International Journal of Psychophysiology 142 (2019) 50–56

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Full Length Article

The relationship between auditory evoked potentials and symptoms of attention-deficit/hyperactivity disorder in adult patients with major depressive disorder

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ARTICLE INFO

Keywords:
LDAEP
ADHD
Adult
Depression

ABSTRACT

Objectives: Loudness dependence of auditory evoked potential (LDAEP) has been proposed as a biological marker for central serotonergic activity in depressive illness. A recent study has suggested that serotonin plays an important role in impulsivity and emotional sensitivity that are prominent clinical manifestations in attention deficit and hyperactivity disorder (ADHD). The objective of this study was to examine the association between LDAEP and ADHD symptoms in major depressive disorder (MDD).

Methods: A total of 60 participants (40 subjects with MDD and 20 healthy controls) aged > 18 years who had LDAEPs performed during electroencephalograms were included in this study. ADHD symptoms, depressive, and anxiety symptoms were evaluated. Psychological characteristics and event-related potentials (ERP) were compared among three groups: depression with ADHD symptoms, depression without ADHD symptoms, and healthy controls.

Results: MDD subjects with ADHD symptoms ($N = 20$) showed significantly lower LDAEP levels than those without ADHD symptoms ($N = 20$) and healthy controls ($N = 20$). LDAEP differences between MDD subjects without ADHD symptoms and healthy controls were not statistically significant. In partial correlation analyses adjusted for age and sex, significant correlations of psychological scales of depression, ADHD symptoms, and LDAEPs were found.

Conclusion: Results of the present study suggest that LDAEP can reflect adult ADHD symptoms in MDD. Auditory evoked potential appears to be a promising candidate as an evaluation tool for inattention and poor impulse control as well as emotional sensitivity.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) frequently has comorbid depressive disorder (Di Trani et al., 2014). Attention deficits are frequently discovered in patients with major depressive disorder (MDD) (Bond et al., 2012). MDD is characterized by deficits in cognitive domains such as attention and concentration (Zuckerman et al., 2018). Previous studies have reported that 5 to 16% of adult patients with MDD also meet the criteria for ADHD (McIntyre et al., 2010).

Adult patients with ADHD and mood disorders are known to experience more severe dysfunctions and worse treatment outcomes compared to those with mood disorders alone (Bond et al., 2012; Turgay and Ansari, 2006). Comorbid ADHD is known to be associated with poorer quality of life and increased costs of mental healthcare services (Fischer et al., 2007; Katzman et al., 2017; McIntyre et al., 2010). Due to differences in treatment and prognosis between MDD alone and comorbid ADHD symptoms (Yüce et al., 2015), early detection of comorbid ADHD symptoms is crucial in clinical practice. However, clinicians are challenged in recognizing and diagnosing comorbid ADHD conditions in MDD because of commonly overlapping symptoms between these two disorders (Katzman et al., 2017).

Previous studies have shown a genetic overlap between ADHD and depression and both disorders involve dopamine reward circuit problems and difficulty in emotional regulation (Yüce et al., 2015).

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https://doi.org/10.1016/j.ijpsycho.2019.06.008
Received 7 March 2019; Received in revised form 10 June 2019; Accepted 13 June 2019
Available online 14 June 2019

Molecular genetics studies have linked several dopaminergic and serotonergic genes to reward functioning, ADHD (Wood and Neale, 2010), and depression (Kato, 2007). There is also evidence indicating that neural activity in dopamine-mediated reward circuitry is linked to constructs in both ADHD and depression, including negative affect, low motivation, and inattention (Durston, 2003; Epstein et al., 2006; Meinzer et al., 2014; Pizzagalli et al., 2008). Each disorder shows symptom overlap, including attention deficits, emotional sensitivity, and poor impulse control.

