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Association between the loudness dependence of auditory evoked potentials and age in patients with schizophrenia and depression

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Abstract

Objective: Although serotonergic dysfunction is significantly associated with major depressive disorder (MDD) and schizophrenia (SCZ), comparison of serotonergic dysfunction in both diseases has received little attention. Serotonin hypotheses have suggested diminished and elevated serotonin activity in MDD and SCZ, respectively. However, the foundations underlying these hypotheses are unclear regarding changes in serotonin neurotransmission in the aging brain. The loudness dependence of auditory evoked potentials (LDAEP) reflects serotonin neurotransmission. The present study compared the LDAEP between patients with SCZ or MDD and healthy controls (HCs). We further examined whether age was correlated with the LDAEP and clinical symptoms.

Methods: This prospective clinical study included 105 patients with SCZ (n = 54) or MDD (n = 51). Additionally, 35 HCs were recruited for this study. The LDAEP was measured on the midline channels via 62 electroencephalography channels.

Results: Patients with SCZ or MDD showed a significantly smaller mean LDAEP than those in HCs. The LDAEP was positively correlated with age in patients with SCZ or MDD.

Conclusions: Changes in central serotonergic activity could be indicated by evaluating the LDAEP in patients with SCZ or MDD. Age-related reductions in serotonergic activity may be screened using the LDAEP in patients with SCZ or MDD.

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Introduction

Serotonergic dysfunction can lead to major pathological features in patients with schizophrenia (SCZ) and major depressive disorder (MDD).[1–3] However, comparison of serotonergic activity between the two diseases has received little attention. Some studies have hypothesized that patients with MDD[4] have diminished serotonin neurotransmitter levels and those with SCZ exhibit elevated serotonergic neurotransmission.[5] However, the pathological complexity underlying these changes in serotonin neurotransmission is not clearly understood.[6–9] MDD is a heterogeneous disorder because only 30% to 40% of patients respond to antidepressants.[10,11] SCZ also shows heterogeneity, and the understanding of the serotonergic neuropathological effects on the brain is unclear.[12,13] Thus, a need exists to compare the changes in the central serotonergic activity in both diseases.

The loudness dependence of auditory evoked potentials (LDAEP), which is measured by electroencephalography (EEG), has been proposed as a clinical biomarker for psychiatric disorders.[14–21] Serotonergic activity is negatively correlated with the LDAEP in the brain,[22] which represent slope variations in the neural responses to auditory stimuli.[23–25] A previous study found that shallower LDAEP slopes reflect elevated serotonin transmission in the dorsal raphe nucleus.[26] Patients with SCZ showed increased serotonergic activity compared with those with other psychiatric disorders and healthy controls (HCs).[18,27,28] However, the significance of the LDAEP in SCZ and MDD has been focused on symptomatic and subclinical changes and treatment responses.[14,19,29–31] In patients with SCZ, the LDAEP predicts the risk of disease progression.[32] The LDAEP also predicts treatment responses to antidepressants and brain stimulation in patients with MDD.[14,33,34]

Serotonin receptor stimulation results in perceptual disturbances such as hallucinations in patients with SCZ,[5] and serotonergic activity has been shown to play important roles in both SCZ and MDD.[35,36] Moreover, antidepressants can increase the number of presynaptic serotonergic neurons in patients with MDD.[37] In addition, serotonin activity may modulate symptom severity and treatment responses in patients with SCZ and MDD.[38–40] Although previous studies have reported that the LDAEP did not differ between patients with MDD and HCs,[18,41] these potentials could predict treatment responses to antidepressants such as selective serotonin reuptake inhibitors (SSRIs) in MDD.[42,43] Furthermore, the effect of age on the LDAEP has been reported through a pathway model in which, according to sex, age predicted the LDAEP in patients with MDD.[44] Patients with SCZ showed a negative correlation between the LDAEP and chronicity of illness, but these findings had a low statistical power.[19]

Serotonergic neurons are altered during aging. For example, elderly people with depression show decreased serotonergic activity,[4,45] and age-related changes in

serotonin neurotransmission modulate sensory perceptions.[46–48] One study found that 5-hydroxytryptamine 2 (5-HT2) receptor binding was significantly attenuated with age in patients with SCZ and HCs.[49]

