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Improved cognitive function in patients with major depressive disorder after treatment with vortioxetine: A EEG study

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Abstract

Introduction: Vortioxetine has a positive effect on cognitive function in patients with major depressive disorder (MDD). This study aimed to examine the changes in cognitive function and EEG (spectral power and mismatch negativity (MMN)) in patients with MDD pre- and postvortioxetine treatment.

Methods: Thirty patients with MDD were included in the study. They were given vortioxetine (10-20mg po per day) for eight weeks. Depression and anxiety severities, social function (Korean version of the social adjustment scale (K-SAS)), and cognitive function (digit-symbol substitution Test (DSST), Korean version of the attentional control questionnaire (K-ACQ), and Korean version of the perceived deficits questionnaire for depression (K-PDQD)) were evaluated. Spectral power of EEG and MMN was also measured pre- and postvortioxetine treatment.

Results: Depression and anxiety severity, social function, and cognitive functioning significantly improved after vortioxetine treatment. Also, there was a significant decrease in the right central delta band and an increase in the right central beta 2 band following vortioxetine treatment. The changes in EEG spectral power were not related to changes in cognitive functions. Baseline MMN significantly predicted changes in DSST score after controlling for the baseline clinical variables.

Conclusion: Vortioxetine treatment improved cognitive function and induced changes in EEG (decreased theta power and increased beta power) in patients with MDD. Our results suggest that greater negative MMN amplitude is associated with greater potential for cognitive improvement following vortioxetine treatment.

KEYWORDS
cognition, Major depressive disorder, MMN, qEEG, vortioxeine

1 | INTRODUCTION

Impaired cognitive functioning is one of the core symptoms in patients with major depressive disorder (MDD). Previous studies have consistently reported impaired cognitive performance on such as memory [1-3] and executive functioning [4-6] in patients with MDD. Such cognitive impairment in MDD patients is believed to be independent of mood symptoms [7] and is often found to persist in period of remission [8]. Furthermore, it is one of the predictive factors for the recurrence of depressive episode [9]. Thus, the cognitive impairment

is an important treatment target of MDD patients to help them get back to healthy functioning and prevent recurrence.

One of the antidepressants, vortioxetine, has been reported to improve the level of cognitive function following treatment. Vortioxetine is a globally approved drug for adult MDD and exerts its effect as an 5HT 3, 7, 1D receptor antagonist, 5-HT1B receptor partial agonist and affects the NE, dopamine, histamine and GABA pathway [10]. Clinical studies conducted among depressive patients showed statistically significant improvement in cognitive function in the vortioxetine treated group compared with the placebo group [11]. Vortioxetine significantly improved both objective and subjective measures of cognitive function in patients with recurrent MDD, and these effects were largely independent from its effect on improving depressive symptoms [8].

The auditory MMN is a preattentive EEG response that is used to identify a violation of a multi-stimulus pattern regularity [12-14] derived from a recent auditory stimulation. It is the negative component of the waveform obtained by subtracting the event-related response to the standard event from the response to the deviant event [15]. MMN is useful for understanding cognitive mechanisms in various psychiatric disorders and is a potential indicator of cognitive dysfunction [16], in which greater negative value indicates higher cognitive function and greater cognitive capacity. In addition, the spectral power of EEG can be used as neurophysiological markers for the efficacy of psychotropic drugs and thus could help enhance our understanding of pharmacokinetic and pharmacodynamic properties of new psychotropic drugs [17]. To our knowledge, there is only one previous study that examined EEG changes following vortioxetine treatment. This EEG study was conducted among healthy volunteers and found that both vortioxetine and escitalopram decreased the power of the theta band (4-8 Hz) and increased the power of the beta (12-32 Hz) and gamma (32-45 Hz) bands. [18] While this study suggests EEG as a potential marker for changes associated with vortioxetine treatment, more studies are needed to test its replicability in patients with MDD and its association with cognitive function.

This study aimed to measure the changes in cognitive function and EEG pre- and postvortioxetine treatment (8 weeks) in patients with MDD. Spectral power and MMN were measured to examine any meaningful changes between pre- and post-treatment. We hypothesized that vortioxetine would (1) improve the cognitive function of patients with MDD, (2) increase the high-frequency band power and decrease the low-frequency band power, and (3) induce greater negative MMN amplitude.