Loudness dependence of auditory evoked potential is a noninvasive Electroencephalogram (EEG) measure that assesses changing patterns of N1-P2 amplitude in response to varying loudness levels of auditory stimulation (Min et al., 2012). It is a measure of auditory cortex activity which is richly innervated by 5-HT (serotonin) neurons, reflecting an increase or decrease in the slope of auditory evoked potentials with increasing tone loudness (Hegerl and Juckel, 1993). It reflects individual differences in cortical sensory processing related to 5-HT (Hegerl and Juckel, 1993). Generally, the slope of the N1/P2 component is steeper (i.e., a stronger LDAEP) when central 5-HT activity is low, and vice versa (Hegerl and Juckel, 1993; Juckel et al., 1997). Along with the above relationship with 5-HT activity, LDAEP is higher in MDD patients than healthy control (Fitzgerald et al., 2009; Lee et al., 2014). Previous studies have predicted treatment response to specific pharmacological interventions (Wyss, 2016). In affective disorders, strong LDAEP (i.e., low serotonergic level) can reflect a favorable response to selective serotonin reuptake inhibitors (SSRI) (Hegerl et al., 2001; Leuchter et al., 2009). However, effects of SSRI on LDAEP are contradictory (Gallinat et al., 2000; Linka et al., 2009; Norra et al., 2008). The vast majority of studies linking 5-HT activity in the auditory cortex with LDAEP have been carried out in cats (Juckel et al., 1997). Evidence in humans for the relation between serotonin and LDAEP is also inconsistent (Kenemans and Kahkonen, 2011). Moreover, it has been suggested that LDAEP is not only influenced by serotonin, but also affected by dopaminergic neurotransmission (Juckel et al., 1997). Effects of high-dose glycine, a modulator of NMDA receptors, on LDAEP have been also studied (O'Neill et al., 2007). In addition to association of LDAEP with serotonergic system related to the characteristics of LDAEP, previous studies have reported that individuals who are sensitive to external stimuli have stronger emotional responses (Jagiellowicz et al., 2011). A specific relationship between emotional sensitivity and LDAEPs has also been reported (Kim et al., 2016). Additionally, previous studies have directly reported that LDAEPs are stronger in more impulsive individuals (Uhl et al., 2012) and that LDAEP could reflect behavioral inhibition (Kim et al., 2016).

Considering that poor impulse control and emotional sensitivity could be observed in ADHD patients (Philipsen, 2006) and the fact that 5-HT systems play a role in ADHD (Oades, 2008), LDAEP slopes might be quantitatively different between patients with MDD alone and those both MDD and ADHD symptoms. Despite a plausible relationship among LDAEPs, symptoms of ADHD, and symptoms of depression (Kim et al., 2016), studies investigating the association between LDAEPs and ADHD symptoms in patients with MDD have not been reported yet. To obtain better understanding of trans-diagnostic factors that overlap in different disorders, an electrophysiological marker that can differentiate MDD and comorbid ADHD symptoms should be developed.

Since LDAEP might be associated with behavioral inhibition and emotional sensitivity, we hypothesized that LDAEP could differ in patients with MDD and those with both MDD and ADHD symptoms depending on the presence or absence of ADHD symptoms. Thus, the aim of this study was to evaluate differences in LDAEP among patients with MDD without ADHD symptoms, those with both MDD and ADHD symptoms, and healthy controls. The present study was conducted to verify the relationship between LDAEP and ADHD symptoms related to emotional sensitivity and behavioral inhibition.

Table 1
Comparison of baseline demographic data among MDD patients with ADHD symptoms, MDD patients without ADHD symptoms, and healthy controls.

	With ADHD symptoms (N = 20)	Without ADHD symptoms (N = 20)	Healthy controls (N = 20)	p
	Mean ± SD or N (%)			
Age (years)	25.90 ± 8.12	26.25 ± 8.65	30.15 ± 5.26	0.15
Gender				
Male	12 (60.0)	8 (40.0)	9 (45.0)	0.42
Female	8 (40.0)	12 (60.0)	11 (55.0)	
Education (years)	12.50 ± 1.67	12.60 ± 2.14	16.40 ± 0.82	< 0.001[a]

[a] With ADHD symptoms vs healthy control, $p < 0.001$; without ADHD symptoms vs healthy control, $p < 0.001$.

2. Subjects and methods

2.1. Participants

Participants with MDD were recruited from the Psychiatry Department of Soonchunhyang University Cheonan Hospital, Korea. Patients with MDD were diagnosed according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders (First et al., 1997). This study was performed on 40 patients with MDD (20 men and 20 women) with a mean age of 26.08 ± 8.29 years. Among depressed patients (N = 40), 12 patients had comorbid anxiety disorder. Twenty matched non-smoking healthy controls were recruited from the local community through newspapers and posters. Participants with any history of neurological or other severe medical diseases and a smoking history within two years were excluded from this study through initial screening interviews. None of these patients had mental retardation, alcohol abuse, electroconvulsive therapy, or head injury. All patients with depression were drug-naïve. They had no history of antidepressant pharmacotherapy. Each participant had normal hearing ability confirmed by the 512-Hz tuning fork test (Burkey et al., 1998). All participants were right-handed. This study and all experimental protocols were approved by the Institutional Review Board and Ethics Committee of Soonchunhyang University Cheonan Hospital (approval number: 2018–10–032-002). The study was performed in accordance with approved guidelines.

