Original Article
https://doi.org/10.9758/cpn.2022.20.3.514 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2022;20(3):514-525

The Loudness Dependence of Auditory Evoked Potentials is associated with the Symptom Severity and Treatment in Boys with Attention Deficit Hyperactivity Disorder

Eun Jin Park[1], Young-Min Park[1], Seung-Hwan Lee[1], Bongseog Kim[2]

[1]Department of Psychiatry, Inje University Ilsan Paik Hospital, Goyang, [2]Department of Psychiatry, Inje University Sanggye Paik Hospital, Seoul, Korea

Objective: The loudness dependence of the auditory evoked potential (LDAEP) is associated with central serotonergic neurotransmission. Recent studies have proposed that LDAEP is also influenced by dopaminergic activity. Evidence shows attention deficit hyperactivity disorder (ADHD) symptoms are associated with dopamine dysfunction. This study aimed to evaluate the relation between ADHD symptoms and LDAEP, as well as medication-mediated changes of LDAEP.
Methods: A total of 38 male children (6－12 years old) with ADHD were analyzed in this study. Symptom severity was assessed using the ADHD rating scale (ARS) and the continuous performance test. To determine LDAEP, the auditory event-related potential was evaluated before medication. Changes in LDAEP were measured after 12 weeks of treatment with methylphenidate.
Results: The subjects had a mean age of 9.24 ± 1.74 years with an average IQ of 109.4 ± 13.8. Before pharmacological treatment with methylphenidate, LDAEP was positively associated with the ARS score after adjusting for age and IQ ($r = 0.592$, $p = 0.005$). LDAEP was correlated with inattention ($r = 0.522$, $p = 0.015$) and hyperactivity-impulsivity ($r = 0.6$, $p = 0.004$). However, the LDAEP of 15 subjects decreased following methylphenidate treatment ($Z = -1.988$, $p = 0.047$).
Conclusion: In boys with ADHD, LDAEP appears to be associated with symptom severity. LDAEP showed a significant association with impulsivity and inattention. Importantly, LDAEP was shown to decrease after drug treatment. Our findings support the utility of LDAEP as a noninvasive and clinically useful method to assess symptom severity in children with ADHD.

KEY WORDS: ADHD; Event-related potential; Auditory evoked potentials; Biomarker; Dopamine.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common childhood mental health disorder [1]. The main symptoms of ADHD, which affects around 3－7% of children and adolescents, are inattention, hyperactivity, and impulsivity [2,3]. The symptoms occur in two or more settings and cause dysfunction in family life and significant difficulties at school and peer relationships. Symptoms of ADHD may persist into adulthood, with an estimated prevalence of 2－5%, and manifest as restlessness, emotional instability, disorganized behavior, and impulsivity [4,5]. Thus, early screening and prompt treatment of ADHD is critical for promoting child and adolescent mental health. It is also essential to identify the biological and physiological characteristics of ADHD to aid in accurate diagnosis and treatment response evaluation.

The specific etiologies of ADHD are still unknown. However, structural neuroimaging studies have found reduced frontal lobe, striatum, and cerebellum volume in ADHD patients. Additionally, ADHD patients have been shown to have decreased cerebral blood flow [6] and increased theta activity in the frontal lobe [7]. Moreover, previous evidence suggests that dysregulation of the dop-

Received: March 26, 2021 / **Revised:** January 20, 2022
Accepted: February 2, 2022
Address for correspondence: Bongseog Kim
Department of Psychiatry, Inje University Sanggye Paik Hospital, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea
E-mail: kimbs328@paik.ac.kr
ORCID: https://orcid.org/0000-0002-2534-6986

aminergic and noradrenergic pathways may be involved in ADHD pathophysiology [8,9]. Overexpression of the presynaptic dopamine transporter (DAT) gene is consistently reported in ADHD [10-12], indicating that dopaminergic dysregulation may be an underlying cause of ADHD [13,14].

Among the class of dopamine reuptake inhibitors that are prescribed for ADHD, methylphenidate (MPH) is the first line-drug. MPH helps maintain alertness and improve attention and inhibitory control [11]. MPH also decreased somatic symptoms and increased brain functional connectivity in adolescents with ADHD [15]. Moreover, studies investigating the effects of MPH provide further evidence supporting the correlation between dopaminergic dysregulation and ADHD [16-19].

Recently, there has been extensive research conducted on event-related potential (ERP) in ADHD. ERP is a non-invasive method designed to evaluate neurophysiological reactions to external stimuli. Additionally, ERP recorded on the scalp reflects cognitive processes associated with attention tasks [20-22]. Furthermore, a variety of ERP trials for children and adolescents with ADHD have explored various aspects of brain function including inhibitory control, attention, performance monitoring, and emotion processing [23-26].

Studies utilizing ERP to examine aspects of ADHD-related brain function have primarily focused on two ERP components, P300 and N100; however, there has been a more recent focus on mismatch negativity [27]. The P300 wave is a well-characterized portion of late-ERP that has been involved in various psychiatric disorders. It is assumed to represent the executive function, working memory, and attention [28-31]. Previous studies have shown lower P300 amplitude and longer P300 latency in children with ADHD relative to normal subjects [32-34]. Moreover, during an auditory oddball task, the P300 amplitude in the central electrode and P300 latency in the frontal electrode positively correlated with symptom severity in treatment-naive children with ADHD [35].

Studies on the loudness dependence of the auditory evoked potential (LDAEP), a type of ERP, are gradually increasing. LDAEP is inversely associated with central serotonergic activity, with a weak LDAEP indicating strong serotonergic neurotransmission, and vice versa [36]. Therefore, several LDAEP studies have been conducted in adults with anxiety and mood disorders [37-41]. Furthermore, recent research studies have investigated childhood maltreatment, the predictability of suicidality, and the response of antidepressants [39,42-44].

A few studies have examined LDAEP in ADHD and found a relationship between LDAEP and ADHD symptoms including inattention, impulsivity, and emotional instability [45,46]. However, these studies were mainly designed for adults with depression, rather than for children with ADHD. In addition to serotonergic activity, recent findings showed that dopaminergic transmission also impacts LDAEP [47,48]. Therefore, determining the relationship between LDAEP and ADHD may yield a greater understanding of dysregulated neurotransmission in ADHD. Considering that it is unknown how LDAEP varies relative to ADHD symptom severity in children, the primary aim of this study was to determine the relationship between ADHD symptoms and LDAEP. The secondary aim was to examine differences in LDAEP after drug treatment with methylphenidate.

METHODS

Participants

A total of 46 children participated in the initial study. Of these, thirty-eight subjects were boys and eight subjects were girls. Among them, twenty-seven children (23 boys and 4 girls) started medication. There were seventeen children (15 boys and 2 girls) who completed all tests and LDAEP before and after 12 weeks of medication. Since the number of girls was small, the data were analyzed after the girl was excluded. Finally, thirty-eight boys (aged 6–12 years) diagnosed with ADHD were analyzed in this study. The subjects were recruited from the Inje University Hospital Psychiatric Clinic. All included children met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD using for the K-SADS-PL (Korean-Schizophrenia and Affective Disorder Schedule for Present and Lifetime: Semi-structured diagnostic interview) by a child and adolescent psychiatrist. Participants diagnosed with any additional mental disorders in the DSM-IV, such as schizophrenia, mood disorder, anxiety disorder, and sleep disorder, or have any significant medical or neurological diseases, were excluded. Patients taking psychiatric medication were also excluded. Symptom severity was assessed using the Korean version of the ADHD rating scale (K-ARS), continuous performance test,

and Clinical global impression-severity (CGI-S). The LDAEP changes were re-evaluated after a 12-week treatment with methylphenidate. Of the twenty-seven children prescribed methylphenidate, a total of 15 children completed LDAEP measurements before and after drug treatment.