The current study was performed to examine the changes in serotonin transmission in patients with SCZ and MDD and the age-related alterations in serotonergic activity. Therefore, we compared the LDAEP between patients with SCZ or MDD and HCs. Additionally, we explored the association between age and LDAEP in patients with SCZ or MDD. We hypothesized that patients with SCZ would have a smaller LDAEP than patients with MDD and HCs, indicating increased serotonin neurotransmission in patients with SCZ. We further hypothesized that the LDAEP would correlate with age in patients with SCZ or MDD.

Methods

Participants

All participants were native Koreans and were diagnosed and screened using the Mini International Neuropsychiatric Interview of the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. Assessments using the Positive and Negative Syndrome Scale (PANSS)[50] were performed in patients with SCZ by a trained psychiatrist who was not involved in the present study. Patients with MDD were evaluated using the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale[51,52] by a trained psychiatrist. In addition, measurements with the Beck Depression Inventory (BDI), which is a self-rating scale, were conducted in patients with MDD and HCs.[53] This prospective clinical research report was approved by the Institutional Review Board of Seoul St. Mary's Hospital College of Medicine, The Catholic University of Korea (approval number: KC09FZZZ0211). Written informed consent was obtained from all participants. All experimental procedures followed the relevant Equator guidelines, and the reporting of this study conforms to STROBE guidelines.[54] All patient details were de-identified.

EEG recordings

The participants were seated in a comfortable chair in a sound-attenuated room. The EEG data were recorded using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) with a head cap mounted with AgCl electrodes according to the international extended 10–20 system. The following 62 scalp electrodes were employed: FP1, FPz, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO5, PO3, POz, PO4, PO6, PO8, CB1, O1, Oz, O2, and CB2. Electrooculography electrodes were placed above and below the left eye to detect vertical movement and at the outer canthus of each eye to measure horizontal movement. Bandpass filtering was applied at 1 to 100 Hz, with a sampling rate of 1000 Hz. Reference electrodes were placed on both mastoids, and the ground electrode was placed on the forehead. The impedance was maintained below 5 kΩ.

LDAEP paradigm and analysis

The auditory stimulation protocol consisted of 500 stimuli with a fixed interstimulus interval of 2000 ms. Tones of 1000 Hz with a duration of 100 ms (rise and fall time: 10 ms) were delivered at five intensities (60, 70, 80, 90, and 100 dB sound pressure level) through MDR-D777 headphones (Sony, Tokyo, Japan). A total of 500 stimuli, including 100 stimuli of each intensity,

were triggered via the STIM2 system (Compumedics USA) to ensure accurate synchronization between the stimuli and EEG recordings. Participants were instructed to listen to sounds and look at a fixation cross displayed on the middle of the monitor screen. To improve compliance with the experiment, the duration of a single EEG session was limited to 15 minutes. A trained evaluator with no information about the origin of the data removed gross artifacts through visual inspection. Artifacts related to eye blinks were removed using an established mathematical procedure.[55] On the basis of the vertical electrooculography results, positive and negative components exceeding 300 μV from before and after the onset stimulus (−100 ms to 300 ms) were removed. Data were epoched in the range of −100 ms to 700 ms. Pre-stimulus baseline correction and linear detrending were applied to all electrodes. Artifacts exceeding ±100 μV were rejected at all electrode sites. Off-line bandpass filtering was applied at 1 to 30 Hz. After preprocessing the data for each sound intensity, the trials were averaged at five electrodes (Fz, Cz, C3, C4, and Oz). N100-P200 peak detection was performed using MATLAB 2019 software (Mathworks Inc., Natick, MA, USA) and Scan 4.5 software (Compumedics USA). For each intensity, the most negative peak amplitude of the N100 component was defined between 80 ms and 160 ms after the stimulus onset, while the most positive peak amplitude of the P200 component was defined between 130 ms and 280 ms. After completion of signal processing, the LDAEP was calculated as the slope variation for five stimulus intensities using the linear regression slope.[44]