2 | METHODS

2.1 | Participants

Thirty-five participants with MDD between ages of 18 and 65 were recruited for this study. Diagnosis of MDD was determined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (APA) by board-certified psychiatrists. Participants were either medication-naïve or did not take any antidepressants at least one month prior to participation. Participants were excluded from the study if they had high risk of suicidality, mental retardation, organic brain pathology, previous use of vortioxetine, abnormal thyroid function test, neurological or internal diseases, pregnancy, and any history of psychotic symptoms, substance abuse, and treatment resistance to antidepressant therapy. All participants were screened by CBC, GOT, GPT, and thyroid function test before participating in the study. If there were any value outside the normal rang in the screening laboratory test, they were excluded in this study.

All participants were given vortioxetine 10 mg po as starting dosage and maintaining for 1 week and 20 mg po for 2nd week. The dosage 10-20 mg po was maintained flexibly after the 2nd week through the end of week 8. The research project has been approved and is conformed to the provisions of the Declaration of Helsinki. After a thorough explanation of the procedure and protocol of the experiment, written informed consent was obtained from all participants following the Institutional Review Board at Inje University Ilsan Paik Hospital (IRB no. 2016-08-017-007).

2.2 | Psychological assessment

2.2.1 | Depression and anxiety

The severity of depression and anxiety as assessed using the Hamilton Depression (Ham-D) and Anxiety (HAM-A) scales [19, 20]. These measures were utilized to measure the changes in depression and anxiety levels over the course of the study. Ham-D includes 17 items that assess different aspects of depressive symptoms based on a scale of 0 = absence of symptom to 4 = severe, while several items range up to 2 or 3 points. Ham-A is composed of 14 items that include psychic (ie, cognitive and affective aspect of anxiety) and somatic (ie, anxiety-related physical complaints) anxiety subscales and is rated on a scale of 0 to 4 based on its severity. Both Ham-D and Ham-A scores were measured at four different time points in the treatment: baseline, 2nd week, 4th week, and 8th week.

2.3 | Social functioning

2.3.1 | Korean version of the social adjustment scale (K-SAS)

A Korean version of social adjustment scale was used to measure the overall level of social adjustment over the past 2 months [21]. This scale is a semi-structured interview consisting of 9 different subscales with a total of 70 questions—instrumental role, chores, finances, family relationships, social leisure, friend relationships, romantic involvement, sexual adjustment, and personal well-being. The items are rated on either a 5-point or 7-point scale, higher score indicating worse performance. The test-retest and inter-rater reliability of K-SAS was 0.85 and 0.89, respectively. A higher score indicates worse performance [22].

2.4 | Cognitive functioning

2.4.1 | Digit-Symbol Substitution Test (DSST)

This test provides digit-symbol pairs (eg, 1/–, 2/⊥... 7/Λ, 8/X, 9/=) and a list of digits [23]. The participants are instructed to draw as many paired symbols as possible for each corresponding digit for 2 min. The score is assessed by the total number of correct symbols written in the given time, greater score indicating greater performance.

2.4.2 | Korean version of the Attentional control questionnaire (K-ACQ)

Korean version of the Attentional control questionnaire was used [24]. This is a self-report questionnaire consisted of 20 items rated on a 4-point scale assessing attentional control of executive functions (eg, "I can quickly switch from one task to another"; "I can become interested in a new topic very quickly when I need to"). The score ranges from 20 to 80, where higher scores indicate greater abilities to control attention. The internal consistency for K-ACQ was $\alpha = 0.89$.

2.4.3 | Korean version of the Perceived deficits questionnaire for depression (K-PDQD)

PDQD is a self-report questionnaire composed of 20 items that include four domains of cognitive function: attention concentration, retrospective memory, prospective memory, and organization/planning [25]. The items are rated on a 5-point scale, where higher scores indicate more severe cognitive dysfunction. The score can range from 0 to 80 with 20 scores for each domain. The internal consistency for K-PDQD was $\alpha = 0.928$, and split half reliability was 0.947.