2.2. Assessment

All participants were assessed for ADHD symptoms using the Korean version of Adult ADHD self-report scales (ASRS) (Heo et al., 2018). The ASRS is a widely used self-reporting scale with 18 items. Each item was evaluated on a 5-point Likert scale to screen for ADHD in the general population (Kessler et al., 2005). It evaluates ADHD symptoms based on the DSM-IV criteria for ADHD during the past six months. Inattention (ASRS inattention score, ASRS-I) and hyperactivity scores (ASRS hyperactivity score, ASRS-H) could be separately calculated. The ASRS consisted of Parts A and B. Six questions of Part A in this scale were found to be the most predictive of symptoms consistent with ADHD. Therefore, we defined MDD patients with ADHD symptoms as having four or more marks in darkly-shaded boxes within Part A. A total ASRS score higher than 31 points was defined as the 50th percentile (Adler et al., 2006). The Korean version of ASRS showed good sensitivity and specificity. Depressive and anxiety symptoms were evaluated using the Beck Depression Inventory (Rhee et al., 1995) and the State-Trait Anxiety Inventory (STAI) (Kim and Shin, 1978), respectively. The STAI is a commonly used measure of trait and state anxiety. It consists of a state anxiety inventory (SAI) and trait anxiety inventory (TAI), each of which comprises of 20 items (Kim and Shin, 1978).

Table 2
Comparison of baseline clinical symptom characteristics among MDD patients with ADHD symptoms, MDD patients without ADHD symptoms, and healthy controls.

	With ADHD symptoms (N = 20)	Without ADHD symptoms (N = 20)	Healthy controls (N = 20)	*p*	*Pairwise test* *P*
	Mean ± SD or N (%)				
Clinical symptom characteristics					With vs. without ADHD
ASRS	43.60 ± 8.26	17.40 ± 10.29	8.95 ± 6.86	< 0.001	< 0.001
Inattention	24.85 ± 5.27	9.45 ± 5.74	6.20 ± 4.82	< 0.001	< 0.001
Hyperactivity	18.75 ± 5.65	8.50 ± 5.31	2.75 ± 2.51	< 0.001	< 0.001
STAI state	64.72 ± 13.78	62.4 ± 9.91	37.23 ± 9.26	< 0.001[a]	0.05
STAI trait	67.44 ± 10.86	63.85 ± 8.56	41.8 ± 10.92	< 0.001[b]	0.09
BDI	35.94 ± 10.46	27.05 ± 10.14	9.67 ± 6.00	< 0.001[c]	0.57

ASRS: Adult ADHD Self Rating Scale, STAI: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory.
[a] MDD with ADHD symptoms vs. healthy control, $p < 0.001$; MDD without ADHD symptoms vs. healthy control, $p < 0.001$.
[b] MDD with ADHD symptoms vs healthy control, $p < 0.001$; MDD without ADHD symptoms vs healthy control, $p < 0.001$.
[c] MDD with ADHD symptoms vs healthy control, $p < 0.001$; MDD without ADHD symptoms vs healthy control, $p < 0.001$.

Table 3
Comparison of the number of epochs of LDAEP used for the analysis among MDD patients with ADHD symptoms, MDD patients without ADHD symptoms, and healthy controls.

