Association Between The Loudness Dependence of The Auditory Evoked Potential and Age in Patients With Schizophrenia and Depression

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Research Article

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Abstract

Background

The loudness dependence of the auditory evoked potential (LDAEP) reflects serotonin neurotransmission. Abnormality in serotonergic activity is dominant in patients with schizophrenia (SCZ) and major depressive disorder (MDD). Patients with SCZ show weak LDAEPs, reflecting high serotonergic activity. Some patients with MDD show high serotonergic activity. Although the changes in serotonin neurotransmission in the aging brain of SCZ and MDD have been observed, the relationship between central serotonergic activity and age remains unclear. The present study compared LDAEP between patients with SCZ and MDD, and healthy controls (HCs). We further examined whether age correlated with LDAEP and clinical symptoms, controlling usage of serotonin-related drugs.

Methods

A total of 105 patients with SCZ and MDD were enrolled (54 patients with SCZ and 51 patients with MDD). Thirty-five HCs were recruited. LDAEP was measured on midline channels (Fz, FCz, Cz, Pz, and Oz) among 62 electroencephalography channels. Positive and negative symptoms were assessed in patients with SCZ while depression and/or anxiety symptoms were evaluated in patients with MDD and HC.

Results

Patients with SCZ and MDD showed smaller mean LDAEP than that of HC group ($p < 0.001$). Age was positively correlated with LDAEPs in patients with SCZ and MDD.

Conclusion

Decreased serotonergic activity with aged brain could be indicated by LDAEP in patients with SCZ and MDD. Changes in LDAEP according to age would be a compensatory mechanism across progression of disease in SCZ and MDD.

Background

The loudness dependence of the auditory evoked potential (LDAEP), measured by electroencephalography (EEG), has been proposed as a clinical biomarker for psychiatric disorders [1–8]. Serotonergic activity is known to be negatively correlated with LDAEP in the brain [9]. Abnormal changes in central serotonin neurotransmission can lead to major pathological features in patients with schizophrenia (SCZ) and major depressive disorder (MDD) [10–12]. LDAEP is associated with depression and psychotic symptoms [13, 14].

The LDAEP represents slope variations of neural responses to auditory stimuli [15–17]. Previous studies have revealed shallower slopes of LDAEP, a reflection of elevated serotonin transmission in the dorsal raphe nucleus [18], are observed in patients with SCZ than in those of other psychiatric disorders as well as healthy controls (HCs) [5, 19, 20]. In this regard, serotonin receptor stimulation resulted in perceptual disturbances such as hallucinations in SCZ [21]. Serotonergic activity has been shown to play an important role in both SCZ and MDD [22, 23]. Antidepressants have been known to induce increased presynaptic serotonergic neurons in patients with MDD [24]. In addition, serotonin activity might modulate symptom severity and treatment response in SCZ and MDD [25–27]. Although previous studies have reported that LDAEP did not differ between patients with MDD and HCs [5, 28], LDAEP could predict treatment response to antidepressants such as selective serotonin reuptake inhibitors (SSRIs) in MDD [29, 30]. Furthermore, the effect of age on LDAEP has been reported through the pathway model that in according to gender, age predicted LDAEP in MDD [31]. Negative correlation in patients with SCZ was found between LDAEP and chronicity of illness but a low level of statistic power [6].

Serotonergic neurons can be altered by aging. For example, elderly people with depression have shown decrease in serotonergic neurons [32, 33]. Aging with the change in serotonin neurotransmission modulated sensory perceptions [34–36]. One study found that 5-HT2 receptor binding was significantly attenuated with age in patients with SCZ and HCs [37].

The current study focused on the changes of serotonin transmission in patients with SCZ and MDD and the age-related alterations in serotonergic activity. To this end, we compared LDAEP between patients with SCZ and MDD and HCs. In addition, we explored the association between age and LDAEPs in patients with SCZ and MDD. We hypothesized that patients with SCZ would have smaller LDAEPs than patients with MDD and HCs, indicating increased serotonin neurotransmission in patients with SCZ. We further hypothesized that LDAEP would correlate with age in patients with SCZ and MDD.