2.5 | EEG

2.5.1 | Spectral power

EEG was obtained using Neuroscan SynAmps2 (Compumedics USA, El Paso, TX, USA) with 64 Ag-AgCl electrodes mounted on a Quik-Cap with accordance with the extended 10-20 system. The vertical electrooculogram (EOG) was recorded with bipolar electrodes, one attached above, and one below the left eye. The horizontal EOG was recorded at the outer canthus of each eye. The impedance of the electrodes was maintained below 5 kΩ. Resting EEG data were recorded while participants were seated on a comfortable chair in a sound-attenuated room for 5 min with eyes closed and were analyzed using CURRY 7 (Compumedics USA, Charlotte, NC, USA). Gross artifacts, such as movement artifacts, were rejected by visual inspection. The preprocessed EEG data were divided into 2 s epochs, and the epochs with significant physiological artifacts (amplitude exceeding ±100 μV) or sleepiness (theta alpha power ratio >= 1) at any site over the 62 electrodes were excluded from analysis. Power spectral analysis was conducted to compress the rhythmic information of the brain wave signals. In power spectral analysis, periodogram function from MATLAB R2017b (MathWorks, Natick, MA, USA) was used in order to calculate power spectral density of each epoch. The spectral power was then averaged with respect to randomly selected 30 epochs. Five participants who had insufficient epochs on either pre- or post-treatment spectral power data were excluded from analysis, resulting in a total of 30 participants.

The band powers were classified into 9 frequency bands: delta (1~4Hz), theta (4~8Hz), alpha (8~12Hz), beta 1 (12~18Hz), beta 2 (18~22Hz), beta 3 (22~30Hz), and beta 4 (18~30Hz), and gamma (30~55Hz) frequency bands [24]. The relative power of each channel was calculated by dividing each band power by the total power of the channel. Six regions were selected for analysis: left frontal (AF3, F3, and F5), right frontal (AF4, F4, and F6), left central (C3, C5, and CP3), right central (C4, C6, and CP4), left parieto-occipital (P5, P7, and PO7), and right parieto-occipital (P6, P8, and PO8). The division and selection of these regions were based on previous spectral power studies [26, 27].

2.5.2 | Mismatch Negativity (MMN)

E-Prime software was used to generate the auditory stimuli (Psychology Software Tools, Pittsburgh, PA, USA). The stimuli consisted of sounds at 85 dB SPL and 1000 Hz. Standard tones with a duration of 50 ms and deviant tones with a duration of 100 ms were presented in a randomized order (probabilities: 10% and 90%, respectively). A total of 750 auditory stimuli were presented with an interstimulus interval of 500 ms The rise and fall times were 10 ms, and the interstimulus interval was 1500 ms The recorded data were preprocessed using CURRY 7 (Compumedics USA) by a trained person and filtered using a 0.1-30 Hz bandpass filter. The data were then epoched from 100 ms prestimulus to 600 ms poststimulus, and the epochs were subtracted from the averaged prestimulus interval value to correct for the baseline. If any remaining epochs contained significant physiological artifacts (amplitude exceeding ±75 μV) in 62 electrodes sites, they were excluded from further analysis. Then, the artifact-free epochs were averaged across trials and subjects for the following analysis. MMN wave values were calculated by subtracting the standard ERP curves from the deviant curves. Given that greater amplitudes were present in the area containing frontocentral electrodes, MMN amplitude was measured as the mean value between the time window of 130 and 280 ms at corresponding sites which were F3, Fz, F4, FC3, FCz, FC4, C3, Cz, and C4 [74]. The time window for the amplitudes was decided based on visual inspection of the grand-averaged waveforms at FCz. Two participants had insufficient epochs for MMN, and thus, 28 data were used for MMN analysis.

TABLE 1 Demographics and clinical/cognitive variables of participants' pre- and post-treatment. Ham-D = Hamilton depression scale, Ham-A: Hamilton anxiety scale; K-SAS = Korean social adjustment scale; DSST = digit-symbol substitution test; ACQ = attention control questionnaire; PDQD = perceived deficits questionnaire for depression

	Pre-treatment (n = 30)	Post-treatment (n = 30)	
	Mean ±SD		*p*-value
Age (year)	45.63 ± 9.41		
Sex (male/female)	3/27		
Education (year)	14.13 ± 2.97		
Ham-D	27.83 ± 6.24	9.60 ± 8.77 (remitted patients n = 17)	<0.001
Ham-A	25.90 ± 6.57	8.97 ± 7.98 (remitted patients n = 19)	<0.001
K-SAS	76.04 ± 13.32	64.57 ± 10.51	<0.001
DSST	41.37 ± 10.50	43.70 ± 9.74	0.071
ACQ	48.10 ± 8.80	52.20 ± 8.64	0.001
PDQD	20.83 ± 16.46	13.97 ± 10.67	0.003
MMN (N = 28)	-3.07 ± 1.12	-2.67 ± 1.19	0.198

2.6 | Statistical analysis

Normality was first tested for each variable using skewness over 2.0 and a kurtosis over 7.0 as criteria indicating moderately non-normal distribution [28]. All variables were within the range of a normal distribution.