Written informed consent and assent were obtained from all parents and children. The study was approved by the institutional review board (IRB No. IB-1101-008).

Intelligence

Children's full-scale, verbal, and performance IQ were assessed using the abbreviated form of the Korean Educational Development Institute's Wechsler Intelligence Scales for Children (KEDI-WISC) [49]. The KEDI-WISC test consisted of arithmetic, vocabulary, block design, and picture arrangement. Scores from the abbreviated test are strongly associated with the WISC Full-Scale IQ, both in the age-standardized Korean version [50] and in the original instrument [51]. The sum of the age-adjusted scaled scores of the arithmetic and vocabulary subtests was used to determine verbal IQ. Performance IQ was calculated as the sum of the block design and picture arrangement subsets [49].

Korean Version of ADHD Rating Scale

Symptom severity was evaluated by using the K-ARS [52]. The K-ARS includes 18 items related to 18 symptoms adopted in the DSM-IV [3], with nine items related to inattention and nine related to impulsivity and hyperactivity. Each item was rated from 0 to 3. The validity and reliability of the K-ARS have been well established [52]. The K-ARS was completed by the participant's parents. In addition, the CGI-S was used to measure the severity of symptoms after pharmacological treatment for 12 weeks. CGI-S is a 7-point scale that allows the clinician to measure the severity of the patient's disease.

Continuous Performance Test

The Korean version of the continuous performance test (CPT) was administered to children with ADHD [53]. Raw data were converted to age-adjusted T scores on the CPT variables. Higher T scores showed poorer performance on the test. The test measures four major outcomes: 1) omission errors, 2) commission errors, 3) response time, and 4) the standard deviation of response times. Omission errors illustrate a failure to respond to targets and are indicative of inattention. Commission errors imply an erroneous response to nontargets and are correlated with impulsivity. The response time indicates the time taken to react after the target is released. The standard deviation of response times (response time variability) is a measure of attention consistency. Among Korean children and adolescents, the CPT was standardized for age, and its validity and reliability were established [54].

Loudness Dependence Auditory Evoked Potentials (LDAEP)

Each participant was tested in a sound-attenuated room during the EEG measurement. The EEG was recorded when the subject was in a resting state without a cognitive function task. By measuring the LDAEP before treatment, the potentially confounding influences of drugs were minimized. The auditory stimulation consisted of 1,000 signals with randomized time intervals between 500 and 900 ms and an interstimulus interval. Five intensities were provided (55, 65, 75, 85, and 95 dB SPL) with randomized tones of 1,000 Hz and an 80-ms duration (with a 10-ms fall and 10-ms rise). EEG data were recorded on the international 10−20 system from 32 scalp sites (impedance < 10 kΩ). Data was collected using a bandpass filter from 0.5 to 100 Hz at a sampling frequency of 1,000 Hz. The stimuli were generated by E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA).

The measured ERPs at the central electrode were the N1 peak and P2 peak. The N1 peak is the negative-most amplitude measured between 80 and 130 ms after the stimulus, while the P2 peak is the positive-most peak between 130 and 230 ms after the stimulus. The peak-to-peak N1/P2 amplitudes were calculated as the slope of the linear regression curve.

Statistical Analysis

All statistical analyses were carried out using the SPSS version 25 program (IBM Co., Armonk, NY, USA). All variables were reported as mean and standard deviation values. The demographic data, symptom severity, cognitive function, and LDAEP were compared using correlation analysis. To control age and IQ effects, we used a partial correlation in LDAEP-related analysis. A multiple linear regression analysis was performed for evaluating the association between symptom severity and LDAEP. The effect of pharmacological treatment on LDAEP and CGI-S

was evaluated by conducting the Wilcoxon signed-rank test. In addition, ANCOVA was used to compare the LDAEP scores between low and high impulsivity groups after adjusting for age and IQ. The analysis was used to control age and total IQ as covariates given that LDAEP could be significantly influenced by age and sex [55]. Group differences were tested at the $p < 0.05$ level.

RESULTS

Demographic Characteristics of Participants

Table 1 shows the demographic and clinical characteristics of participants. A total of 38 male children diagnosed with ADHD participated in this study. The mean age was 9.24 ± 1.74 years, and the mean IQ was 109.4 ± 13.8. The participants had a mean ARS score of 22.4 ± 10.0, a mean inattention subscale score of 11.8 ± 5.4, and a mean hyperactivity-impulsivity subscale score of 10.8 ± 5.9. Additionally, the average LDAEP was 0.74 ± 0.94 (Table 1).

Correlation Analysis of LDAEP with ADHD Symptoms

LDAEP had a significant association with the total ARS score (r = 0.483, $p = 0.006$). It was also related to the inattention subscale (r = 0.570, $p = 0.004$) and hyperactivity-impulsivity subscale (r = 0.527, $p = 0.008$). Statistical significance was also noted after adjustment for age and intelligence (total ARS score: r = 0.592, $p = 0.005$; inattention subscale: r = 0.522, $p = 0.015$; hyperactivity-impulsivity subscale: r = 0.6, $p = 0.004$) (Fig. 1). In the multiple linear regression analysis, after adjusting for age and IQ, higher LDAEP was significantly associated with higher total ARS score (B = 0.510, t = 3.008, $p = 0.006$), inattentive subscale score (B = 0.515, t = 2.668, $p = 0.015$), and hyperactivity-impulsivity subscale score (B = 0.569, t = 3.271, $p = 0.004$).

In the CPT, children with ADHD were divided into two groups based on the T score of the visual commission error. The high-impulsivity group had a T score of ≥ 65, and the low-impulsivity group had a T score of < 65. The two groups of subjects showed significantly different LDAEP levels (F = 4.539, $p = 0.043$) after controlling for the covariates of age and IQ. LDAEP levels in the high-impulsivity group were higher than those in the low-impulsivity group (1.07 ± 1.14 vs. 0.43 ± 0.76, respectively) (Table 2, Fig. 2). In logistic regression analysis, a trend was observed showing that LDAEP levels could predict impulsivity ($p = 0.055$, Table 3).