Methods

Participants

Fifty-four outpatients with SCZ (18 men, 36 women) and 51 outpatients with MDD (13 men, 38 women) were enrolled. The mean ages of the patients with SCZ and MDD were 38.98 ± 16.32 years and 34.72 ± 10.98 years, respectively. Thirty-five HCs (17 men, 18 women) were recruited through the community newspaper. 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). 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*. The Positive and Negative Syndrome Scale (PANSS) [38] was assessed in patients with SCZ by a trained psychiatrist who was not

involved in the present study. The Hamilton Depression and Anxiety rating scales (HAMD and HAMA) [39, 40] were evaluated in patients with MDD by a trained psychiatrist. In addition, the Beck Depression Inventory (BDI), which is a self-rating scale, was measured in patients with MDD and HCs[41]. The present study 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 provided, and all experimental procedures followed the relevant institutional guidelines and regulations for all participants.

EEG recordings

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 (EOG) was 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 1–100 Hz, with a sampling rate of 1,000 Hz. Reference channels 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 comprised 500 stimuli with fixed interstimulus intervals 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 SPL) through MDR-D777 headphones (Sony, Tokyo, Japan). A total of 500 stimuli comprised of each intensity of 100 stimuli were triggered via the STIM2 system (Compumedics USA, El Paso, TX, USA) to ensure accurate synchronization between the stimuli and EEG recordings. A fixation cross was displayed in the middle of the monitor screen. A trained person 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 [42]. Based on vertical EOG, positive and negative components exceeding 300 μV from before and after onset stimulus (-100 ms to 300 ms) were removed. Data were epoched in the range of -100 ms and 700 ms. Pre-stimulus baseline correction and linear detrend were applied to all electrodes. Artifacts exceeding ± 100 μV were rejected at all electrode sites. Off-line bandpass filtering between 1 Hz to 30 Hz was applied. The trials of each intensity were averaged at midline electrodes, respectively (Fz, FCz, Cz, Pz, and Oz). N100-P200 peak detection was performed using MATLAB 2019 software (Mathworks Inc., Natick, MA, USA) and Scan 4.5 software. 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. Finally, LDAEP was calculated based on the linear regression slope, whereby the slope variations of the sound intensities were ascertained by subtracting N100 from P200. The mean LDAEP was also calculated by averaging the LDAEPs at all five midline electrodes (Fz, FCz, Cz, Pz, and Oz).

Statistical analyses

Demographic data including age, sex, and symptom scores were analyzed using the chi-squared test, multivariate analysis of variance, or t-test as appropriate. To test the interaction effect between LDAEP and group, we analyzed the group differences in LDAEP using repeated measures analysis of covariance. The between-subject factor was group, and the within-subject factors were the LDAEPs at the five electrode sites. Age and sex were controlled as covariates. In addition, for each single electrode, LDAEP was compared among the groups based on the multivariate analysis of covariance (MANCOVA), controlling for age and sex as covariates. LDAEPs were also compared between patients with SCZ and MDD with covariates, age, sex, and drug usage. In MANCOVA analyses, the significance level was set at $p < 0.008$ (two-tailed), considering the multiple comparison issue based on the Bonferroni correction [43]. Furthermore, partial correlation was performed among age, LDAEP, and symptom severity in each group, controlling for drug and sex. Binary classification of medication was designed for the presence or absence of drug usage that could modulate LDAEP (Table 4). Forty-seven patients with SCZ and twelve patients with MDD administered serotonin-related drugs in the current study. In terms of correlation analyses, p-values were adjusted via the 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, N.Y., USA).

Results

The comparisons of demographic data and LDAEP are displayed in Table 1. Patients with MDD had higher BDI scores than HCs ($t = 9.75$, $p < 0.001$). For the comparisons of LDAEPs, the interaction effect between LDAEP and group was significant ($f = 17.61$, $p < 0.001$, $\eta_p^2 = 0.20$); patients with SCZ and MDD showed a smaller LDAEP than HCs, respectively ($f_{(2, 135)} = 11.02$, $p < 0.001$, $\eta_p^2 = 0.14$, SCZ, adjusted $p < 0.001$; MDD, adjusted $p = 0.005$) (Table 1 and Figs. 1 and 2). With regard to each electrode, significant differences were found at Fz (SCZ < HC*, MDD < HC*, $\eta_p^2 = 0.17$), FCz (SCZ < HC*, MDD < HC*, $\eta_p^2 = 0.19$), Cz (SCZ < HC*, MDD < HC*, $\eta_p^2 = 0.14$), Pz (not significant), and Oz (SCZ < MDD*, $\eta_p^2 = 0.12$) (*adjusted $p < 0.008$). Furthermore, patients with MDD showed a higher LDAEP than that of SCZ at Oz electrode ($f_{(1, 100)} = 10.93$, $p = 0.001$, $\eta_p^2 = 0.09$), controlling for age, sex, and drug usage (Tables 2 and 4).

