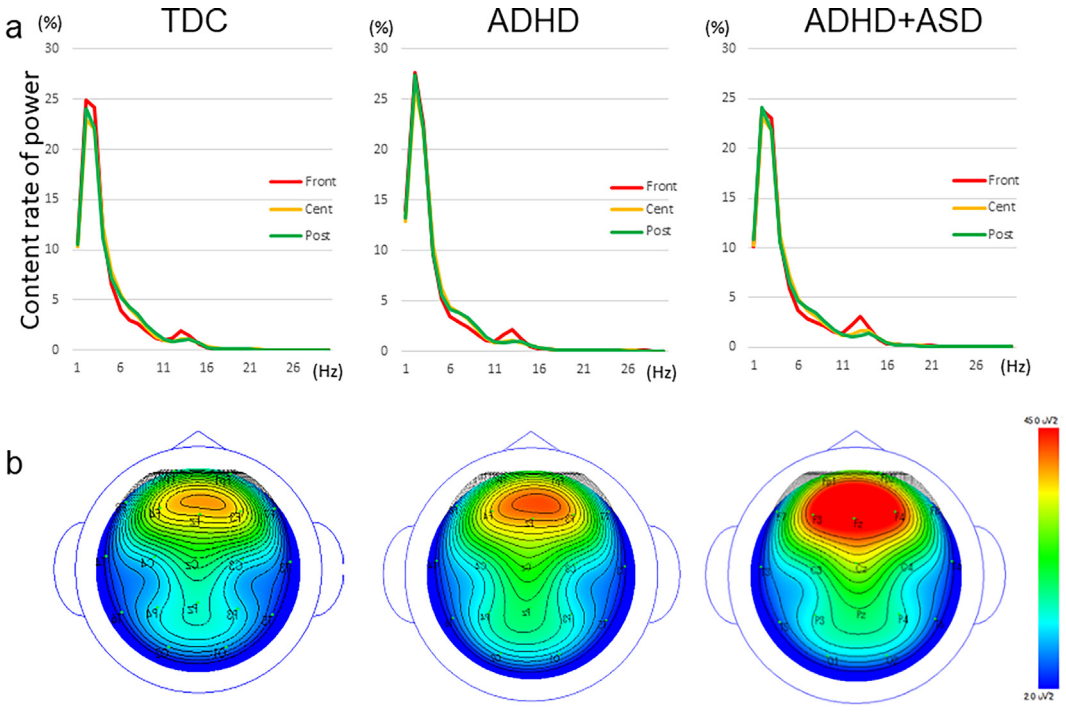


Fig. 2. Power spectrum analysis of electroencephalography (EEG) frequency during sleep stage 2. The rate of power in all frequencies (2a) and 12-Hz mapping (2b) are shown in typically developing children (TDC), children with attention deficit-hyperactivity disorder (ADHD), and children with ADHD + autism spectrum disorders (ASD). In Fig. 2a, the relative power is increased at the frontal regions (red line) in each group, in the order of TDC, ADHD, and ADHD + ASD compared to the central (yellow line) and posterior (green line) regions. Twelve-hertz power mapping shows increased power from the frontal pole to the frontal regions, in the order of TDC, ADHD, and ADHD + ASD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