Statistical analyses

Demographic data, including age, sex, and symptom scores, were analyzed using the chi-squared test, one-way analysis of variance with a post-hoc test, or a t-test as appropriate. To determine the interaction effect between the LDAEP and group, we analyzed the group differences in the LDAEP using repeated-measures analysis of covariance. The between-subject factor was group, and the within-subject factors were the LDAEP at the five electrode sites. Age and sex were controlled as covariates. In addition, for each single electrode, the LDAEP was compared among the groups based on multivariate analysis of covariance (MANCOVA), controlling for age and sex as covariates. The LDAEP was also compared between patients with SCZ and those with MDD with age, sex, and drug usage serving as covariates. In the MANCOVA analyses, the significance level was set at $p < 0.008$ (two-tailed), considering multiple comparisons based on the Bonferroni correction.[56] Furthermore, partial correlation analysis was performed among age, LDAEP, and symptom severity in each group after controlling for drug usage and sex. Binary classification of medication was performed based on the presence or absence of the use of drugs that could modulate the LDAEP (Table 1). Forty-seven patients with SCZ and 12 patients with MDD were administered serotonin-related drugs in the current study. In the correlation analyses, p-values were adjusted using Bonferroni correction with a significance level of $p < 0.003$. All statistical procedures were performed using IBM SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Additionally, we calculated the required sample size using G*Power software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Nordrhein-Westfalen, Germany).[57] This study used F-tests with MANCOVA with repeated measures and within-between interactions. The effect size of this study was set at 0.25, the alpha value was set at 0.05, and

Table 1. Drug information in patients with SCZ and MDD.

DRUG	SCZ	N	MDD
Amisulpride	7		–
Aripiprazole	9		–
Blonanserin	3		–
Clozapine	1		–
Olanzapine	16		–
Paliperidone	11		–
Quetiapine	11		–
Risperidone	1		–
Alprazolam	–		5
Escitalopram	–		1
Etizolam	–		1
Lorazepam	–		2
Mirtazapine	–		1
Paroxetine	–		2
Sertraline	–		1
Venlafaxine	–		5
5-HT-related drug	47		12

Drugs shown in bold are serotonin receptor antagonists used to treat patients with SCZ.
Abbreviations: MDD, major depressive disorder; SCZ, schizophrenia; 5-HT, 5-hydroxytryptamine.

the power was set at 0.80. The minimum sample size required was 125.

Results

Fifty-four outpatients with SCZ (18 men and 36 women) and 51 outpatients with MDD (13 men and 38 women) were selectively enrolled according to the research participation criteria. The mean ages of patients with SCZ and MDD were 38.98 ± 16.32 years and 34.72 ± 10.98 years, respectively. Thirty-five HCs (17 men and 18 women) were recruited through community newspapers. Their mean age was 41.40 ± 11.38 years. The age of all participants ranged from 16 to 82 years (mean age: 38.03 ± 13.56 years). Comparisons of demographic data and the LDAEP are shown in Table 2. We compared BDI scores between two groups, patients with MDD and HCs. Patients with MDD had higher BDI scores than HCs ($t = 9.75$, $p < 0.001$). For the comparison of the LDAEP, the interaction effect between the LDAEP and group was significant ($f = 11.39$, $p < 0.001$, $\eta_p^2 = 0.14$); patients with SCZ or MDD exhibited a smaller LDAEP than those in HCs ($f_{(2,\ 135)} = 10.10$, $p < 0.001$, $\eta_p^2 = 0.13$, SCZ, adjusted $p < 0.001$; MDD, adjusted $p = 0.007$) (Table 2 and Figure 1 and 2). Significant differences were found at the Fz (SCZ < HC*, MDD < HC*, $\eta_p^2 = 0.17$), Cz (SCZ < HC*, MDD < HC*, $\eta_p^2 = 0.14$), C3 (SCZ < HC*, $\eta_p^2 = 0.08$), C4 (SCZ < HC*, $\eta_p^2 = 0.10$), and Oz (SCZ < MDD*, $\eta_p^2 = 0.12$) (*adjusted $p < 0.008$) electrodes. Furthermore, patients with MDD showed a larger LDAEP than those with SCZ at the Oz electrode ($p < 0.008$, $\eta_p^2 = 0.12$) after controlling for age, sex, and drug usage (Tables 1 and 2).