Changes in spectral power and MMN between pre- and post-treatment were examined using paired-sample t test. Pearson's correlation analysis was then used to investigate the correlation between EEG variables (post-pre) and psychological symptom (post-pre) and between EEG variables (post-pre) and cognitive function (post-pre). Bootstrap resampling (n = 5,000) was used to correct for multiple t test and correlations [29]. Bootstrapping is a weaker method than the Bonferroni test for solving the multiple test issue; however, the robustness and stability of the bootstrap test have been approved by many previous studies [30-32] and have been widely used in EEG analysis [33-35].

The predictive value of baseline spectral power and MMN on the treatment effectiveness of depressive symptoms and cognitive functions were investigated using regression analyses. For dependent variables, changes (post-pre) in psychological and cognitive scores (ie, Ham-D, Ham-A, K-SAS, DSST, ACQ, or PDQD) were used. Baseline spectral powers and MMN that showed a significant correlation with the relevant psychological/cognitive scores at baseline were included as independent variables (predictors). Age, education, sex, and baseline Ham-D and baseline Ham-A scores were entered as covariates in the first block, and baseline spectral power or MMN was entered in the second block. The significance level was set at $P < .05$ (two-tailed). Statistical analyses were performed using SPSS 21 (SPSS, INC., Chicago, IL, USA).

3 | RESULTS

3.1 | Descriptive statistics and treatment effect

Participants' demographics are shown with mean and standard deviation (SD) in Table 1. Changes (post-pre) in scores for all clinical and psychological variables were statistically significant ($P < .05$) except DSST, which showed a marginally significant increase ($P = .071$).

3.2 | Spectral power analysis

Spectral power change is presented in Table 2. Spectral power decreased significantly in the right central theta (0.137 ± 0.043 vs. 0.128 ± 0.038, t = 2.136, $P = .041$), increased in the right central beta 2 (0.065 ± 0.033 vs. 0.073 ± 0.041, $t = -2.289$; $P = .032$), and marginally significantly increased in the left frontal beta 2 (0.043 ± 0.023 vs. 0.050 ± 0.034, $t = -2.131$, $P = .051$) from pre- to post-treatment (Figure 1). There were no significant results for other regions.

For correlation analysis, there were significant negative correlations between changes in the beta 2 power of the left frontal region and the changes in Ham-D ($r = -0.501$, $P = .005$) and Ham-A ($r = -0.450$, $P = .013$) scores, as well as between changes in the beta 2 power of the right central region and the changes in Ham-A scores ($r = -0.382$, $P = .037$). There were no other significant correlations found.

3.3 | MMN

MMN did not show any statistically significant change from pre- to post-treatment (Table 1). Therefore, no further correlational analysis was conducted.

3.4 | Regression analysis

To determine the predictive variables to include for each regression analysis, correlation analysis was conducted between psychological/cognitive variables with spectral power bands and MMN at baseline. There were significant negative correlations of DSST with spectral powers at left pari-occipital delta ($r = -0.362$, $P = .049$), right

TABLE 2 Spectral power change in patients with major depressive disorder, pre- and postvortioxetine treatment