The Change of LDAEP and CGI-S after Medication

The LDAEP was measured after 12 weeks of methylphenidate treatment. A total of 15 children were analyzed. LDAEP tended to decrease after drug use and was statisti-

Table 1. Demographic characteristics of participants

Variable	Whole samples (n = 38, all boys)	
	Mean ± SD	Range
Age	9.24 ± 1.74	6 to 12
Total IQ (n = 33)	109.4 ± 13.8	86 to 138
LDAEP_baseline (n = 38)	0.74 ± 0.94	−0.76 to 4.32
ADHD rating scale (n = 31)		
Total ARS score	22.4 ± 10.0	4 to 50
Inattention subscale	11.8 ± 5.4	1 to 24
Hyperactivity-Impulsivity subscale	10.8 ± 5.9	3 to 26
Continuous performance test (T score)		
Visual omission error	59.8 ± 18.1	42 to 100
Visual commission error	66.9 ± 17.1	40 to 100
Visual reaction time	59.2 ± 10.8	43 to 78
Visual reaction time SD	59.8 ± 15.4	36 to 100
Auditory omission error	62.8 ± 18.0	40 to 100
Auditory commission error	60.1 ± 15.6	41 to 100
Auditory reaction time	66.6 ± 10.2	32 to 82
Auditory reaction time SD	53.69 ± 10.7	36 to 84

LDAEP, loudness dependence of the auditory evoked potential; ADHD, attention deficit hyperactivity disorder; SD, standard deviation; ARS, ADHD rating scale; IQ, intellectual quotient.

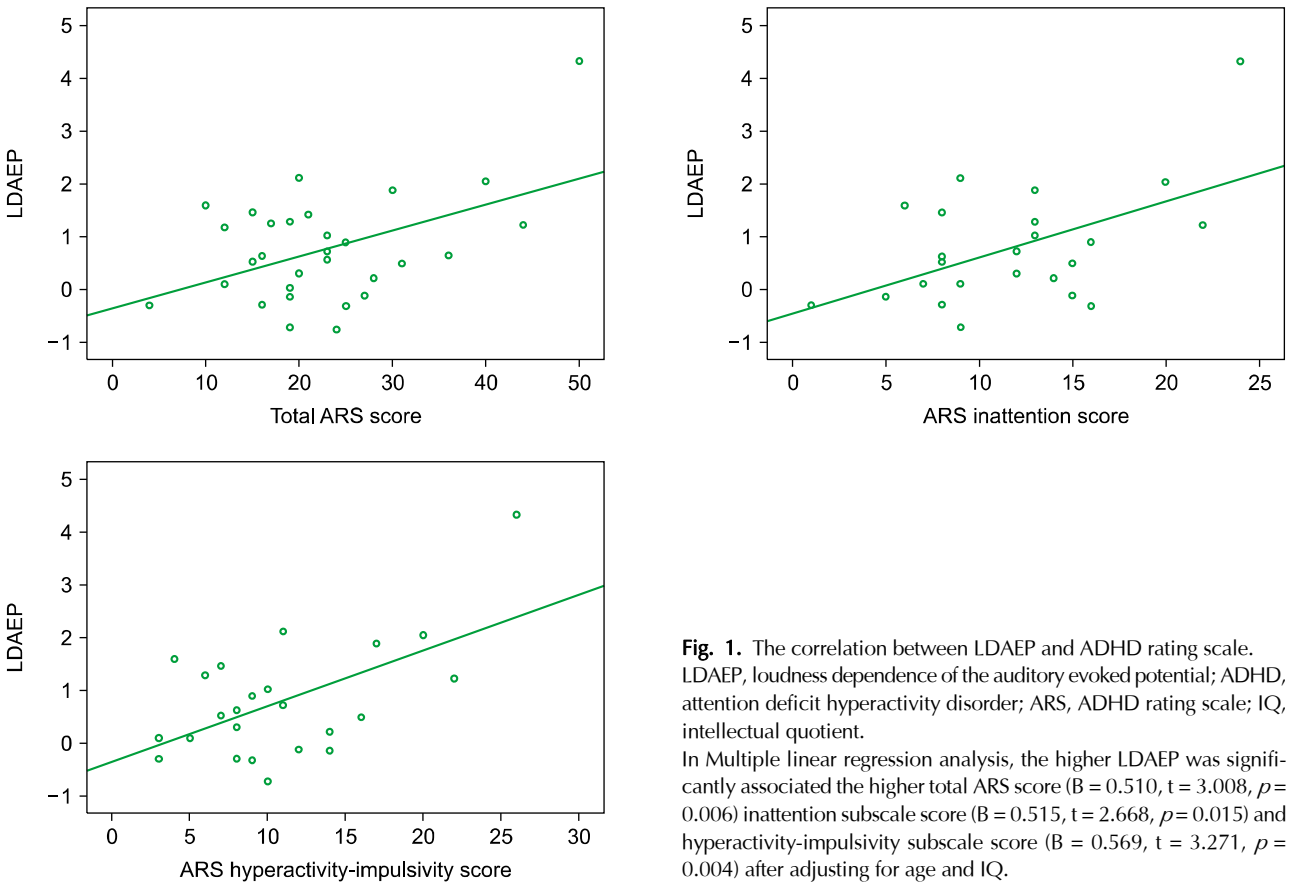

Fig. 1. The correlation between LDAEP and ADHD rating scale.
LDAEP, loudness dependence of the auditory evoked potential; ADHD, attention deficit hyperactivity disorder; ARS, ADHD rating scale; IQ, intellectual quotient.
In Multiple linear regression analysis, the higher LDAEP was significantly associated the higher total ARS score (B = 0.510, t = 3.008, p = 0.006) inattention subscale score (B = 0.515, t = 2.668, p = 0.015) and hyperactivity-impulsivity subscale score (B = 0.569, t = 3.271, p = 0.004) after adjusting for age and IQ.

Table 2. The difference in LDAEP between low and high impulsivity group

Variable	Low impulsivity group (n = 17)	High impulsivity group (n = 16)	p value
Age	9.53 ± 1.54	8.69 ± 1.85	0.179
LDAEP_baseline	0.43 ± 0.76	1.07 ± 1.14	0.043[a]
Total IQ	111 ± 15	107 ± 12	0.567
ADHD rating scale			
Total ARS	18.8 ± 7.2	27.4 ± 11.6	0.080
Inattention ARS	9.7 ± 4.2	14.5 ± 6.1	0.096
Hyperactivity-Impulsivity ARS	8.7 ± 4.2	14.3 ± 7.1	0.072
Continuous performance test (T score)			
Visual omission error	55.1 ± 18.4	64.8 ± 16.8	0.008
Visual commission error	53.6 ± 5.8	81.13 ± 13.2	< 0.001
Visual reaction time	60.7 ± 10.5	57.5 ± 11.2	0.402
Visual reaction time SD	54.2 ± 12.5	65.8 ± 16.3	0.031
Auditory omission error	66.76 ± 16.7	58.33 ± 19.1	0.114
Auditory commission error	57.1 ± 9.9	63.5 ± 20.1	0.710
Auditory reaction time	71.0 ± 7.1	61.6 ± 11.0	0.006
Auditory reaction time SD	54.82 ± 11.1	52.4 ± 10.4	0.682

Values are presented as mean ± standard deviation.
LDAEP, loudness dependence of the auditory evoked potential; ADHD, attention deficit hyperactivity disorder; SD, standard deviation; ARS, ADHD rating scale; IQ, intellectual quotient.
The high-impulsivity group had a T score of ≥65 and the low-impulsivity group had a T score of < 65. The two groups of subjects showed signicantly dierent LDAEP levels (F = 4.539, p = 0.043) after controlling age and IQ as covariates. Mann Whitney U test was conducted to compare two groups.
[a]ANCOVA after adjusting for age and total IQ.

cally significant (Z = −1.988, p = 0.047). Moreover, CGI-S decreased significantly after methylphenidate treatment (p = 0.001) (Table 4, Fig. 3).