In the sub-group analyses, significant correlations were found between age and LDAEP (Table 3 and Figure 3). Age was positively correlated with the Fz ($r = 0.50$, $p < 0.001$), Cz ($r = 0.41$, $p = 0.002$), C3 ($r = 0.51$, $p < 0.001$), and C4 ($r = 0.42$, $p = 0.002$) electrode results and the mean LDAEP ($r = 0.47$, $p < 0.001$) in patients with SCZ. Patients with MDD showed positive correlations between age and the LDAEP at the Fz electrode ($r = 0.45$, $p = 0.001$) and the mean LDAEP ($r = 0.43$, $p = 0.002$).

Significant correlations were found between age and the LDAEP in all patients with SCZ or MDD (Fz, $r = 0.49$, $p < 0.001$; Cz, $r = 0.38$, $p < 0.001$; C3, $r = 0.48$, $p < 0.001$; C4, $r = 0.40$, $p < 0.001$; mean LDAEP, $r = 0.45$, $p < 0.001$). However, symptom severity was not correlated with age or the LDAEP in patients with SCZ or MDD and HCs (Table 3).

Discussion

The current study focused on the disharmonic phenomena between reduction in

Table 2. Demographic data and the results of LDAEP comparison.

VARIABLES	SCZ(a)	MDD(b)	HC(c)	STATISTICS
N	54	51	35	Group-Age, $p = 0.064$
Are (years)	38.98 (16.32)	34.72 (10.98)	41.40 (11.38)	Group-Sex χ^2, $p = 0.084$
Sex (M/F)	18/36	13/38	17/18	
PANSS				
Positive	29.43 (6.06)			—
Negative	18.69 (6.57)			
General	52.94 (8.50)			
Total	101.06 (14.75)			
HAMD		20.43 (5.42)		
HAMA		22.11 (6.85)		
BDI		28.52 (11.92)	8.54 (7.03)	$t = 9.75$, $p < 0.001$
Accepted LDAEP trials				
60 dB	95.05 (7.44)	97.21 (3.96)	98.80 (1.77)	—
70 dB	95.64 (7.59)	97.72 (3.75)	98.45 (2.24)	
80 dB	95.00 (7.83)	97.68 (3.90)	98.34 (3.13)	
90 dB	94.92 (8.39)	97.82 (3.47)	98.94 (1.89)	
100 dB	94.87 (8.54)	98.02 (2.99)	98.57 (2.62)	
LDAEP slope				*Interaction Effect* Group & LDAEP $f = 11.39$, $p < 0.001$, $\eta_P^2 = 0.14$
Mean LDAEP	0.87 (0.68)	0.99 (0.50)	1.48 (0.79)	$a < c^*$, $b < c^*$ $\eta_P^2 = 0.13$
Fz	1.02 (0.94)	0.87 (0.71)	1.95 (1.05)	$a < c^*$, $b < c^*$, $\eta_P^2 = 0.17$
Cz	1.20 (0.88)	1.45 (0.71)	2.08 (1.17)	$a < c^*$, $b < c^*$, $\eta_P^2 = 0.14$
C3	1.05 (0.87)	1.14 (0.62)	1.65 (0.88)	$a < c^*$, $\eta_P^2 = 0.08$
C4	0.93 (0.72)	1.09 (0.51)	1.52 (0.88)	$a < c^*$, $\eta_P^2 = 0.10$
Oz	0.11 (0.32)	0.40 (0.34)	0.18 (0.33)	$a < b^*$, $\eta_P^2 = 0.12$

Bonferroni correction was performed and the significance level was set at $^*p < 0.008$.

Mean LDAEP indicates the grand averaged value for Fz, FCz, Cz, Pz, and Oz.