	With ADHD symptoms (N = 20)	Without ADHD symptoms (N = 20)	Healthy controls (N = 20)	*p*
	Mean ± SD or N (%)			
Stimuli intensity				
60 dB	185.32 ± 15.21	183.25 ± 16.28	184.31 ± 12.91	0.41
70 dB	184.51 ± 15.91	182.39 ± 17.30	183.75 ± 12.29	0.43
80 dB	184.37 ± 16.49	183.28 ± 16.37	184.17 ± 12.38	0.68
90 dB	185.48 ± 15.18	182.29 ± 17.14	184.32 ± 12.61	0.22
100 dB	184.57 ± 15.16	182.64 ± 15.68	183.84 ± 13.27	0.46

2.3. Data acquisition and analysis

During EEG task, each participant was tested in a sound-attenuated EEG room. EEG was acquired using a NeuroScan SynAmps amplifier (Compumedics USA, E1 Paso, TX, USA) with 64 Ag-AgCl electrodes mounted on a Quik Cap using an extended 10–20 placement scheme. The ground electrode was located on the forehead and the physically linked reference electrode was attached to both mastoids. Vertical electrooculogram (EOG) was positioned above and below the left eye and horizontal EOG was placed at the outer canthus of each eye. The impedance was kept below 10 kΩ. All data were processed with a 0.1–100 Hz band-pass filter and sampled at 1000 Hz. Recorded EEG data were preprocessed using CURRY 8. Gross artifacts were rejected by visual inspection of a trained person without prior information regarding the origin of the data. Artifacts related to eye movement or eye blinks were removed using the mathematical procedure in the preprocessing software. Data were filtered using a 0.1–30 Hz band-pass filter and epoched from 100 ms pre-stimulus to 600 ms post-stimulus. These epochs were subtracted from the average value of the pre-stimulus interval for baseline correction. If any remaining epochs contained significant physiological artifacts (amplitude exceeding ± 75 μV) in any of 62 electrode sites, they were excluded from further analysis. Only artifact-free epochs were averaged across trials and participants for event-related potential (ERP) analysis.

2.4. Loudness dependence auditory evoked potentials (LDAEP)

LDAEP was calculated as amplitude change of the evoked N1/P2 component in response to different auditory stimulus intensities (Hegerl et al., 2001). Auditory stimulation comprised of 1000 stimuli with an inter-stimulus interval that was randomized between 500 and 900 ms. Tones of 1000 Hz and 80-ms duration (10-ms rise and 10-ms fall) were presented at five intensities (60, 70, 80, 90, and 100 dB SPL) through MDR-D777 headphones (Sony, Tokyo, Japan). These stimuli were generated with *E*-Prime software (Psychology Software Tools, Pittsburgh, PA, USA). For these five sound intensities and each subject, N1 peak (most negative peak between 80 and 180 ms from the stimulus) and P2 peak (most positive peak between 150 and 250 ms from the stimulus) at Cz electrode were then determined (Hagenmuller et al., 2016). Peak-to-peak N1/P2 amplitudes were calculated for the five stimulus intensities. LDAEP was calculated as the slope of linear regression. The number of epochs of LDAEP used for the analysis did not significantly differ among groups of depression with ADHD symptoms, depression without ADHD symptoms, and healthy controls (Table 3).

2.5. Statistical analyses

The Kolmogorov–Smirnov test revealed that collected data were normally-distributed. Analysis of variance (ANOVA) was used to examine differences in demographic and clinical symptom variables among the three groups of subjects. ANOVA with age and gender as covariates was carried out to compare peak amplitude of LDAEPs at Cz electrodes across the three groups (Min et al., 2012). Fisher's least significant difference (LSD) post-hoc test was used. A Chi-squared analysis or Fisher's exact test was used for categorical data. In addition, relationships between variables in patients with depression were determined using Pearson's correlation analysis. When LDAEP was included in the correlation analysis, partial Pearson's correlation analysis was used to control for age and gender as covariates with a 5000-bootstrap resampling technique to correct for multiple correlations. Although Bonferroni correction is a strict method to avoid problems from multiple tests, it has a disadvantage in that Bonferroni correction is unnecessarily conservative that might lead to inappropriate smaller *p*-values (Hommel, 1988). Bootstrap test is a weaker method than Bonferroni test in solving multiple comparison problem. However, robustness and stability of bootstrap have been recognized by various previous studies (Haukoos and Lewis, 2005; Pernet et al., 2013; Ruscio, 2008). Also, bootstrap test has been widely used in EEG analysis (Kim et al., 2016; Pernet et al., 2011). For these reasons, we decided that bootstrap method was appropriate in our study. The significance level was set at $p < 0.05$ (two-tailed). All statistical analyses were performed using SPSS 21 (SPSS, Inc., Chicago, IL, USA).