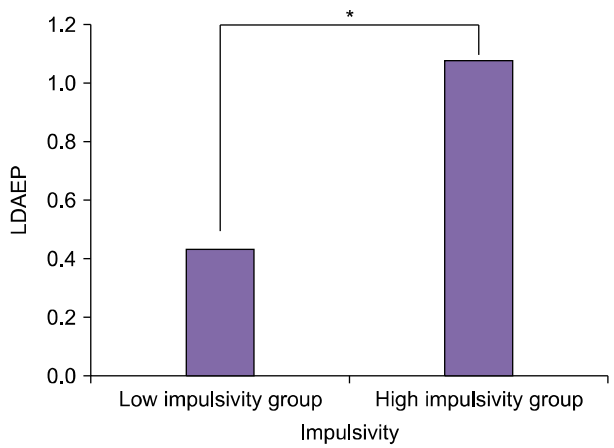

Fig. 2. LDAEP differences between high-impulsivity and low-impulsivity groups.
LDAEP, loudness dependence of the auditory evoked potential; IQ, intellectual quotient.
The two groups of subjects showed significantly different LDAEP levels (F = 4.539, p = 0.043) after controlling age and IQ as covariates.
*p value < 0.05.

DISCUSSION

This study identified an association between LDAEP and symptom severity in children with ADHD. Moreover, changes in LDAEP were observed after taking the ADHD medication, methylphenidate. LDAEP had a significant association with the severity of ADHD symptoms including impulsivity and inattention. In particular, LDAEP was higher in the highly impulsive group than in the less impulsive group. Pharmacological treatment with MPH significantly decreased LDAEP in accordance with symptom improvement. Importantly, LDAEP was found to be positively correlated with the impulsive symptoms of ADHD in the CPT. These results suggest that LDAEP may act as a specific indicator of cognitive dysfunction in children with ADHD.

Our study showed a significant correlation between ADHD core symptoms and LDAEP. The correlation between LDAEP and inattention and impulsivity reported here are similar to previous findings. In previous studies, LDAEP has been reported to be higher among more impulsive individuals [56] and reflect behavioral inhibition

Table 3. Logistic regression analysis of LDAEP in relation to impulsivity

Variable	B	SE	Wals	F	p value	Exp(B)	95% confident interval	
							Lower	Higher
LDAEP_baseline	1.086	0.566	3.676	1	0.055	2.961	0.976	8.985
Age	−0.417	0.263	2.516	1	0.113	0.659	0.393	1.103
Total IQ	−0.05	0.033	2.334	1	0.127	0.951	0.893	1.014

LDAEP, loudness dependence of the auditory evoked potential; IQ, intellectual quotient; SE, standard error.

Table 4. Changes of LDAEP and CGI-S after medication

Variable	Sample with medication (n = 15)		
	Mean ± SD	Range	p value
Age	9.33 ± 1.8	6 to 12	
Total IQ	114 ± 13.6	86 to 134	
Total ARS score	26.3 ± 11.34	12 to 50	
Dose of MPH (mg)	38.3 ± 12.5	18 to 63	
CGI-S			
CGI-S_baseline	5.41 ± 1.12	4 to 7	Z = −3.332
CGI-S_after MPH trial	3.27 ± 0.88	1 to 3	p = 0.001
LDAEP			
LDAEP_baseline	1.02 ± 1.13	−0.14 to 4.32	Z = −1.988
LDAEP_after MPH trial	0.63 ± 1.17	−0.81 to 3.52	p = 0.047

MPH, methylphenidate; LDAEP, loudness dependence of the auditory evoked potential; ADHD, attention deficit hyperactivity disorder; SD, standard deviation; ARS, ADHD rating scale; IQ, intellectual quotient; CGI-S, clinical global impression severity.
Wilcoxon signed-rank test was conducted.

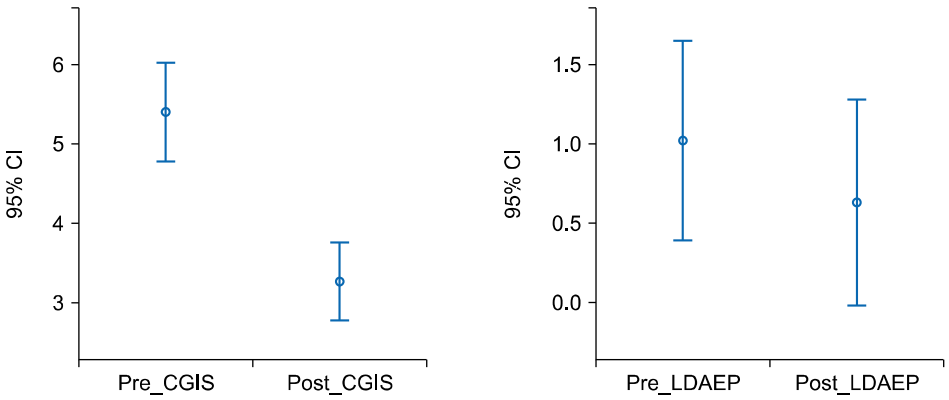

Fig. 3. Differences in LDAEP and CGI-S after medication (methylphenidate).
LDAEP, loudness dependence of the auditory evoked potential; CGI-S, clinical global impression-severity; CI, confidence interval.
LDAEP tended to decrease after drug use and was statistically significant ($p = 0.047$). CGI-S decreased significantly after taking the drug ($p = 0.001$).

and emotional sensitivity [46]. Additionally, an functional magnetic resonance imaging study showed that immediate reward behavior, which is related to impulsivity, is associated with stronger LDAEP [57]. Low serotonergic activity, as evaluated by a high LDAEP, was linked to impulsivity, according to Mavrogiorgou *et al.* [57]. It's possible that the serotonergic system in the orbitofrontal area controls impulsive reward-oriented decision-making. In a recent study, LDAEP was found to be significantly correlated with ADHD symptoms and the inattention subscale in depressed adults; however, it was unrelated to the hyperactive subscale [45]. Interestingly, Kim *et al.* [45] reported that LDAEP decreased with more severe symptoms, which contrasts with our findings. The researchers explained these results by suggesting that LDAEP could be differently reflected in depressed adults with ADHD symptoms. A direct comparison of the inattention of depressed adult patients with that of children with ADHD may be limited. Comorbidities like depression and anxiety were not evaluated as confounding factors in our study. These limitations should be considered.

After 12 weeks of treatment with MPH, we observed an improvement in ADHD symptoms and a significant reduction in LDAEP. To our best knowledge, no study has been conducted thus far to evaluate changes in LDAEP after MPH administration in ADHD patients. In a similar study, Beucke *et al.* [58] examined the effects of L-Dopa treatment on LDAEP in patients with Parkinson's disease. Similar to ADHD, Parkinson's disease is associated with dopamine deficiency. In that study, L-Dopa was administered for 12 weeks to determine the relationship between the improvement of symptoms and changes in LDAEP. Prior to L-Dopa treatment, there was a significant difference in LDAEP of control subjects and Parkinson's disease patients. However, no significant difference was observed between groups following L-Dopa treatment for 12 weeks. Furthermore, there was a trending correlation between LDAEP and DAT activity in unmedicated Parkinson's disease patients, suggesting a possible relationship between low serotonergic activity and the loss of dopamine detected in Parkinson's disease.