Table 1
Demographic data and the results on LDAEP comparison

VARIABLES	SCZ(a)	MDD(b)	HC(c)	STATISTICS
	MEAN(SD)			
N	54	51	35	GROUP-AGE, p = 0.064 GROUP-SEX $\chi 2$, p = 0.084
AGE(years)	38.98(16.32)	34.72(10.98)	41.40(11.38)	
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				
60dB	95.05(7.44)	97.21(3.96)	98.80(1.77)	—
70dB	95.64(7.59)	97.72(3.75)	98.45(2.24)	
80dB	95.00(7.83)	97.68(3.90)	98.34(3.13)	
90dB	94.92(8.39)	97.82(3.47)	98.94(1.89)	
100dB	94.87(8.54)	98.02(2.99)	98.57(2.62)	
LDAEP slope				*Interaction Effect* Group & LDAEP f = 17.61, p < 0.001, $\eta_p^2 = 0.20$
Mean LDAEP	0.87(0.68)	1.09(0.65)	1.42(0.72)	a < c*, b < c* $\eta_p^2 = 0.14$
Fz	1.02(0.94)	0.87(0.71)	1.95(1.05)	a < c*, b < c*, $\eta_p^2 = 0.17$
FCz	1.19(0.95)	1.22(0.73)	2.29(1.21)	a < c*, b < c*, $\eta_p^2 = 0.19$
Cz	1.20(0.88)	1.45(0.71)	2.08(1.17)	a < c*, b < c*, $\eta_p^2 = 0.14$
Pz	0.68(0.59)	0.93(0.48)	0.83(0.44)	ns
Oz	0.11(0.32)	0.40(0.34)	0.18(0.33)	a < b*, $\eta_p^2 = 0.12$

Comparisons on LDAEP slope. Bonferroni correction was performed and significance level was set at *p < 0.008

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

Table 2
Comparison of LDAEP between patients with SCZ and MDD

VARIABLES	SCZ	MDD	STATISTICS
	MEAN(SD)		
Mean LDAEP	0.84(0.66)	0.97(0.50)	$f = 1.68, p = 0.197, \eta_p^2 = 0.01$
Fz	1.02(0.94)	0.87(0.71)	$f = 0.01, p = 0.984, \eta_p^2 = 0.01$
FCz	1.19(0.95)	1.22(0.73)	$f = 0.26, p = 0.609, \eta_p^2 = 0.01$
Cz	1.20(0.88)	1.45(0.71)	$f = 2.14, p = 0.146, \eta_p^2 = 0.02$
Pz	0.68(0.59)	0.93(0.48)	$f = 2.99, p = 0.087, \eta_p^2 = 0.02$
Oz	0.11(0.32)	0.40(0.34)	**$f = 10.93, p = 0.001, \eta_p^2 = 0.09$**
Bonferroni correction was performed and significance level was set at $p < 0.008$ Age, sex, and drug were controlled			

In the sub-group analyses, significant correlations were found between age and LDAEP (Table 3 and Fig. 3). Age was positively correlated with Fz ($r = 0.50$, $p < 0.001$), FCz ($r = 0.44$, $p = 0.001$), Cz ($r = 0.41$, $p = 0.002$), and mean LDAEP ($r = 0.44$, $p = 0.001$) in the patients with SCZ. In the patients with MDD, there were positive correlations between age and LDAEPs at Fz ($r = 0.45$, $p = 0.001$) and mean LDAEP ($r = 0.43$, $p = 0.002$).