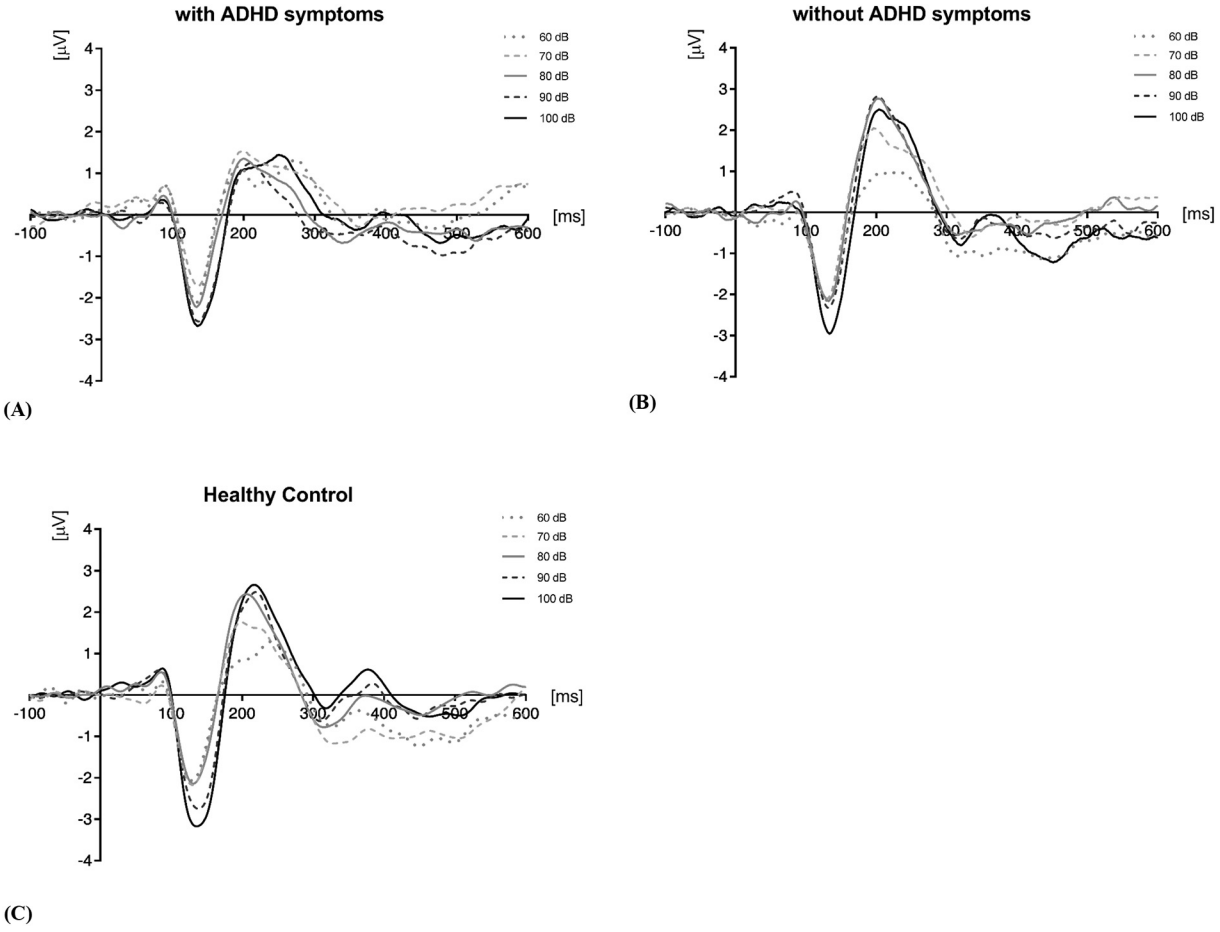

Fig. 1. Grand average of loudness dependence of the auditory evoked potential (LDAEP) event-related potentials (ERPs) at the Cz electrode for MDD patients with ADHD symptoms (A), MDD patients without ADHD symptoms (B), and healthy controls (C).

3. Results

3.1. Participants

Table 1 and Table 2 present baseline demographic and clinical characteristics of MDD patients with or without ADHD symptoms and healthy controls. There was no significant group difference according to age or gender (Table 1). The healthy control group had significantly more education years than patients with depression ($p < 0.001$). MDD patients with ADHD symptoms showed significantly higher ASRS scores than MDD patients without ADHD symptoms. These results revealed no significant differences in STAI state, STAI trait, or BDI between MDD patients with ADHD symptoms and those without ADHD symptoms (Table 2).