Abbreviations: LDAEP, loudness dependence of auditory evoked potentials; SCZ, schizophrenia; MDD, major depressive disorder; HC, healthy control; PNASS, Positive and Negative Syndrome Scale; BDI, Beck Depression Inventory; M, male; F, female; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale SD, standard deviation.

the LDAEP and the age-related increase in the LDAEP in patients with SCZ and MDD. We observed the following significant results. First, patients with SCZ and MDD showed a lower mean LDAEP than HCs. Second, patients with SCZ showed a lower LDAEP than patients with MDD at the Oz electrode. Third, age was positively correlated with the LDAEP in patients with SCZ and MDD.

A small LDAEP indicates high levels of serotonergic activity in patients with SCZ,[28] corroborating the serotonin hypothesis for SCZ.[49] Serotonin blocking agents are effective in patients with SCZ because an increased level of serotonergic activity leads to hallucinogenic actions. Additionally, 5-HT2A antagonists improve working memory, learning, and cognitive symptoms by modulating the serotonin system, which affects cognitive functions such as memory, concentration, and learning.[58] Patients with SCZ had a smaller mean LDAEP at the midline electrodes than HCs. The present study suggests that patients with SCZ have serotonergic dysregulation, which is potentially caused by alterations in serotonergic projections to

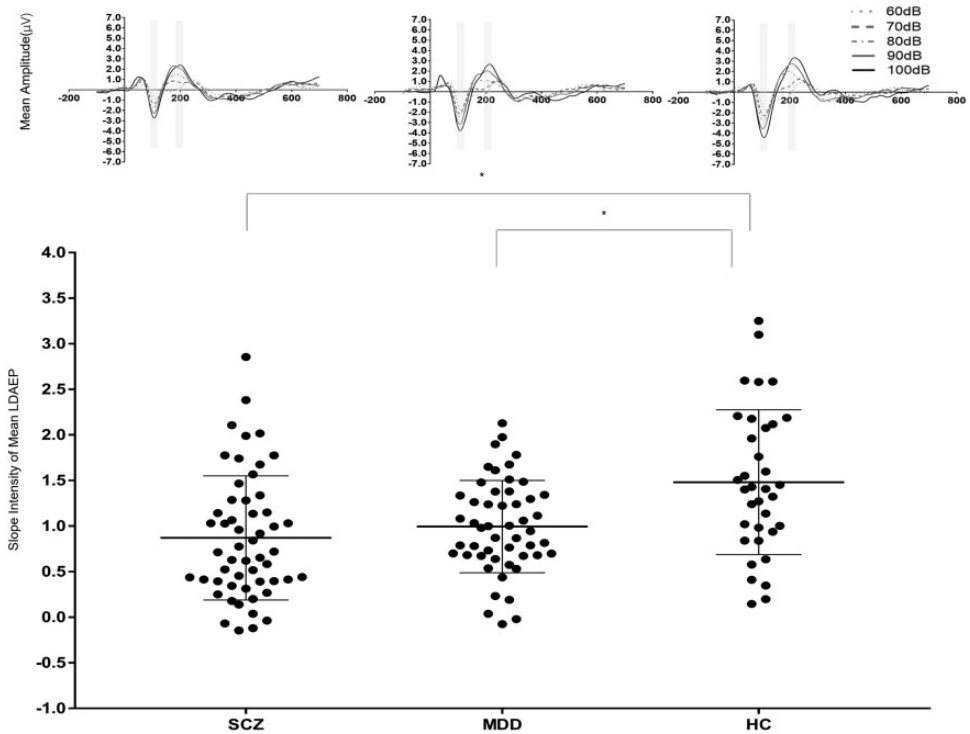

Figure 1. Comparison of the slope intensity of the mean loudness dependence of auditory evoked potentials between groups. LDAEP, loudness dependence of auditory evoked potentials; SCZ, schizophrenia; MDD, major depressive disorder; HC, healthy control.