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

SCZ(n = 54)												MDD(n = 51)					
	1	2	3	4	5	6	7	8	9	10	11		1	2	3	4	5
1. Age	1											1. Age	1				
2. Fz	**0.50***	1										2. Fz	**0.45***	1			
3. FCz	**0.44***	0.98*	1									3. FCz	0.41	0.96*	1		
4. Cz	**0.41***	0.89*	0.94*	1								4. Cz	0.35	0.82*	0.92*	1	
5. Pz	0.34	0.58*	0.65*	0.77*	1							5. Pz	0.36	0.48*	0.58*	0.70*	1
6. Oz	-0.01	0.12	0.18	0.25	0.57*	1						6. Oz	0.19	0.14	0.24*	0.40*	0.69*
7. Positive	0.25	0.1	0.07	0.01	0.02	-0.02	1					7. HAMD	0.07	0.04	0.01	-0.01	0.07
8. Negative	0.09	0.3	0.33	0.34	0.32	0.13	-0.02	1				8. HAMA	0.12	0.11	0.09	0.07	0.18
9. General	-0.02	0.27	0.32	0.29	0.31	0.14	0.3	0.28	1			9. BDI	-0.12	0.06	0.09	0.15	0.31
10. Total	0.13	0.33	0.37	0.32	0.33	0.13	0.59*	0.60*	0.83*	1		10. Mean LDAEP	**0.43***	0.89*	0.95*	0.96*	0.77*
11. Mean LDAEP	**0.44***	0.93*	0.96*	0.97*	0.81*	0.36	0.05	0.35	0.32	0.36	1						
SCZ + MDD(n = 105)												**HC(n = 35)**					
	1	2	3	4	5	6	7						1	2	3	4	5
1. Age	1											1. Age	1				
2. Fz	**0.49***	1										2. Fz	-0.03	1			
3. FCz	**0.44***	0.97*	1									3. FCz	-0.88	0.95*	1		
4. Cz	**0.38***	0.86*	0.93*	1								4. Cz	-0.17	0.92*	0.94*	1	
5. Pz	**0.33***	0.54*	0.62*	0.75*	1							5. Pz	-0.12	0.74*	0.73*	0.79*	1
6. Oz	0.06	0.13	0.21	0.34*	0.63*	1						6. Oz	-0.22	0.32	0.32	0.34	0.67*
7. Mean LDAEP	**0.44***	0.91*	0.96*	0.96*	0.79*	0.42*	1					7. BDI	0.03	-0.23	-0.2	-0.21	-0.01
												8. Mean LDAEP	-0.12	0.96*	0.97*	0.97*	0.85*
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																	

Table 4. Drug information in patients with SCZ and MDD

DRUG	SCZ	MDD
	N	
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

Bold drugs in SCZ are serotonin receptor antagonist

For all the patients with SCZ and MDD, significant correlations were found between age and LDAEPs (Fz, $r = 0.49$, $p < 0.001$; FCz, $r = 0.44$, $p < 0.001$; Cz, $r = 0.38$, $p < 0.001$; mean LDAEP, $r = 0.44$, $p < 0.001$). However, symptom severity was not correlated with age or LDAEP in the patients with SCZ and MDD, and HCs (Table 3).

Discussion

The current study focused on the disharmonic phenomena between the decrease of LDAEP and the age-related increased 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 compared to patients with MDD at the Oz electrode. Third, age was positively correlated with LDAEP in patients with SCZ and MDD.

Low levels of LDAEP entail high levels of serotonergic activity in patients with SCZ [20], corroborating the serotonin hypothesis of SCZ[37]. In this regard, we found smaller mean LDAEP at midline electrodes in patients with SCZ than in HCs. The present study suggests that patients with SCZ have serotonergic dysregulation, potentially caused by alterations in serotonergic projections to the dorsal hippocampus from the median raphe nucleus of the brainstem where corresponds with midline electrodes [44]. The selected EEG channels are suitable sites qualifying signal for referencing both mastoid. The longer distancing from the reference electrodes acquires the clear and larger amplitudes. However, LDAEP was not involved with symptom severity that would be caused from multi-dimensional relationships among LDAEP, serotonin activity, and clinical symptomatology. This argument is associated to which sub-type receptor has specificity on LDAEP and clinical symptoms. Recently, 5HT1A was positively correlated with LDAEP and 5HTT binding was negatively correlated with LDAEP [9]. Regarding the differences in each electrode among the groups, patients with SCZ and MDD exhibited smaller LDAEPs than HCs. Patients with MDD showed a higher LDAEP than patients with SCZ at the Oz electrode. In terms of MDD, they showed failures of responding to SSRI administration when they had low LDAEP and patient with high LDAEP were favorable responder [29, 45]. SSRIs help to maintain presynaptic serotonergic neurons by inhibiting serotonin transporter binding to its receptor in MDD [46]. Further studies are warranted to elucidate the relationship between aging and several clinical domains, such as cognitive function, motor behaviors, and sub-clinical symptoms after controlling for medications. When observed findings could be related with age, the impact of drug should be considered carefully on interpretating results. This fact, in general, has supposed to take for granted because the physiological complexity underlying mechanism of drug.