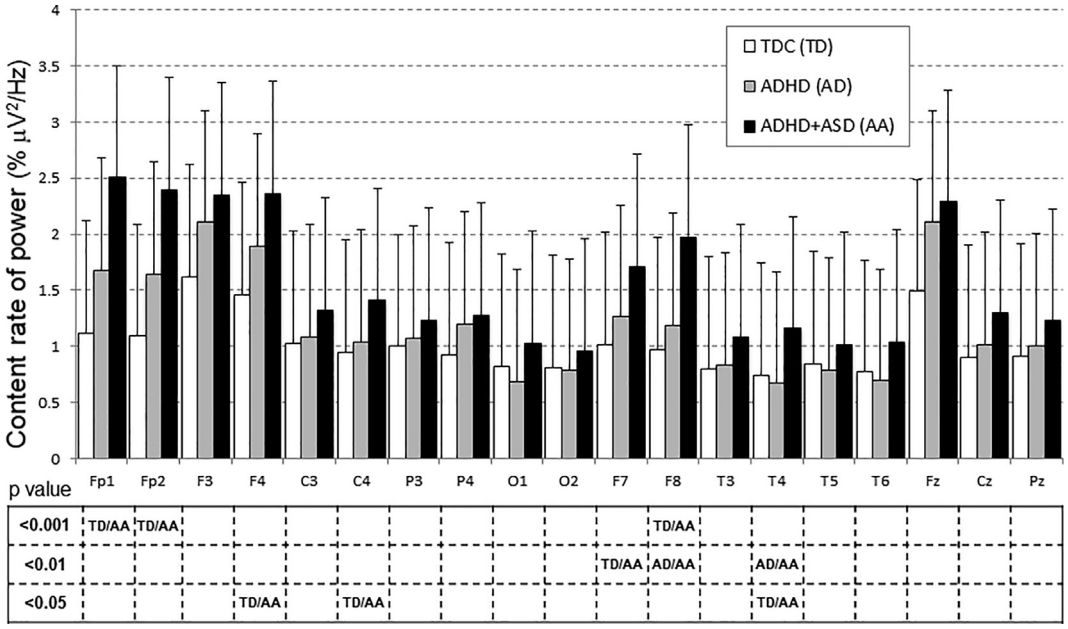


Fig. 3. The 12-Hz relative power in each group during sleep stage 2. The relative power of the 12-Hz band frequency tended to be higher in the order of typically developing children (TDC), children with attention deficit-hyperactivity disorder (ADHD), and children with ADHD + autism spectrum disorders (ASD) at the frontal pole (Fp1, Fp2) and frontal regions (F7, F8).

between the epileptic-discharge and non-epileptic-discharge groups or between the induced-sleep and natural-sleep groups.

### 4.4. Correlation between slow spindles and the cognitive function tests

We also evaluated the association between slow spindles and the cognitive function tests. The relative power at 12 Hz correlated significantly ($r = 0.368$, $p = 0.0242$) with the variability of reaction time in the CPT (Fig. 4). There was no significant correlation between the relative power at 12 Hz and commission errors ($r = 0.159$, $p = 0.344$), omission errors ($r = 0.227$, $p = 0.171$), and the Stroop score in the DN-CAS ($r = -0.143$, $p = 0.400$, data not shown).

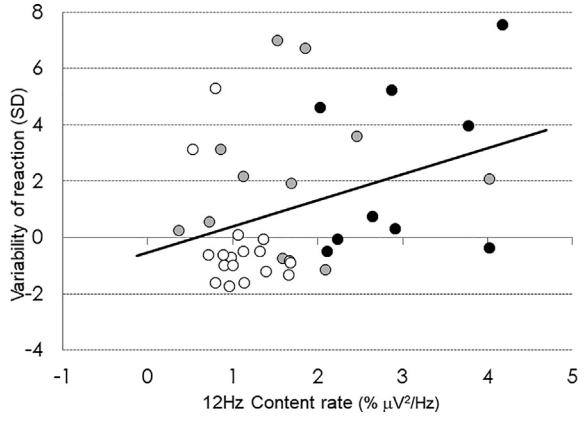


Fig. 4. Correlation between slow spindles and the variability of reaction times. The 12-Hz relative power significantly correlated with the variability of reaction times in the continuous performance test ($r = 0.368$, $p = 0.0242$; open circles, typically developing children; gray circles, children with attention deficit-hyperactivity disorder (ADHD); closed circles, children with ADHD + autism spectrum disorders). SD = standard deviation.

## 5. Discussion

### 5.1. Why is the relative power of frontal slow spindles in children with ADHD higher than in TDC?

According to our results, the relative power at 12 Hz was significantly higher in the ADHD + ASD group and tended to be higher in the ADHD group, compared to the TDC group, at the frontal regions. However, the relative power at 14 Hz showed no significant differences among groups. There may be two possible reasons for the presence of higher atypical spindles in ADHD. First, atypical spindles may be caused by abnormalities in the thalamocortical (TC) network between the thalamic nuclei and the frontal cortex related to the Na+ channel. Ayoub et al reported that carbamazepine enhanced slow frontal spindle activity conjointly with an increment in slow oscillation power. It has been reported that carbamazepine acts to reduce the efficacy of Na+ channels [21,22]. The high relative power of frontal spindles in ADHD may reflect abnormality of the Na+ channel in the TC neuronal network. Abnormality of Na+ channels is well characterized in Dravet syndrome (DS), which is a severe infantile epileptic syndrome involving

mutation of the *SCN1A* gene that codes a Na+ channel (Nav1.1) [23]. In DS, loss of function of Na + channels was reported, and patients with DS often have developmental disabilities such as inattention, hyperactivity, and mental retardation [24]. Thus, Na+ channel abnormality in the TC network, especially from the thalamus to the frontal may generate higher slow spindle activity.