the dorsal hippocampus from the median raphe nucleus of the brainstem, which corresponds with the midline electrodes.[59] The selected EEG channels are suitable sites for qualifying signals by referencing both mastoids. The long distances from the reference electrodes yielded clear and relatively large amplitudes. Furthermore, EEG signals are generated in pyramidal neurons within the deep cortical areas.[60,61] The neurons within the cortex are oriented vertically on the scalp, which allows calculation of the EEG sources related to functional changes from the recorded signals on the scalp and functional magnetic resonance imaging.[62–64] However, the LDAEP was not associated with symptom severity, which was caused by the complex relationships among the LDAEP, serotonin activity, and clinical symptoms. This argument is associated with the specificities of receptor subtypes for the LDAEP and clinical symptoms. Recently, 5-HT1A was positively correlated with the LDAEP, and serotonin transporter binding was negatively correlated with the LDAEP.[22] Regarding the differences among groups at each electrode, patients with SCZ and MDD exhibited a smaller LDAEP than that in HCs. Patients with MDD failed to respond to SSRI administration when they had a low LDAEP, and patients with a high LDAEP were favorable responders.[34,42] SSRIs facilitate the maintenance of presynaptic serotonergic neurons by inhibiting serotonin transporter binding to its receptor in MDD.[65] In contrast, patients with MDD showed a higher LDAEP than those with

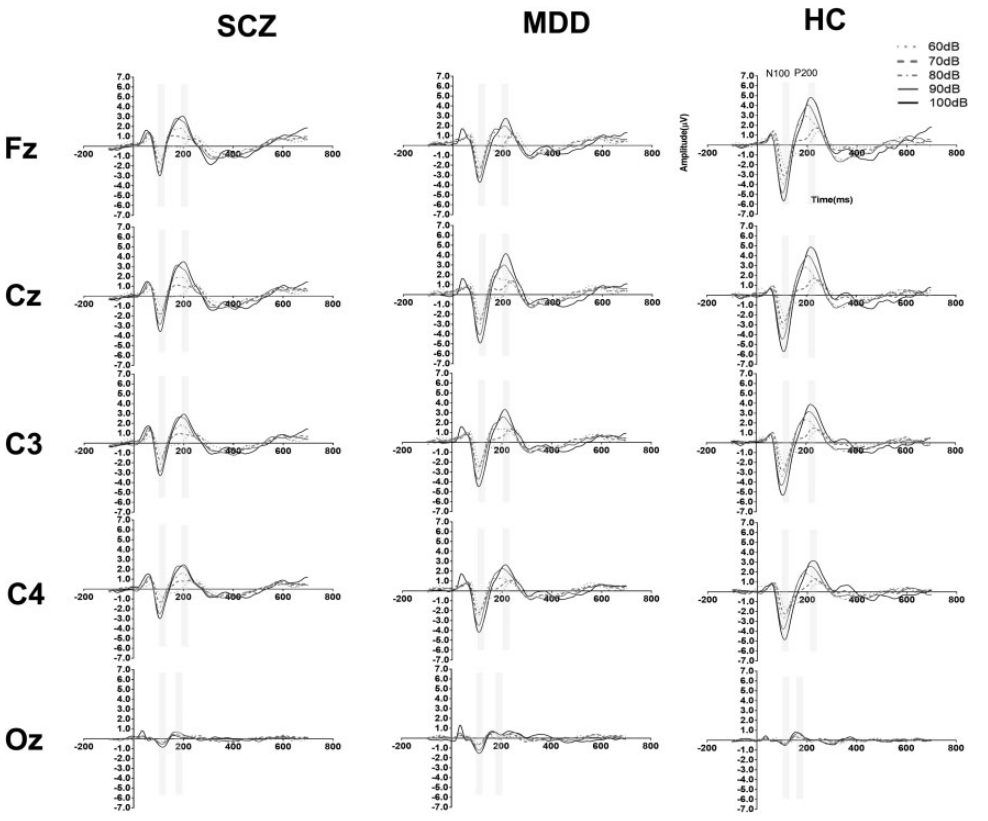

Figure 2. Comparison of N100 and P200 amplitudes at selected electrodes between groups. SCZ, schizophrenia; MDD, major depressive disorder; HC, healthy control.