In this study, therefore, two critical impacts on LDAEP have claimed that first, a natural decline of serotonergic activity as patients get older could be addressed. Second, both natural effect of aging and intentional use of drug might be appeared in complex to be decreased serotonin activation. With aging, patients with SCZ might show decreased psychotic symptoms, improved cognitive function, and reduced use of antipsychotics [47]. However, the neurophysiological mechanisms of the age-related improvements in SCZ have not been clearly understood. Down regulation of serotonin neurotransmission could induce a reduction of clinical symptoms and a relief of cognitive impairment in older SCZ patients [48, 49]. This is partially in line with the results from

the current cross-sectional study observing correlations between age and LDAEP. However, further longitudinal studies including information on duration of illness and pharmacological history would be needed to expand our findings.

The current study intends to explain the paradoxical relationship between lower LDAEP in patients with MDD and SCZ compared to HCs and its increase with age in SCZ and MDD. In conclusion, the increased LDAEP as patients get older might be explained to protect the brain against the serotonergic hyperactivity with the disease progression. LDAEP could predict treatment responses in effect of age in patients with MDD and SCZ. This study included relatively small sample size and lacked the information such as illness of duration and drug dosage. Future longitudinal studies with larger sample size and full details in pharmacological history would expand our findings.

Abbreviations

LDAEP
Loudness dependence of the auditory evoked potential, SCZ:Schizophrenia, MDD:Major depressive disorder, HCs:Healthy controls, EEG:Electroencephalography, SSRIs:Selective serotonin reuptake inhibitors, PANSS:Positive and negative syndrome scale, HAMD:Hamilton depression rating scales, HAMA:Hamilton anxiety rating scales, BDI:Beck depression Inventory, MANCOVA:Multivariate analysis of covariance.

Declarations

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea (approval number KC09FZZZ0211). Informed consent was signed by all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The data presented in the current study are available from the first author (K-I J) or corresponding author (J-H C) upon reasonable request.

competing interest

All authors declare no conflicts of interest.

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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.