Region	week	*M*	*SD*	*t*	*p*	Region	week	*M*	*SD*	*t*	*p*
Delta (1~4Hz)						Beta 2 (18~22Hz)					
Left frontal	w 0	0.326	0.140	-0.221	0.828	Left frontal	w 0	0.043	0.023	-2.131	0.054
	w 8	0.331	0.134				w 8	0.050	0.034		
Right frontal	w 0	0.358	0.162	0.108	0.915	Right frontal	w 0	0.041	0.020	-2.137	0.066
	w 8	0.357	0.144				w 8	0.047	0.028		
Left central	w 0	0.281	0.116	-0.439	0.659	Left central	w 0	0.071	0.037	-0.574	0.572
	w 8	0.290	0.137				w 8	0.074	0.047		
Right central	w 0	0.306	0.122	0.959	0.350	Right central	w 0	0.065	0.033	-2.289	0.031
	w 8	0.288	122				w 8	0.073	0.041		
Left pari-occipital	w 0	0.212	0.115	0.910	0.363	Left pari-occipital	w 0	0.051	0.031	-2.043	0.059
	w 8	0.202	0.103				w 8	0.058	0.039		
Right pari-occipital	w 0	0.183	0.079	0.899	0.374	Right pari-occipital	w 0	0.052	0.032	-1.380	0.201
	w 8	0.174	0.075				w 8	0.056	0.043		
Theta (4~8Hz)						Beta 3 (22~30Hz)					
Left frontal	w 0	0.129	0.037	0.072	0.943	Left frontal	w 0	0.048	0.037	-0.864	0.423
	w 8	0.129	0.043				w 8	0.051	0.048		
Right frontal	w 0	0.128	0.044	0.803	0.429	Right frontal	w 0	0.045	0.035	-0.948	0.404
	w 8	0.124	0.040				w 8	0.049	0.049		
Left central	w 0	0.126	0.040	0.748	0.478	Left central	w 0	0.0585	0.033	0.567	0.580
	w 8	0.123	0.034				w 8	0.056	032		
Right central	w 0	0.137	0.043	2.136	0.044	Right central	w 0	0.054	0.028	-0.722	0.479
	w 8	0.127	0.038				w 8	0.056	0.031		
Left pari-occipital	w 0	0.129	0.055	-0.029	0.977	Left pari-occipital	w 0	0.036	0.023	-0.211	0.833
	w 8	0.129	0.048				w 8	0.037	0.026		
Right pari-occipital	w 0	0.126	0.050	-0.382	0.702	Right pari-occipital	w 0	0.033	0.027	0.1632	0.874
	w 8	0.128	0.051				w 8	0.033	0.024		
Alpha (8~12Hz)						Beta 4 (18~30Hz)					
Left frontal	w 0	0.338	0.153	0.696	0.478	Left frontal	w 0	0.087	0.054	-1.650	0.110
	w 8	0.328	0.158				w 8	0.098	0.070		
Right frontal	w 0	0.313	0.163	-0.224	0.826	Right frontal	w 0	0.082	0.051	-1.691	0.112
	w 8	0.316	0.161				w 8	0.092	0.066		

(Continues)

TABLE 2 (Continued)

Region	week	*M*	*SD*	*t*	*p*	Region	week	*M*	*SD*	*t*	*p*
Left central	w 0	0.314	0.128	0.187	0.844	Left central	w 0	0.124	0.061	-0.157	0.879
	w 8	0.311	0.150				w 8	0.125	0.070		
Right central	w 0	0.281	0.114	-0.885	0.389	Right central	w 0	0.113	0.053	-1.854	0.075
	w 8	0.396	0.136				w 8	0.124	0.063		
Left pari-occipital	w 0	0.450	0.151	-0.069	0.943	Left pari-occipital	w 0	0.084	0.048	-1.473	0.150
	w 8	0.151	0.167				w 8	0.091	0.057		
Right pari-occipital	w 0	0.496	0.135	0.517	0.596	Right pari-occipital	w 0	0.081	0.051	-0.902	0.373
	w 8	0.489	0.156				w 8	0.086	0.058		
Beta 1 (12~18Hz)						Gamma (30~55Hz)					
Left frontal	w 0	0.076	0.032	-0.885	0.392	Left frontal	w 0	0.049	0.039	1.304	0.239
	w 8	0.080	0.036				w 8	0.042	0.027		
Right frontal	w 0	0.073	0.032	-0.884	0.401	Right frontal	w 0	0.051	0.041	1.510	0.177
	w 8	0.077	0.032				w 8	0.041	0.030		
Left central	w 0	0.118	0.050	-0.952	0.337	Left central	w 0	0.047	0.028	1.047	0.305
	w 8	0.122	0.052				w 8	0.041	0.022		
Right central	w 0	0.123	0.059	-1.339	0.192	Right central	w 0	0.048	0.027	0.794	0.430
	w 8	0.133	0.063				w 8	0.043	0.025		
Left pari-occipital	w 0	0.106	0.061	-0.828	0.416	Left pari-occipital	w 0	0.026	0.017	0.637	0.550
	w 8	0.113	0.067				w 8	0.024	0.016		
Right pari-occipital	w 0	0.098	0.057	-1.383	0.196	Right pari-occipital	w 0	0.023	0.014	-0.180	0.866
	w 8	0.109	0.073				w 8	0.024	0.017		