The second possible reason is immaturity of the sleep system in children with ADHD. Numerous studies have revealed poor sleep quality in patients with ADHD [3–5], although these reports have not included analyses of spindle abnormalities during sleep. In a developmental study of spindles, the power of frontal spindles was highest in children around the ages of 4–5 years, decreased remarkably with age, and became stable at approximately 13 years of age [17]. Some reports have indicated immaturities of frontal functions in ADHD [25,26]. The immaturity of the brain system may be associated with the higher degree of immature spindles in children with ADHD.

### 5.2. The relationship between frontal slow spindles and cognitive function

In our results, frontal slow-spindle activities had a positive correlation with the variability of reaction times in the CPT and tended to have a negative correlation with the Stroop test score in all subjects. These results imply that frontal slow spindles reflect executive function. That is, the relative power of frontal slow spindles may be a developmental biomarker for attention and/or interference suppression. In previous studies, the number of fast spindles was significantly correlated with narrative memory and sensorimotor functioning in healthy children (mean age, 8.19 years) [14]. In another LORETA analysis, fast spindle activities in the left frontal and parietal areas were enhanced when adults acquired a new visuomotor skill [27]. On the other hand, for slow spindles, greater slow-spindle activities predicted fast reaction times during cognitive tasks in preschool children (mean age, 4.3 years) [28]. In another study, higher slow-spindle activities at the frontal lobe were exhibited in children with higher IQ scores (mean age, 9.56 years) [29]. However, our data showed that slow-spindle activity in children with atypical development, such as in ADHD, is greater than in TDC. Higher slow spindle activity indicates dysfunction and hyperfunction in the frontal lobe. Previous studies have reported such findings only in TDC. Therefore, these paradoxical findings may be attributed to a different mechanism in patients with ADHD. In the future, we have to clarify the mechanism underlying slow spindle activity. For patients with ADHD and ADHD + ASD, EEG analysis of slow spindles has the potential to be used as a diagnostic biomarker.

### 5.3. Slow-spindle activity in ADHD was enhanced in children with ADHD + ASD

In our results, higher slow-spindle activity was observed in children with ADHD with ASD comorbidity. For attention function, and/or inhibition function, children with ADHD + ASD had enhanced dysfunction compared to children with only ADHD and/or children with ASD in previous reports [30,31]. Our results support the notion that patients with ADHD + ASD have more severe executive dysfunctions. On the other hand, it is possible that higher slow-spindle activity is a feature of ASD; however, previous PSG studies have shown decreased central spindles and unchanged frontal spindles in patients with ASD [32] and decreased total spindles in patients with Asperger syndrome [33]. As far as we can tell, abnormally higher slow-spindle activity may be a feature associated with ADHD and ADHD + ASD.

### 5.4. Limitations

First, our EEG frequency analysis was based on only one 1-h recording because of limitations pertaining to the nature of the sample. The frequency analysis in sleep stage 2 may be different from that acquired by all-night recording. However, the convenience of the method is important for establishing a biomarker for developmental disorders. Moreover, we compared ADHD with TDC using the same method.

Second, some subjects required medication to induce sleep. We compared the EEG data acquired from the induced-sleep group and non-induced-sleep group and found that there were no significant differences between the groups (data not shown). Given the nature of our sample, it is difficult to record EEG during natural sleep. In our study, the induced-sleep group included only a few individuals; therefore, we need to analyze EEG data with a larger sample to delineate the impact of sleep-induction medication.

### 5.5. Future directions

First, we should examine a group of children with only ASD using our method and certify the relationship between sleep spindles and developmental disorders. If the difference in slow spindles in each disorder is elucidated, slow-spindle analysis could be used as a biomarker of executive function. EEG analysis is a simple and easily employable method in general hospitals and clinics.

Second, to clarify the pathogenesis of higher slow-spindle activity in children with ADHD, we should examine the direct relationship between slow sleep spindles and the secretion of GABA or glutaminergic acid

using magnetic resonance spectroscopy and other methods, especially in the thalamus and frontal lobe.

## 6. Conclusions

In children with ADHD, slow sleep spindles showed higher activity in the frontal regions, which was correlated with executive function, especially with attention. In addition, higher slow-spindle activities may be more prominent in children with ADHD + ASD than in children with only ADHD. That is, children with ADHD + ASD may have more pronounced executive dysfunction. Thus, these results indicate that slow sleep spindles in children with ADHD may reflect executive function, and slow frontal spindles may be useful as a biomarker of inattention and executive dysfunction in children with ADHD.

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## Declaration of Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and /or publication of this article.

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