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Figures

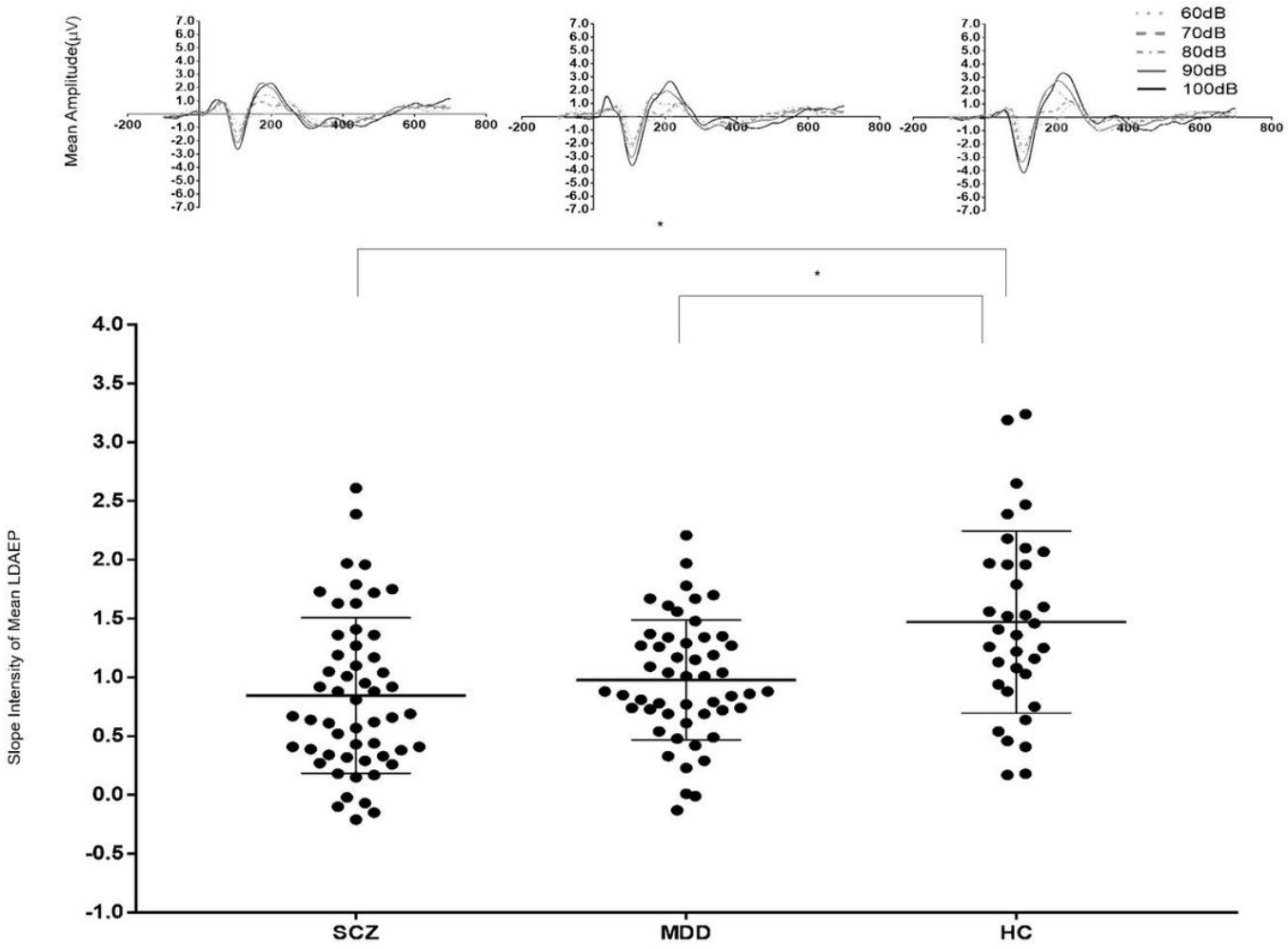

Figure 1

Comparison of the slope intensity of mean LDAEP between groups.