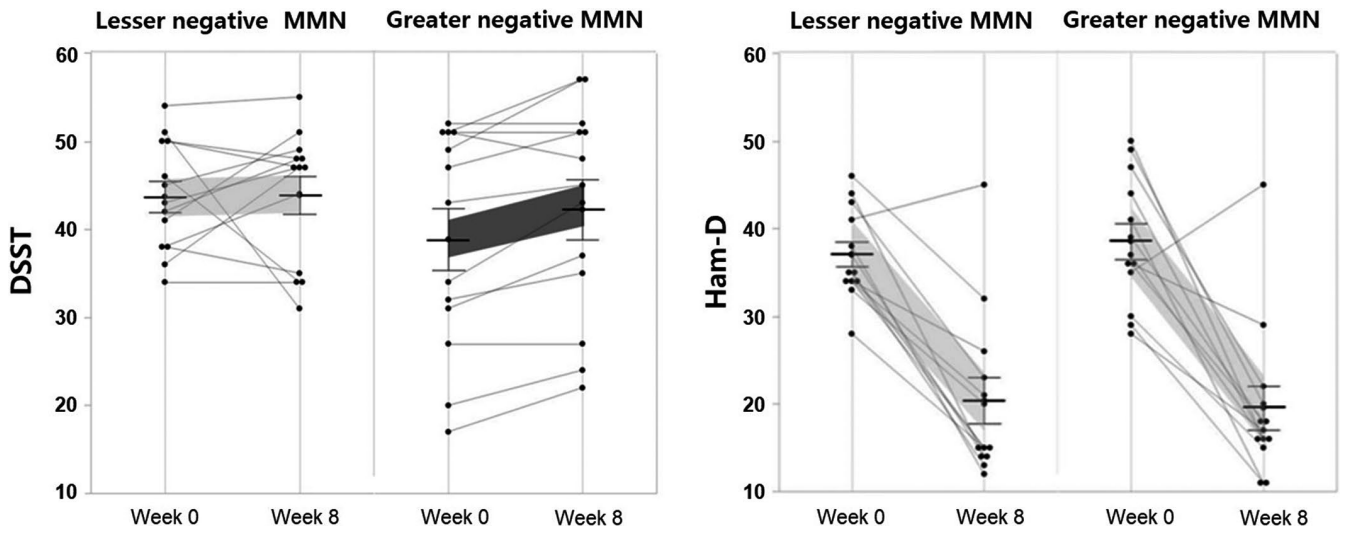

FIGURE 1 Parallel plot for low and high MMN group pre- and post-treatment for A, DSST and B, Ham-D scores. The groups are divided for visualization purpose. Note. MMN = mismatch negativity; DSST = digit-symbol substitution test; Ham-D = Hamilton depression scale

TABLE 3 Regression analysis examining predictor of change in digit-symbol substitution test from pretreatment to post-treatment. *P <.05, **P <.01, ***P<.005, Ham-D= Hamilton depression scale, Ham-A: Hamilton anxiety scale; MMN=mismatch negativity

	Predicting variables	F-value	R^2	β	t-value	*df*
model 1		4.803**	0.432			5
	Baseline Ham-D			-0.322	-1.434	
	Baseline Ham-A			1.058***	3.916	
	Age			-0.449	-2.573	
	Sex			-0.164	-0.813	
	Education			-0.078	-1.552	
model 2		4.206***	0.536			9
	MMN			0.397*	2.367	
	Left Pari-occipital Delta			0.087	0.578	
	Right Frontal Gamma			0.220	1.143	
	Right Central Gamma			-0.141	-0.727	

frontal gamma (r = −0.370, P = .044), right central gamma (r = −0.507, P = .004), and MMN (r = −0.486, P = .012). ACQ showed significantly positive correlations with left central delta (r = 0.390, P = .033), right central delta (r = 0.373, P = .042), right pari-occipital delta (r = 0.394, P = .031), and MMN (r = 0.473, P = .015). PDQD was significantly positively correlated with left frontal beta 1 (r = 0.386, P = .039), and right frontal beta 1 (r = 0.467, P = .011), and K-SAS was significantly correlated with MMN (r = 0.442, P = .035). Ham-D was significantly positively correlated with right central gamma (r = 0.390, P = .033). There was no other significant correlation of clinical/cognitive variables with spectral power bands and MMN at baseline.

For DSST, a regression analysis was conducted with DSST changes as a dependent variable and spectral powers at left pari-occipital delta, right frontal gamma, right central gamma, and MMN as predictors. The results indicated that baseline MMN significantly predicted changes in DSST scores after treatment (β = 0.397, P = .031), with an adjusted R^2 of 0.536 (Table 3). No other predictors were statistically significant. Figure 2 shows changes in DSST scores in groups of participants with high and low baseline MMN, which was created based on median split for the purpose of visualization. For ACQ, PDQD, K-SAS, and Ham-D scores changes, regression analysis did not find any significant results.