In another recent study of LDAEP in Parkinson's disease patients, the absolute value of LDAEP decreased after 12 weeks of taking dopaminergic medication [59]. A study of cats also reported a decrease in LDAEP after the application of the dopamine agonist, apomorphine [60]. Similarly, in our study, LDAEP decreased after MPH administration, which may be linked to increased dopamine concentration. However, changes in LDAEP can be associated with changes in both serotonin and dopamine, Further research is required to elucidate detailed associations.

LDAEP has been studied mainly in association with brain serotonin levels, but increasing evidence shows that LDAEP is related to dopamine. Previous studies have revealed an inverse association between LDAEP and dopamine metabolite levels [47]. Furthermore, LDAEP is positively related to DAT after adjusting for age and sex [61]. These results support the hypothesis of dopamine being a major modulator in the generation of LDAEP and dopamine-serotonin interaction. Clearly, several findings have shown that serotoninergic deficiency is associated with a lack of dopamine [62-64]. A molecular genetic study showed that there are several dopaminergic and serotonergic genes related to reward functioning in ADHD [65]. In addition, studies have shown a link between dopamine and serotonin through LDAEP [66,67]. The availability of brain DAT and SERT in patients with the obsessive-compulsive disorder was significantly correlated with LDAEP

[67,68]. Taken together, these results indicate that LDAEP is likely associated with both dopamine and serotonin activity.

In the current study, we found that LDAEP decreased after methylphenidate treatment in ADHD patients. Since Impaired dopaminergic transmission is believed to be associated with symptoms [10,12,13], it is possible that altered dopaminergic neurotransmission is associated with methylphenidate-mediated changes in LDAEP. As the monoaminergic systems of the brain may interact, further studies are needed to investigate the relationship between LDAEP and various neurotransmitters in ADHD.

LDAEP has been utilized to study various mental disorders for two decades [36,69]. Researchers have focused mainly on the relationship between LDAEP and mood and anxiety disorders such as depression, obsessive-compulsive disorder, bipolar disorder, and suicidality [70-73]. Notably, mental health disorders, such as depression and anxiety, are common comorbidities that occur with ADHD. Children with ADHD have high rates of depression and anxiety (25−41%) [74-76]. Recently, Oh *et al.* [77] also showed a temporal connection between depression and MPH use in adolescents with ADHD. Therefore, the association between LDAEP and ADHD can also be interpreted in terms of emotional comorbidities [43,70,78]. In the present study, we did not directly investigate the relationship between LDAEP and anxiety/depression. Further studies are needed to explore the relationship between anxiety/depression and LDAEP in subjects with ADHD.

Since LDAEP is mainly linked to serotonin, it is worth paying attention to recent research on ADHD and serotonin. Some studies have reported the association of serotonergic genes with ADHD [79-84]. Also, ADHD symptoms, such as impulsivity and emotional dysregulation, are associated with serotonin [85,86]. Furthermore, methylphenidate influences blood serotonin levels [87], and the effect of the serotonergic gene expression with methylphenidate treatment was reported [88]. It may be necessary to view ADHD in the context of multiple neurotransmitter-mediated neural pathways. Further research is needed to clarify this.

It is crucial to identify biomarkers of ADHD to aid in early diagnosis and treatment. Proposed ADHD biomarkers include the degree of specific cognitive function [89,90], the activation of particular brain regions [91], and the expression of specific genes [10,84]. However, these approaches are invasive and expensive making them difficult to perform in children with ADHD. In contrast, ERPs, which are non-invasive and relatively easy to perform, are highly correlated with specific cognitive functions that may be dysregulated in ADHD [92]. Due to the correlative relationship between LDAEP and neurotransmitter levels, the LDAEP study in ADHD children could provide additional information.

This study has several limitations. First, there was a relatively small sample size that did not include healthy controls. The small sample size should be considered when interpreting the results of this study. Second, only boys were analyzed in the study. The prevalence of ADHD in boys is three to five times higher than in girls [3]. In addition, ERP results are dependent on sex [93,94]. Therefore, the selective inclusion of only boys may have limited participant variation. Third, this study did not analyze the difference according to the subtype of ADHD. Further research related to subtypes is needed in the future. Depression and anxiety were not evaluated in this study, as children with severe depression and anxiety disorders were also excluded to focus on ADHD core symptoms. Due to the small number of participants, we could not investigate changes in LDAEP according to the degree of improvement in symptoms after drug treatment. The ERP studies presented in the reference were measured while performing cognitive tasks such as the Go/NoGo test, but this study measured LDAEP in the resting state. It is necessary to consider this part when comparing and interpreting the results. The strength of this study is that individuals with formal ADHD diagnosis participated and symptom severity was evaluated in both rating scale and standardized cognitive test. Additionally, results were statistically analyzed after adjusting age and intelligence. Notably, a previous ERP study revealed that intelligence influences attention and impulsivity in ADHD children [95]. Thus, adjusting for intelligence and age strengthens our results that show a relationship between ERP and symptoms and cognitive tests in children.

To support our findings and validate the usefulness of LDAEP in ADHD, future studies using a larger cohort and normal control are needed. To our best knowledge, this is the first study to investigate a direct association between LDAEP and ADHD symptom severity and the effect of treatment in children.

The present study suggests that changes in LDAEP were associated with ADHD symptoms and treatment effects.

According to our results, LDAEP may be a significant indicator of the neurophysiological characteristics of ADHD. Furthermore, our findings support the utility of LDAEP as a noninvasive and clinically applicable method to assess symptom severity in children with ADHD.

■ **Funding**

None.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Study concept and design: Eun Jin Park, Young-Min Park, Seung-Hwan Lee, Bongseog Kim. Analysis and interpretation of data: Eun Jin Park, Young-Min Park, Seung-Hwan Lee, Bongseog Kim. Statistical analysis: Eun Jin Park, Young-Min Park. Study supervision: Bongseog Kim.