3.2. Loudness dependence auditory evoked potentials (LDAEP)

The three groups of subjects showed significantly different LDAEP levels ($F = 9.60$, $p < 0.001$). LDAEP levels in healthy controls were higher (stronger) than those in the other two groups (LDAEP in MDD with ADHD: 0.34 ± 0.67; LDAEP in MDD without ADHD: 0.84 ± 0.78; LDAEP in healthy controls: 1.28 ± 0.57). MDD patients with ADHD symptoms had significantly lower LDAEPs than MDD patients without ADHD symptoms ($p = 0.02$) and healthy controls ($p < 0.001$). Although there were significant differences in LDAEPs between depressed patients without ADHD and healthy controls, LDAEPs in healthy controls showed a tendency to be significantly lower compared to those in depressed patients without ADHD ($p = 0.05$). When we controlled education years with age and gender as covariates, the three groups showed significantly different LDAEP levels ($F = 6.95$, $p = 0.002$). MDD patients with ADHD symptoms had significantly lower LDAEPs than MDD patients without ADHD symptoms ($p = 0.01$) and healthy controls ($p = 0.001$). However, LDAEPs were not significantly different between healthy controls and depressed patients without ADHD ($p = 0.11$). The grand average of the loudness dependence of the auditory evoked potential (LDAEP) event-related potentials (ERPs) at the Cz electrode for each group is shown in Fig. 1.

3.3. Correlation analysis of LDAEPs with psychological characteristics

LDAEPs were significantly correlated with ADHD symptoms (ASRS) ($r = -0.396$, $p = 0.014$) (Fig. 2.A). In subscales of ASRS scores, inattention ($r = -0.442$, $p = 0.006$) was also significantly correlated with LDAEP (Fig. 2B). LDAEP was significantly correlated with depression measures such as BDI ($r = 0.506$, $p < 0.001$) (Fig. 2C). However, LDAEP was not significantly correlated with hyperactivity ($r = -0.300$, $p = 0.071$) or other subscale of ASRS scores.

4. Discussion

This study aimed to investigate whether LDAEP was different in patients with MDD and those with both MDD and ADHD symptoms depending on the presence or absence of ADHD symptoms. First, depressed patients with ADHD symptoms showed lower (weaker) LDAEP than those without ADHD symptoms and healthy controls. Second, LDAEP was significantly correlated with ASRS scores and the inattention subscale of ASRS.