4 | DISCUSSION

This study aimed to investigate the changes in cognitive functioning after vortioxetine treatment in patients with MDD and the relationship between cognitive function and EEG such as MMN and spectral power. There was a significant increase in cognitive function after vortioxetine treatment. Also, there were changes in spectral power in which the theta power of the right central region decreased, and the beta 2 power of the right central and left frontal regions increased after treatment. Baseline MMN score predicted changes in DSST score after controlling for baseline depression and anxiety scores.

After 8 weeks of vortioxetine treatment, patients with MDD showed significant improvement in cognitive function. These results are in line with the previous studies that showed a positive change in cognitive function after receiving vortioxetine in patients with MDD [8, 11, 36]. For instance, DSST was significantly improved after 8 weeks of vortioxetine treatment, which was also associated with enhanced executive function, attention, and memory [8, 36]. In addition, our study found meaningful changes in the K-SAS score, which reflects a significant improvement in general quality of life of the participants. In our study, significant changes in cognitive function were only observed in the subjective scales, such as ACQ. No significant changes were found in the objectively evaluated scales, such as DSST. This discrepancy in results could be due to the relatively short period of intervention in this study, and thus being unable to sufficiently capture the patient's cognitive improvement. However, similar results were reported in a previous 6-month antidepressant treatment study, which found a significant improvement only in the subjective cognitive function, but not in the objective cognitive test [37]. These findings suggest that a longer treatment period, perhaps more than 6 months, would be necessary to induce the objective cognitive improvement in patients with MDD. Further research is needed to test this hypothesis.

Second, this study found significant changes in the spectral power. There was a significant decrease in the right central theta, a significant increase in the right central beta 2, and a marginally significant increase in the left frontal beta 2 regions after vortioxetine treatment. These results are similar to a previous study on the effects of vortioxetine in healthy individuals that found decreased power in theta band and increased power in beta and gamma bands [18]. In the present study, the beta 2 band (18-22 Hz) power was altered among multiple beta bands. EEG beta 2 activity is known to be associated with negative mood [38, 39], which is a core symptom of MDD. Moreover, changes in the beta 2 and theta bands took place in the frontal and central parts, which are the regions that are mainly involved with executive functions [40, 41]. More specifically, theta power at the frontal and central regions is associated with cognitive control [41] and error commission [42], and beta power is maximal at central region during successful inhibitory control [43, 44]. Although the activation of electrode level does not directly reflect the underlying cortical activation, our results suggest that spectral power changes are associated with changes in cognitive function.

Yet, although the changes in spectral power were related to the changes in depression and anxiety severities, they did not show any significant correlations with changes in cognitive functioning. Also, the spectral power did not have predictive power for the changes in cognitive and psychological variables. These insignificant findings might indicate that the changes in cognitive function after treatment are associated with other neural features such as functional connectivity and synchronization rather than spectral power. Functional connectivity, for instance, was correlated with changes in attentional control, rumination, and cognitive reappraisal after emotion regulation therapy [45], and beta phase synchronization was correlated with cognitive change after electroconvulsive therapy [46]. Another possible explanation is that the changes in EEG power following vortioxetine treatment are related to changes in depression and anxiety symptoms irrelevant to cognitive functions. According to a previous meta-analysis, spectral power does not appear to be clinically reliable for predicting depression treatment response [47].

Another topic of interest in this study was to explore the changes in MMN pre- and postvortioxetine treatment. We found no significant changes in MMN, suggesting that MMN is not a meaningful index of the changes in cognitive function after 8 weeks of treatment. This result is in line with a previous study that found that melancholia score, one of the predictors of poor treatment response, had no significant correlation with MMN [48]. Another study also demonstrated that MMN amplitudes may not be a disease-specific marker, but rather markers for functional outcomes related to higher-order cognitive and psychosocial functioning [48]. Further studies are needed to better understand the role of MMN as a specific biomarker of functional outcomes in patients.