■ **ORCID**

Eun Jin Park	https://orcid.org/0000-0003-4046-1517
Young-Min Park	https://orcid.org/0000-0002-4993-1426
Seung-Hwan Lee	https://orcid.org/0000-0003-0305-3709
Bongseog Kim	https://orcid.org/0000-0002-2534-6986

REFERENCES

1. Biederman J, Faraone SV, Taylor A, Sienna M, Williamson S, Fine C. *Diagnostic continuity between child and adolescent ADHD: findings from a longitudinal clinical sample. J Am Acad Child Adolesc Psychiatry 1998;37:305-313.*
2. Biederman J. *Attention-deficit/hyperactivity disorder: a life-span perspective. J Clin Psychiatry 1998;59 Suppl 7:4-16.*
3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR®. 4th ed. Washington, D.C.:American Psychiatric Association;2000.*
4. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugué M, Carpentier PJ, *et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;10:67.*
5. Matte B, Anselmi L, Salum GA, Kieling C, Gonçalves H, Menezes A, *et al. ADHD in DSM-5: a field trial in a large, representative sample of 18- to 19-year-old adults. Psychol Med 2015;45:361-373.*
6. Park MH, Kim JW, Yang YH, Hong SB, Park S, Kang H, *et al. Regional brain perfusion before and after treatment with methylphenidate may be associated with the G1287A polymorphism of the norepinephrine transporter gene in children with attention-deficit/hyperactivity disorder. Neurosci Lett 2012;514:159-163.*
7. Lee I, Lee J, Lim MH, Kim KM. *Comparison of quantitative electroencephalography between tic disorder and attention-deficit/hyperactivity disorder in children. Clin Psychopharmacol Neurosci 2021;19:739-750.*
8. Lee TH, Lee CH, Kim IH, Yan BC, Park JH, Kwon SH, *et al. Effects of ADHD therapeutic agents, methylphenidate and atomoxetine, on hippocampal neurogenesis in the adolescent mouse dentate gyrus. Neurosci Lett 2012;524:84-88.*
9. Durell T, Adler L, Wilens T, Paczkowski M, Schuh K. *Atomoxetine treatment for ADHD: younger adults compared with older adults. J Atten Disord 2010;13:401-406.*
10. Mereu M, Contarini G, Buonaguro EF, Latte G, Managò F, Iasevoli F, *et al. Dopamine transporter (DAT) genetic hypofunction in mice produces alterations consistent with ADHD but not schizophrenia or bipolar disorder. Neuropharmacology 2017;121:179-194.*
11. Pribilova N, Paclt I, Kollarova P, Kohoutova M, Dezortova M, Hajek M, *et al. Long term pharmacotherapy by methylfenidate or atomoxetine DAT 1 10/10 ADHD children in correlation with results of the imaging methods. Neuro Endocrinol Lett 2016;37:289-294.*
12. Todd RD, Huang H, Smalley SL, Nelson SF, Willcutt EG, Pennington BF, *et al. Collaborative analysis of DRD4 and DAT genotypes in population-defined ADHD subtypes. J Child Psychol Psychiatry 2005;46:1067-1073.*
13. Oh KS, Shin DW, Oh GT, Noh KS. *Dopamine transporter genotype influences the attention deficit in Korean boys with ADHD. Yonsei Med J 2003;44:787-792.*
14. Cheon KA, Kim BN, Cho SC. *Association of 4-repeat allele of the dopamine D4 receptor gene exon III polymorphism and response to methylphenidate treatment in Korean ADHD children. Neuropsychopharmacology 2007;32:1377-1383. Erratum in: Neuropsychopharmacology 2007;32:1431.*
15. Kim SM, Min KJ, Han DH. *Effects of methylphenidate on somatic symptoms and brain functional connectivity in adolescents with ADHD: a pilot study. Clin Psychopharmacol Neurosci 2022;20:259-270.*
16. da Silva N Jr, Szobot CM, Anselmi CE, Jackowski AP, Chi SM, Hoexter MQ, *et al. Attention deficit/hyperactivity disorder: is there a correlation between dopamine transporter density and cerebral blood flow? Clin Nucl Med 2011;36:656-660.*
17. Hong SB, Kim JW, Cho SC, Shin MS, Kim BN, Yoo HJ. *Dopaminergic and noradrenergic gene polymorphisms and response to methylphenidate in Korean children with attention-deficit/hyperactivity disorder: is there an interaction? J Child Adolesc Psychopharmacol 2012;22:343-352.*
18. Silberstein RB, Levy F, Pipingas A, Farrow M. *First-dose methylphenidate-induced changes in brain functional connectivity are correlated with 3-month attention-deficit/hyperactivity disorder symptom response. Biol Psychiatry 2017;82:679-686.*
19. Childress AC, Komolova M, Sallee FR. *An update on the phar-*

macokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. Expert Opin Drug Metab Toxicol 2019;15:937-974.

20. Hasler R, Perroud N, Meziane HB, Herrmann F, Prada P, Giannakopoulos P, *et al. Attention-related EEG markers in adult ADHD. Neuropsychologia 2016;87:120-133.*
21. Chmielewski WX, Tiedt A, Bluschke A, Dippel G, Roessner V, Beste C. *Effects of multisensory stimuli on inhibitory control in adolescent ADHD: it is the content of information that matters. Neuroimage Clin 2018;19:527-537.*
22. Gu C, Liu ZX, Tannock R, Woltering S. *Neural processing of working memory in adults with ADHD in a visuospatial change detection task with distractors. PeerJ 2018;6:e5601.*
23. Janssen TWP, Geladé K, van Mourik R, Maras A, Oosterlaan J. *An ERP source imaging study of the oddball task in children with Attention Deficit/Hyperactivity Disorder. Clin Neurophysiol 2016;127:1351-1357.*
24. Raz S, Dan O. *Behavioral and neural correlates of facial versus nonfacial stimuli processing in adults with ADHD: an ERP study. Neuropsychology 2015;29:726-738.*
25. Grane VA, Brunner JF, Endestad T, Aasen IE, Kropotov J, Knight RT, *et al. Correction: ERP correlates of proactive and reactive cognitive control in treatment-naïve adult ADHD. PLoS One 2016;11:e0163404. Erratum for: PLoS One 2016;11:e0159833.*
26. Chronaki G. *Event-related potentials and emotion processing in child psychopathology. Front Psychol 2016;7:564.*
27. Cheng CH, Chan PS, Hsieh YW, Chen KF. *A meta-analysis of mismatch negativity in children with attention deficit-hyperactivity disorders. Neurosci Lett 2016;612:132-137.*
28. Polich J. *Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 2007;118:2128-2148.*
29. Heinrich H, Grunitz J, Stonawski V, Frey S, Wahl S, Albrecht B, *et al. Attention, cognitive control and motivation in ADHD: linking event-related brain potentials and DNA methylation patterns in boys at early school age. Sci Rep 2017;7:3823.*
30. Paul-Jordanov I, Bechtold M, Gawrilow C. *Methylphenidate and if-then plans are comparable in modulating the P300 and increasing response inhibition in children with ADHD. Atten Defic Hyperact Disord 2010;2:115-126.*
31. Lugo-Candelas C, Flegenheimer C, Harvey E, McDermott JM. *Neural correlates of emotion reactivity and regulation in young children with ADHD symptoms. J Abnorm Child Psychol 2017;45:1311-1324.*
32. Gomarus HK, Wijers AA, Minderaa RB, Althaus M. *ERP correlates of selective attention and working memory capacities in children with ADHD and/or PDD-NOS. Clin Neurophysiol 2009;120:60-72.*
33. Wiersema JR, Roeyers H. *ERP correlates of effortful control in children with varying levels of ADHD symptoms. J Abnorm Child Psychol 2009;37:327-336.*
34. Liotti M, Pliszka SR, Higgins K, Perez R 3rd, Semrud-Clikeman M. *Evidence for specificity of ERP abnormalities during response inhibition in ADHD children: a comparison with reading disorder children without ADHD. Brain Cogn 2010;72:228-237.*
35. Yamamuro K, Ota T, Iida J, Nakanishi Y, Suehiro Y, Matsuura H, *et al. Event-related potentials correlate with the severity of child and adolescent patients with attention deficit/hyperactivity disorder. Neuropsychobiology 2016;73:131-138.*
36. O'Neill BV, Croft RJ, Nathan PJ. *The loudness dependence of the auditory evoked potential (LDAEP) as an in vivo biomarker of central serotonergic function in humans: rationale, evaluation and review of findings. Hum Psychopharmacol 2008;23:355-370.*
37. Lee BH, Park YM, Lee SH, Shim M. *Prediction of long-term treatment response to selective serotonin reuptake inhibitors (SSRIs) using scalp and source loudness dependence of auditory evoked potentials (LDAEP) analysis in patients with major depressive disorder. Int J Mol Sci 2015;16:6251-6265.*
38. Lee BH, Park YM. *How childhood maltreatment is related to suicidality, bipolarity and central serotonergic activity in patients with major depressive disorder: a cross-sectional pilot study. Psychiatry Investig 2016;13:190-195.*
39. Park YM, Lee SH. *Can the loudness dependence of auditory evoked potentials and suicidality be used to differentiate between depressive patients with and without bipolarity. Psychiatry Investig 2013;10:143-147.*
40. Park YM. *Relationship between serotonergic dysfunction based on loudness dependence of auditory-evoked potentials and suicide in patients with major depressive disorder. Psychiatry Investig 2015;12:421-424.*
41. Park YM, Lee SH. *Clinical usefulness of loudness dependence of auditory evoked potentials (LDAEP) in patients with bipolar disorder. Psychiatry Investig 2013;10:233-237.*
42. Park YM. *The hypothesis on the prediction of treatment response with buspirone augmentation along with serotonergic antidepressant in patients with major depressive disorder using loudness dependence of auditory evoked potentials: two cases and review of the literature for evidence. Psychiatry Investig 2020;17:222-224.*
43. Park YM, Kim DW, Kim S, Im CH, Lee SH. *The loudness dependence of the auditory evoked potential (LDAEP) as a predictor of the response to escitalopram in patients with generalized anxiety disorder. Psychopharmacology (Berl) 2011;213:625-632.*
44. Hwang M, Lee YJ, Lee M, Kang B, Lee YS, Hwang J, *et al. Relationship between the loudness dependence of the auditory evoked potential and the severity of suicidal ideation in patients with major depressive disorder. Clin Psychopharmacol Neurosci 2021;19:323-333.*
45. Kim JS, Kim DW, Kwon YJ, Lee HY, Kim S, Shim SH. *The relationship between auditory evoked potentials and symptoms of attention-deficit/hyperactivity disorder in adult patients with major depressive disorder. Int J Psychophysiol 2019;142:50-56.*
46. Kim JS, Kim S, Jung W, Im CH, Lee SH. *Auditory evoked potential could reflect emotional sensitivity and impulsivity. Sci Rep*