SCZ at the Oz electrode. Additionally, patients with MDD showed lower N100 amplitudes in the Cz channel (Supplementary table). Serotonergic deficits are common in patients with MDD even though heterogeneous pathological phenotypes exist.[2] Changes in serotonergic activity are closely associated with mood changes in MDD, bipolar disorder, and SCZ.[66–68] Controversy exists regarding whether the LDAEP reflects the state or is a trait-dependent biomarker of central serotonergic function.[69,70] The LDAEP could have fluctuated during the investigation according to the status of patients. Thus, longitudinal studies are needed. Moreover, the influence of drug usage should be considered carefully when interpreting the results because it is a potential factor underlying the influence of drug administration on the serotonin pathway in the human brain.[71]

Thus, the findings of this study outlined two critical aspects in relation to the LDAEP. First, patients exhibit a natural decline in serotonergic activity as they get older. Second, both the natural effect of aging and the effects of drugs may act in tandem to decrease serotonin activity. With aging, patients with SCZ might show decreased psychotic symptoms, improved cognitive function, and reduced use of antipsychotics.[72] However, the neurophysiological mechanisms of the age-related improvements in SCZ are not clearly understood. Downregulation of serotonin neurotransmission could induce a reduction in

Table 3. Partial correlations among age, LDAEP, and symptom scales in the study groups.

SCZ (n = 54)

	1	2	3	4	5	6	7	8	9	10	11
1. Age	1										
2. Fz	**0.50***	1									
3. Cz	**0.41***	0.89*	1								
4. C3	**0.51***	0.91*	0.93*	1							
5. C4	**0.42***	0.83*	0.90*	0.87*	1						
6. Oz	−0.01	0.12	0.25	0.19	0.34	1					
7. Positive	0.25	0.10	0.01	0.10	0.08	−0.02	1				
8. Negative	0.09	0.30	0.34	0.32	0.26	0.13	−0.02	1			
9. General	−0.02	0.27	0.29	0.29	0.36	0.14	0.30	0.28	1		
10. Total	0.13	0.33	0.32	0.35	0.36	0.13	0.59*	0.60*	0.83*	1	
11. Mean LDAEP	**0.47***	0.94*	0.97*	0.96*	0.94*	0.32	0.07	0.32	0.32	0.36	1

MDD (n = 51)

	1	2	3	4	5	6	7	8	9	10
1. Age	1									
2. Fz	**0.45***	1								
3. Cz	0.35	0.82*	1							
4. C3	0.41	0.84*	0.88*	1						
5. C4	0.37	0.76*	0.86*	0.79*	1					
6. Oz	0.19	0.14	0.40	0.32	0.47*	1				
7. HAMD	0.07	0.04	−0.01	-0.04	0.01	0.14	1			
8. HAMA	0.12	0.11	0.09	0.06	0.07	0.18	0.83*	1		
9. BDI	−0.12	0.06	0.09	0.07	0.13	0.29	0.57*	0.58*	1	
10. Mean LDAEP	**0.43***	0.89*	0.96*	0.93*	0.91*	0.46*	0.01	0.10	0.18	1

SCZ + MDD (n = 105)

	1	2	3	4	5	6	7
1. Age	1						
2. Fz	**0.49***	1					
3. Cz	**0.38***	0.86*	1				
4. C3	**0.48***	0.88*	0.91*	1			
5. C4	**0.40***	0.80*	0.89*	0.84*	1		
6. Oz	0.06	0.13	0.34	0.24	0.41*	1	
7. Mean LDAEP	**0.45***	0.92*	0.96*	0.95*	0.93*	0.39*	1

HC (n = 35)

	1	2	3	4	5	6	7	8
1. Age	1							
2. Fz	−0.03	1						
3. Cz	−0.17	0.92*	1					
4. C3	−0.17	0.92*	0.94*	1				
5. C4	−0.22	0.83*	0.86*	0.83*	1			
6. Oz	−0.22	0.32	0.34	0.41	0.37	1		
7. BDI	0.03	−0.23	−0.21	−0.23	−0.16	0.04	1	
8. Mean LDAEP	−0.16	0.95*	0.97*	0.97*	0.91*	0.45	−0.21	1

Bold values indicate significant age-LDAEP correlations.

*Significance level was set at the Bonferroni corrected p-value ($p < 0.003$).

Medication and sex were controlled.