MDD patients with ADHD symptoms had significantly lower

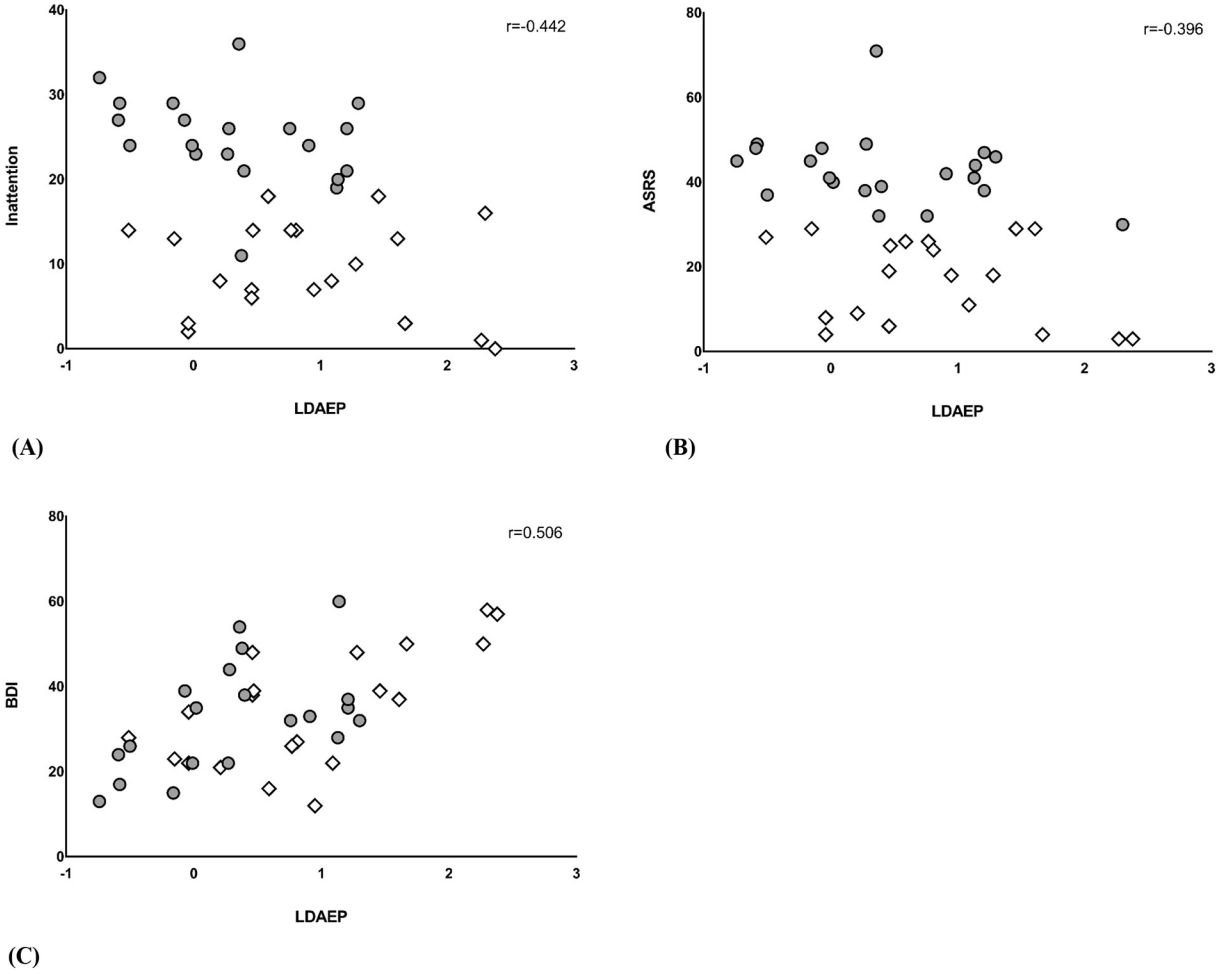

Fig. 2. The loudness dependence of the auditory evoked potential (LDAEP) showed a significant correlation with Adult ADHD self-report scales (ASRS), the inattention subscale of ASRS (ADHD symptom scales), and the Beck Depression Inventory (BDI) depressive symptom scale. (A) Scatter plots of LDAEPs at Cz electrode and ASRS in patients with depression (N = 40). (B) Scatter plots of LDAEPs at Cz electrode and the inattention subscale of ASRS in patients with depression (N = 40). (C) Scatter plots of LDAEPs at Cz electrode and BDI in patients with depression (N = 40).
ASRS: Adult ADHD self-report scales, BDI: Beck Depression Inventory.
Circles indicate MDD subjects with ADHD symptoms (N = 20). Diamonds indicate MDD subjects without ADHD symptoms (N = 20).

LDAEPs than MDD patients without ADHD symptoms and healthy controls in this study. Considering that LDAEP was inversely associated with central serotonergic system (O'Neill et al., 2008), our results were not in line with previous studies (Park, 2018; Fitzgerald et al., 2009). Lower LDAEPs were observed in individuals homozygous for the long allele of 5-HT transporter (5-HTT) promoter (Gallinat et al., 2003). This long allele was associated with ADHD in previous studies (Curran et al., 2005; Li et al., 2007). Besides the serotonergic system, lower LDAEPs could decrease responsiveness to exogenous stimuli and a weak loudness dependency reflects lower exogenous attention (Buchsbaum and Silverman, 1968; Wyss, 2016). Behavioral expressions of sensory modulation disorder, a subtype of sensory processing disorder, are often similar to those of ADHD in pediatric and adult populations. High comorbidity rates of these two diagnoses are also reported (Mazor-Karsenty et al., 2018). Lower LDAEP in patients with both MDD and ADHD symptoms observed in this study might reflect decreased responsiveness to exogenous stimuli in situation that needed attention. The relation between stimulus intensity dependence and personality factors such as impulsiveness, aggressiveness, and sensation seeking behavior has been studied (Linka et al., 2007; Zuckerman et al., 1974). Considering that the above personality factors were often observed in patients with ADHD symptoms (Graziano et al., 2015), our results might suggest that LDAEP could reflect adult ADHD symptoms in MDD.