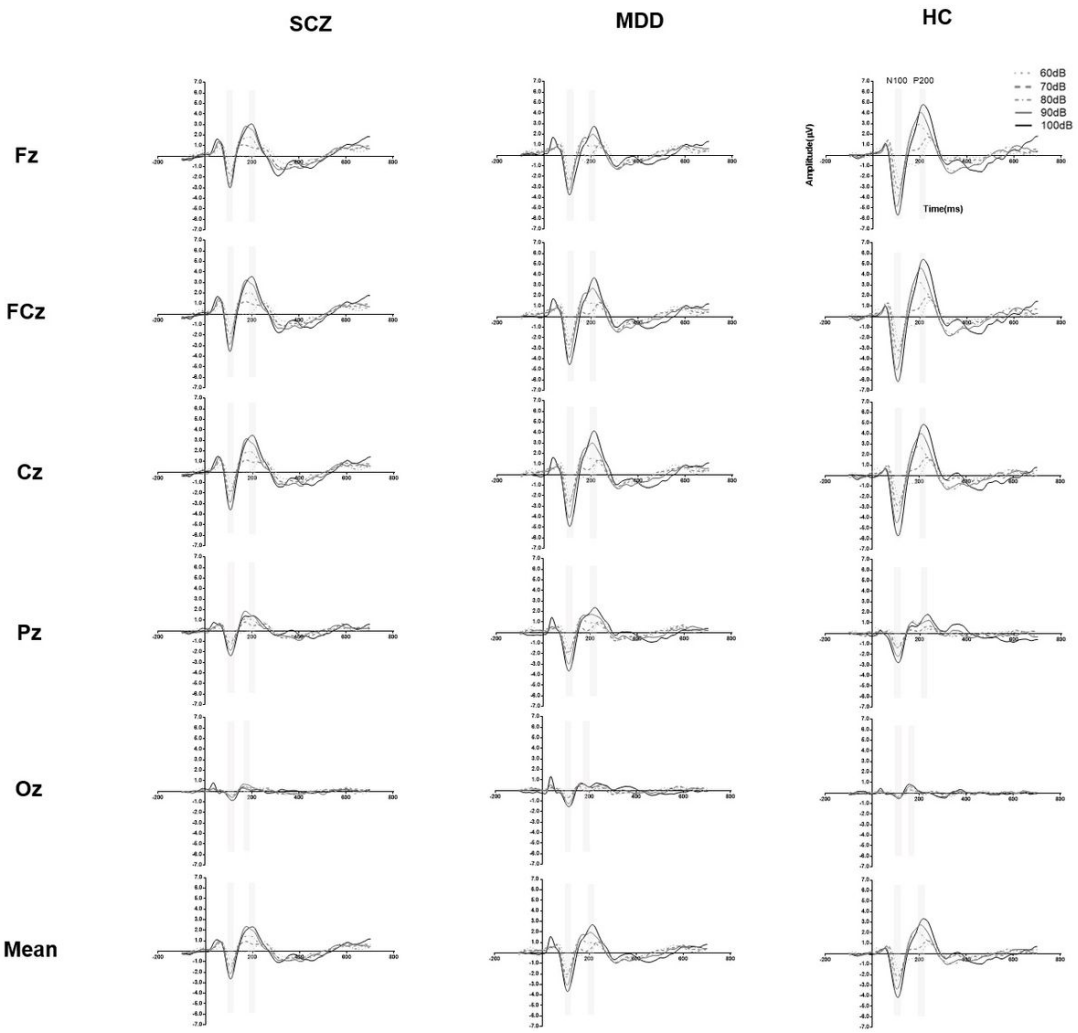

Figure 2

N100 and P200 amplitudes in selected electrodes between groups.

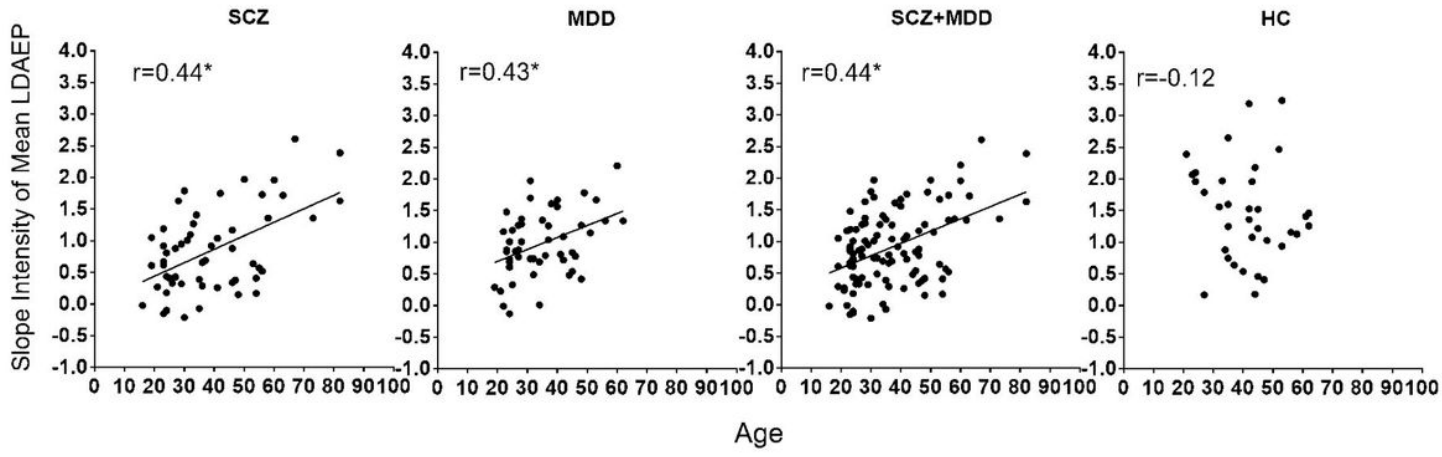

Figure 3

Partial correlations between age and mean LDAEP. *Significance level was set at an adjusted p-value ($p < 0.003$).