Abbreviations: LDAEP, loudness dependence of auditory evoked potentials; SCZ, schizophrenia; MDD, major depressive disorder; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

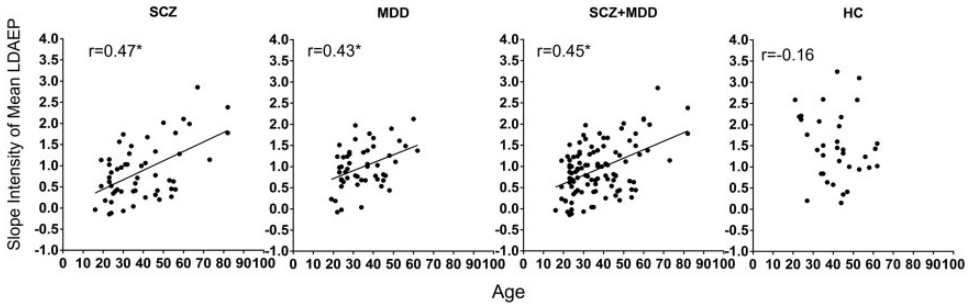

Figure 3. Partial correlations between age and mean loudness dependence of auditory evoked potentials. *Significance level was set at an adjusted p-value ($p < 0.003$). LDAEP, loudness dependence of auditory evoked potentials; SCZ, schizophrenia; MDD, major depressive disorder; HC, healthy control.

clinical symptoms and relief of cognitive impairment in older SCZ patients.[73,74] This is partially consistent with the results from the current cross-sectional study, which observed correlations between age and the LDAEP. However, there was no effect of age in HCs. A correlation between age and duration of illness could be observed for people with psychiatric disorders, which would worsen the physical health outcome,[75] but healthy individuals might appear to be less affected by aging. In addition, comparisons of the LDAEP among drug naive patients or those using the same types of drugs should be examined to control for specific pharmacological effects. Further studies are warranted to elucidate the relationship between aging and clinical domains such as cognitive function, motor behaviors, and sub-clinical symptoms after controlling for medications. Age-related changes in brain disorders have not been fully explored. The natural decline in serotonin during aging could affect cognitive and sensory functions. In pathological conditions, both functional and negative effects may exist because of serotonin reduction. Our finding is a stepping stone toward understanding the neurophysiological mechanisms of age and serotonergic function.

This study had some limitations. Drug usage and dosage data were not fully controlled, and information regarding parameters such as the duration of illness was lacking. Moreover, the sample size was insufficient to verify the present results. Future longitudinal studies with larger sample sizes and full pharmacological history details could help expand our findings.

The current study was conducted to explain the paradoxical relationship between the lower LDAEP in patients with MDD and SCZ compared with that in HCs and the age-related increase in the LDAEP in patients with SCZ and MDD. In conclusion, the reduction of central serotonergic activity with age in patients with SCZ and MDD may be screened using the LDAEP. Thus, LDAEP assessments may be used to predict treatment responses in relation to the effect of age in patients with MDD and SCZ.

Acknowledgements

This study was pre-printed without peer review and is linked at the three websites listed below.
1. https://www.researchgate.net/publication/353961196_Association_Between_The_Loudness_Dependence_of_The_Auditory_Evoked_Potential_and_Age_in_Patients_With_Schizophrenia_and_Depression
2. https://assets.researchsquare.com/files/rs-711908/v1/4fe01004-e905-4672-afb7-166https://www.researchgate.net/publication/353961196_Association_Between_The_Loudness_Dependence_of_The_Auditory_Evoked_Potential_and_Age_in_Patients_With_Schizoph

renia_and_Depression61008481.pdf?c=1634549362
3. https://europepmc.org/article/ppr/ppr383677

Author contributions

K-IJ and J-HC contributed to the conception and design of the study. K-IJ and CL contributed to the acquisition and analysis of data. K-IJ contributed to drafting the article. K-IJ, SK, CL, and J-HC contributed to the review of the article. J-HC and CL contributed to the supervision of the study. All authors approved the final version of the article.

Declaration of conflicting interest

All authors declare no conflicts of interest.

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Supplemental material

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