2016;6:37683.
47. Juckel G, Kawohl W, Giegling I, Mavrogiorgou P, Winter C, Pogarell O, *et al. Association of catechol-O-methyltransferase variants with loudness dependence of auditory evoked potentials. Hum Psychopharmacol 2008;23:115-120.*
48. Lee IH, Yang YK, Chen PS, Huang HC, Yeh TL, Lu RB, *et al. Loudness dependence of auditory evoked potentials (LDAEP) correlates with the availability of dopamine transporters and serotonin transporters in healthy volunteers-a two isotopes SPECT study. Psychopharmacology (Berl) 2011;214:617-624.*
49. Park KS, Yoon JR, Park HJ, Park HJ, Kwon KU. *Development of KEDI-WISC, individual intelligence test for Korean children. Seoul:Seoul Korean Educational Development Institute;1996.*
50. Kim MK, Kim ZS. *A study on the abbreviated form of the K-WISC. Seoul J Psychiatry 1986;11:194-201.*
51. Kaufman AS. *A four-test short form of the WISC-R. Contemp Educ Psychol 1976;1:180-196.*
52. So YK, Noh JS, Kim YS, Ko SG, Koh YJ. *The reliability and validity of Korean parent and teacher ADHD rating scale. J Korean Neuropsychiatr Assoc 2002;41:283-289.*
53. Greenberg LM, Waldman ID. *Developmental normative data on the test of variables of attention (T.O.V.A.). J Child Psychol Psychiatry 1993;34:1019-1030.*
54. Shin MS, Cho S, Chun SY, Hong KE. *A study of the development and standardization of ADHD Diagnostic System. J Korean Acad Child Adolesc Psychiatry 2000;11:91-99.*
55. Min JA, Lee SH, Lee SY, Chae JH, Lee CU, Park YM, *et al. Clinical characteristics associated with different strengths of loudness dependence of auditory evoked potentials (LDAEP) in major depressive disorder. Psychiatry Res 2012;200:374-381.*
56. Gow RV, Rubia K, Taylor E, Vallée-Tourangeau F, Matsudaira T, Ibrahimovic A, *et al. Abnormal centroparietal ERP response in predominantly medication-naive adolescent boys with ADHD during both response inhibition and execution. J Clin Neurophysiol 2012;29:181-189.*
57. Mavrogiorgou P, Enzi B, Klimm AK, Köhler E, Roser P, Norra C, *et al. Serotonergic modulation of orbitofrontal activity and its relevance for decision making and impulsivity. Hum Brain Mapp 2017;38:1507-1517.*
58. Beucke JC, Uhl I, Plotkin M, Winter C, Assion HJ, Endrass T, *et al. Serotonergic neurotransmission in early Parkinson`s disease: a pilot study to assess implications for depression in this disorder. World J Biol Psychiatry 2010;11:781-787.*
59. Park HK, Lee JJ, Park YM. *Preserved serotonergic activity in early-onset Parkinson`s disease. Can J Neurol Sci 2020;47:344-349.*
60. Juckel G, Molnár M, Hegerl U, Csépe V, Karmos G. *Auditory-evoked potentials as indicator of brain serotonergic activity--first evidence in behaving cats. Biol Psychiatry 1997;41:1181-1195.*
61. Plotkin M, Beucke JC, Juckel G, Winter C, Bruhn H, Kupsch A. *Serotonin transporters, dopamine transporters and LDAEP in early Parkinson`s disease. J Nucl Med 2007;48 (Suppl 2):8.*
62. Doly S, Quentin E, Eddine R, Tolu S, Fernandez SP, Bertran-Gonzalez J, *et al. Serotonin 2B receptors in mesoaccumbens dopamine pathway regulate cocaine responses. J Neurosci 2017;37:10372-10388.*
63. Fischer AG, Ullsperger M. *An update on the role of serotonin and its interplay with dopamine for reward. Front Hum Neurosci 2017;11:484.*
64. Ishii T, Kimura Y, Ichise M, Takahata K, Kitamura S, Moriguchi S, *et al. Anatomical relationships between serotonin 5-HT2A and dopamine D2 receptors in living human brain. PLoS One 2017;12:e0189318. Erratum in: PLoS One 2018;13:e0197201.*
65. Wood AC, Neale MC. *Twin studies and their implications for molecular genetic studies: endophenotypes integrate quantitative and molecular genetics in ADHD research. J Am Acad Child Adolesc Psychiatry 2010;49:874-883.*
66. O'Neill BV, Guille V, Croft RJ, Leung S, Scholes KE, Phan KL, *et al. Effects of selective and combined serotonin and dopamine depletion on the loudness dependence of the auditory evoked potential (LDAEP) in humans. Hum Psychopharmacol 2008;23:301-312.*
67. Pogarell O, Tatsch K, Juckel G, Hamann C, Mulert C, Pöpperl G, *et al. Serotonin and dopamine transporter availabilities correlate with the loudness dependence of auditory evoked potentials in patients with obsessive-compulsive disorder. Neuropsychopharmacology 2004;29:1910-1917.*
68. Mavrogiorgou P, Enzi B, Steinmann S, Mulert C, Juckel G. *Relationship between neuroanatomical and serotonergic hypotheses of obsessive-compulsive disorder: a combined functional magnetic resonance imaging-evoked potential study. J Clin Psychiatry 2018;79:17m11811.*
69. Pauletti C, Mannarelli D, Locuratolo N, Maffucci A, Currà A, Marinelli L, *et al. Serotonergic central tone in Parkinson's disease with fatigue: evidence from the loudness dependence of auditory evoked potentials (LDAEP). Neurosci Lett 2021;764:136242.*
70. Park YM, Lee SH, Kim S, Bae SM. *The loudness dependence of the auditory evoked potential (LDAEP) in schizophrenia, bipolar disorder, major depressive disorder, anxiety disorder, and healthy controls. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:313-316.*
71. Uhl I, Illes F, Graßnickel V, Echterhoff S, Norra C, Juckel G. *Loudness dependence of auditory evoked potentials (LDAEP) in clinical monitoring of suicidal patients with major depression: a pilot study. Eur Arch Psychiatry Clin Neurosci 2012;262:487-492.*
72. Kim JS, Kim S, Lee HS, Kwon YJ, Lee HY, Shim SH. *Auditory evoked potentials and suicidal behaviors in patients with major depressive disorders. Sci Rep 2021;11:7255.*
73. Hagenmuller F, Heekeren K, Meier M, Theodoridou A, Walitza S, Haker H, *et al. The Loudness Dependence of Auditory Evoked Potentials (LDAEP) in individuals at risk for developing bipolar disorders and schizophrenia. Clin Neurophysiol 2016;127:1342-1350.*