More importantly, baseline MMN significantly predicted the improvement in DSST scores following treatment. While further research is needed to clarify the mechanisms underlying these findings, the results suggest that negative baseline MMN is associated with greater potential for improvement in cognitive function following vortioxetine treatment. In other words, the capacity for

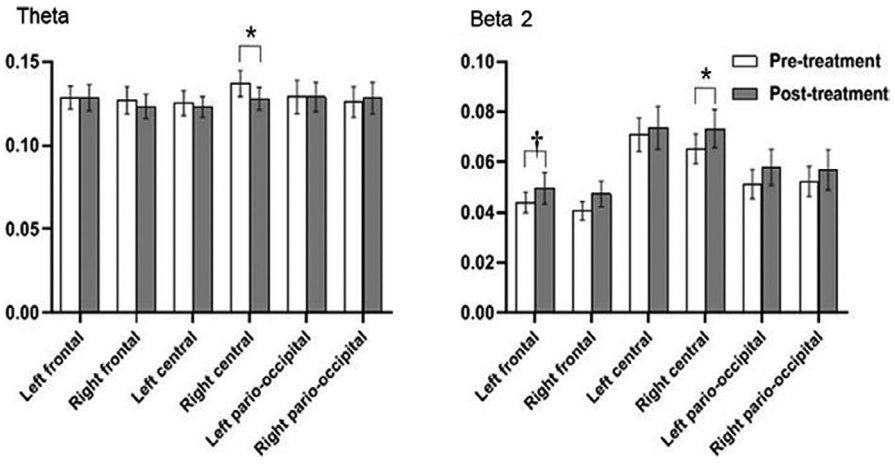

FIGURE 2 Differences in theta and beta 2 bands pre- and post-treatment with bootstrapping (n = 5,000)
†< .06, *P <.05

improvement in cognitive functioning after vortioxetine treatment might be greater among individuals with greater negative amplitude of MMN. Baseline MMN amplitude could thus be a meaningful indicator of cognitive reserve of antidepressant treatment. This might account for the insignificant findings on the effect of vortioxetine treatment on DSST in a previous study [49]. Although only a few studies have examined MMN in patients with MDD, there are a lot of studies that assessed MMN in patients with schizophrenia. Studies on schizophrenia have used MMN as an indicator of the neuroplasticity of the brain [50], where greater MMN amplitude was regarded as a good prognostic factor that reflects a low psychosis progress in high-risk patients [51] and good social functioning in both healthy participants [52] and patients with schizophrenia [53]. In addition, in most of these studies, MMN was mainly considered as a state marker rather than a trait marker [54,55]. For MDD, there are no previous human studies that evaluated MMN pre- and post-treatment. To our knowledge, this study was the first study to test the possibility whether MMN, a marker of neuroplasticity, could be a state or trait marker in patients with MDD. In our study, there were no significant changes between pre- and post-8 weeks vortioxetine treatment. With the current results, it is difficult to determine whether MMN is a state marker or a trait marker. However, considering past studies for schizophrenia and the results implying that improvement in cognitive functions takes time in depression, MMN may be a trait-like state marker in depression. Further research is needed in these areas.

This study has several limitations. First, this study is not a placebo-controlled design. Secondly, the number of participants was relatively small. Third, treatment was given for 8 weeks, which is a relatively short period of time to observe any reliable cognitive benefits.

Vortioxetine treatment improved cognitive function and induced changes in EEG (decreased theta power and increased beta power) in patients with MDD. Our results suggest that greater negative MMN amplitude is associated with greater potential for cognitive improvement following vortioxetine treatment. Further research is needed on these topics.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The research project has been approved and is conformed to the provisions of the Declaration of Helsinki by Institutional Review Board at Inje University Ilsan Paik Hospital (IRB no. 2016-08-017-007).

INFORMED CONSENT

After a thorough explanation of the procedure and protocol of the experiment, written informed consent was obtained from all participants.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

n/a.

ANIMAL STUDIES

n/a.

AUTHOR CONTRIBUTION

HK analyzed the data and wrote the paper. SYB collected the data and wrote the paper. YWK collected and analyzed the data. SHL designed the study and wrote the paper. SHL and HK reviewed and revised the paper. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Since our data contain potentially sensitive personal information, it is forbidden to share these data with a third party without obtaining additional written form of informed consent for information sharing, according to the bioethics law and personal information protection act in South Korea. We did not obtain the additional written consent for information sharing and sharing the data would violate the law and the ethical policy. South Korea's Ministry of Justice imposes the ethical and legal restrictions on using, opening, and transferring personal information, even though the data are de-identified. You may contact the Ministry of Justice, South Korea, for data requests: Ministry of Justice, Building #1, Government Complex-Gwacheon, 47, Gwanmun-ro, Gwacheon-si, Gyeonggi-do, Republic of Korea, 13 809. Tel: +82-2–2110-3000. Web: https://www.moj.go.kr/moj_eng/1772/ subview.do.

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