Moreover, the difference in LDAEPs between depressed patients without ADHD and healthy controls was only observed as a trend, similar to a previous study comparing between depressed patients with or without suicidality and healthy volunteers (Grassnickel et al., 2015). That study revealed that there was a trend toward higher LDAEPs in healthy volunteers compared to non-suicidal depressed patients. The absence of a clear loudness-dependent anomaly in MDD without ADHD suggests that LDAEP might not be the only biomarker of LDAEP. It might be a biomarker not simply reflecting emotionality such as depression and anxiety, but reflecting various behavioral manifestations such as inattention and poor impulse control influenced by serotonergic function. That is, specific alterations of LDAEP are not expected in major depression in general, but confined to subgroups of depressed patients (Linka et al., 2007). A number of studies have cast doubt on the usefulness of LDAEP as a biomarker, citing no treatment effect on LDAEPs or non-specificity of LDAEP for 5HT (Gallinat et al., 2000; Leiser et al., 2011; Linka et al., 2007), despite the serotonergic system has clinical importance in psychiatric illness (O'Neill et al., 2008; Pogarell et al., 2007). However, unexpectedly, the hyperactivity subscale was not significantly correlated with LDAEP despite it had a significant correlation with ASRS. It might be attributed to small sample size, absence of proper control such as ADHD alone group in this study, or correlation analysis without including a healthy control group. In the

correlation analysis including healthy control group, the hyperactivity subscale was significantly correlated with LDAEP. In this text, further study including a group of participants with ADHD but no depression with a larger sample size is needed to verify the usefulness of LDAEP as a biomarker in various behavioral manifestations.

The present study also found that LDAEPs were significantly correlated with ADHD symptoms as well as group difference seen above. This significant correlation suggested that auditory evoked potential reflected ADHD symptoms. Interestingly, in the subscale of ASRS scores, inattention was also significantly correlated with LDAEPs. Patients with ADHD have long been known to show impaired sustained attention in terms of top-down controlled discrimination (Oades, 2000). Ability to sustain attentional processing and its inhibitory control of the activity of catecholamine neurons at neurophysiological level exerts a homeostatic role. It has been described as setting the tone at a system level (Jacobs et al., 1990). Salient stimuli at both perceptual and physiological levels are likely to evoke responses in the 5-HT system (Oades, 2007). Together with evidence for the involvement of genetic variants of 5-HT synthesis and transport in the expression of attentional abilities (Posner et al., 2007), one can anticipate a role of the 5-HT system in characteristics of attentional function shown by those with ADHD (Oades, 2007). Regarding the relationship of inattention with the 5-HT system, an interesting association between the inattention subscale and LDAEP is plausible.

This study has a few limitations. First, the relatively small sample size should be considered when interpreting results of this study. Further studies are needed to confirm results of this study with larger samples. Second, ADHD symptoms were evaluated using a self-reporting questionnaire in this study. Although the ASRS was verified to be able to screen ADHD symptoms effectively (Heo et al., 2018) and an adequate tool for our study design, we could not include comorbid ADHD diagnosed patients through confirmatory analyses for ADHD. Further studies are needed to confirm our results in depressed patients with ADHD using standardized clinicians' diagnostic tools. Additionally, although LDAEP is known to be a reliable indicator of serotonin, further studies comparing LDAEP with more direct measurement of central serotonin levels are necessary before drawing firm conclusions. Lastly, individuals with official ADHD diagnosis were not included in this study. To clarify the usefulness of LDAEP as a candidate marker to solve trans-diagnostic problems, further study with an official ADHD diagnosed group would be needed.

Despite the above limitations, to the best of our knowledge, this study was the first to explore the relationship between LDAEPs and the presence of ADHD symptoms in depressed patients. Results of the present study suggest that LDAEP may be a useful tool for evaluating mood symptoms with comorbidities such as ADHD in depressed individuals. Detection of an electrophysiological marker to differentiate MDD with comorbid ADHD symptoms could help clinicians provide proper treatment for depressed patients with comorbid ADHD symptoms.

Acknowledgement

This work was supported by a grant (No. 2018R1C1B5044454) of the National Research Foundation of Korea (NRF) funded by the Korea government (MSIT) and a grant (2017R1D1A3B03030974) of the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education. This study was also supported by Soonchunhyang University.

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