74. Reimherr FW, Marchant BK, Gift TE, Steans TA. *ADHD and anxiety: clinical significance and treatment implications. Curr Psychiatry Rep 2017;19:109.*
75. Mitchison GM, Njardvik U. *Prevalence and gender differences of ODD, anxiety, and depression in a sample of children with ADHD. J Atten Disord 2019;23:1339-1345.*
76. Seo JC, Jon DI, Shim SH, Sung HM, Woo YS, Hong J, *et al. Prevalence and comorbidities of attention deficit hyperactivity disorder among adults and children/adolescents in Korea. Clin Psychopharmacol Neurosci 2022;20:126-134.*
77. Oh Y, Joung YS, Kim J. *Association between ADHD medication and depression: a 10-year follow-up self-controlled case study. Clin Psychopharmacol Neurosci 2022;20:320-329.*
78. Graßnickel V, Illes F, Juckel G, Uhl I. *Loudness dependence of auditory evoked potentials (LDAEP) in clinical monitoring of suicidal patients with major depression in comparison with non-suicidal depressed patients and healthy volunteers: a follow-up-study. J Affect Disord 2015;184:299-304.*
79. Baptista J, Belsky J, Mesquita A, Soares I. *Serotonin transporter polymorphism moderates the effects of caregiver intrusiveness on ADHD symptoms among institutionalized preschoolers. Eur Child Adolesc Psychiatry 2017;26:303-313.*
80. van Rooij D, Hartman CA, van Donkelaar MM, Bralten J, von Rhein D, Hakobjan M, *et al. Variation in serotonin neurotransmission genes affects neural activation during response inhibition in adolescents and young adults with ADHD and healthy controls. World J Biol Psychiatry 2015;16:625-634.*
81. Park S, Lee JM, Kim JW, Cho DY, Yun HJ, Han DH, *et al. Associations between serotonin transporter gene (SLC6A4) methylation and clinical characteristics and cortical thickness in children with ADHD. Psychol Med 2015;45:3009-3017.*
82. Banerjee E, Nandagopal K. *Does serotonin deficit mediate susceptibility to ADHD? Neurochem Int 2015;82:52-68.*
83. Brammer WA, Lee SS. *Prosociality and negative emotionality mediate the association of serotonin transporter genotype with childhood ADHD and ODD. J Clin Child Adolesc Psychol 2013;42:809-819.*
84. Landaas ET, Johansson S, Jacobsen KK, Ribasés M, Bosch R, Sánchez-Mora C, *et al. An international multicenter association study of the serotonin transporter gene in persistent ADHD. Genes Brain Behav 2010;9:449-458.*
85. Retz W, Retz-Junginger P, Supprian T, Thome J, Rösler M. *Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. Behav Sci Law 2004;22:415-425.*
86. Oades RD. *Role of the serotonin system in ADHD: treatment implications. Expert Rev Neurother 2007;7:1357-1374.*
87. Molina-Carballo A, Naranjo-Gómez A, Uberos J, Justicia-Martínez F, Ruiz-Ramos MJ, Cubero-Millán I, *et al. Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. J Psychiatr Res 2013;47:377-383.*
88. Thakur GA, Grizenko N, Sengupta SM, Schmitz N, Joober R. *The 5-HTTLPR polymorphism of the serotonin transporter gene and short term behavioral response to methylphenidate in children with ADHD. BMC Psychiatry 2010;10:50.*
89. Cheung CH, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, *et al. Cognitive and neurophysiological markers of ADHD persistence and remission. Br J Psychiatry 2016;208:548-555.*
90. Pasini A, Sinibaldi L, Paloscia C, Douzgou S, Pitzianti MB, Romeo E, *et al. Neurocognitive effects of methylphenidate on ADHD children with different DAT genotypes: a longitudinal open label trial. Eur J Paediatr Neurol 2013;17:407-414.*
91. Monden Y, Dan H, Nagashima M, Dan I, Tsuzuki D, Kyutoku Y, *et al. Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: an fNIRS study. Neuroimage Clin 2012;1:131-140.*
92. Snyder SM, Rugino TA, Hornig M, Stein MA. *Integration of an EEG biomarker with a clinician's ADHD evaluation. Brain Behav 2015;5:e00330.*
93. Nagy E, Potts GF, Loveland KA. *Sex-related ERP differences in deviance detection. Int J Psychophysiol 2003;48:285-292.*
94. Guillem F, Mendrek A, Lavoie ME, Pampoulova T, Stip E. *Sex differences in memory processing in schizophrenia: an event-related potential (ERP) study. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1-10.*
95. Buchmann J, Gierow W, Reis O, Haessler F. *Intelligence moderates impulsivity and attention in ADHD children: an ERP study using a go/nogo paradigm. World J Biol Psychiatry 2011;12 Suppl 1:35-39.*