

Research paper

EEG beta and low gamma power correlates with inattention in patients with major depressive disorder



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ABSTRACT

Background: Inattention is a common feature of major depressive disorder (MDD). The aim of this study was to explore the relationship between quantitative electroencephalography (qEEG) power of a specific band and inattention severity in patients with MDD.

Methods: EEG recordings of 73 patients with MDD were collected in during both eyes closed and eyes open conditions. Inattention was assessed by the inattention sub-scale of the Korean version of the Adult ADHD scale (K-AADHD). The severity of symptoms associated with depression and anxiety was assessed with the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), and the Beck Depression Inventory (BDI). Multiple regression and Hayes mediation model were applied for the statistical analysis to verify the effects of clinical variables on inattention score.

Results: The beta (12–30 Hz) and low gamma (30–50 Hz) powers in fronto-central regions were negatively correlated with inattention scores. Symptom severity scores strongly predicted inattention scores; in particular, the BDI accounted for 23.9% of the variance. In mediation analysis, BDI fully mediated the path of anxiety to inattention.

Limitations: The medication effect and comorbidity in our participants were not fully controlled. A subjective assessment tool was hired to measure inattention.

Conclusions: Beta and low gamma power of the fronto-central regions might be a reliable measure of attention deficits in patients with MDD, which in turn, seems to be related to the severity of subjective depressive symptoms. Further work is needed to confirm this finding on larger, drug and comorbidity-free samples, and to test the clinical utility.

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1. Introduction

Major depressive disorder (MDD) is a common mental disorder with a lifetime prevalence rate of 17–21% (Iosifescu et al., 2009; Kessler et al., 2005; Savitz and Drevets, 2009), and it is associated with a high degree of subjective distress and psychosocial disability (Judd et al., 2000). The prevalence of comorbidity is very high in MDD in the form of anxiety disorders, personality disorders, substance abuse and medical illnesses, and is costly to individuals and society (Ballenger, 2000).

MDD is characterized by deficits in cognitive domains such as attention, concentration and executive functions, as well as learning and memory (Barabassy et al., 2010; Baune et al., 2006; Jaeger et al., 2006). Executive function, which is involved in the

control of memory and attention, is significantly impaired in adults with MDD in acute episode (Rogers et al., 2004). Preiss et al. (2010) suggested that the ability to sustain attention supports various cognitive functions and difficulties in the domain of attention which is one of the earliest signs of MDD. During the past decade, several studies have indicated that cognitive dysfunction is a critical determinant of health outcome in adults with MDD who are otherwise in symptomatic remission (Conradi et al., 2011; Jaeger et al., 2006). It has been reported that functional outcomes in patients with MDD are associated with, or mediated by, cognitive disturbances (McIntyre et al., 2013). Recently, it was revealed that perceived inattention of MDD patients significantly predicted poor workplace performance, as well as a lower quality of life (McIntyre et al., 2015).

The incidence of inattention in patients with MDD has not been systematically evaluated. In one national comorbidity survey, it was reported that 18.6% of the adult patients with MDD met criteria for attention deficit hyperactivity disorder (ADHD) (Kessler et al., 2006). Sustained attention impairment has also been

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reported in adolescents with MDD during the depressed state (Cataldo et al., 2005; Wilkinson and Goodyer, 2006).

QEEG, quantitative methods of analysis, enables the characterization of brain signal oscillations and it has been used as a tool to investigate physiological and pathological cognitive processes (Basar and Guntekin, 2013; Millan et al., 2012). Across decades, high-frequency EEG activity has been repeatedly associated with attentional process in healthy individuals and in a number of different clinical conditions (Barry et al., 2003). Recently, Gola et al. (2013) found that decreased beta band activity during the visual attention task reflects difficulty in activation and deficits in sustaining attentional processes. MacLean et al. (2012) showed that high resting state beta band power is related to high accuracy in the attentional blink task, while increased alpha band power is related to lower performance. In contrast, patients with ADHD had decreased beta and gamma power, in comparison to age-matched healthy controls (Clarke et al., 2001; Matsuura et al., 1993; Roh et al., 2015). However, clinical applications of EEG to ADHD patients still very controversial with the question being whether the knowledge gained from EEG has any practical diagnostic value and clinical utility (Johnstone et al., 2013; Lenartowicz and Loo, 2014; Loo and Makeig, 2012).

In this study we hypothesized that patients with MDD would have symptoms of inattention and these are associated with qEEG changes, especially in beta and low gamma band power. Therefore, the goals of this study were to clarify whether the symptoms of inattention could be reflected by the qEEG band power, and to explore how anxiety and depressive symptom severity affects inattention and qEEG power in patients with MDD.

2. Materials and methods

2.1. Subjects

A total of 73 patients with MDD (mean age = 38.71 ± 13.85 years, 33 male) were recruited. Of these, 38 had a comorbidity, such as general anxiety disorder (GAD, n=2), obsessive-compulsive disorder (OCD, n=3), panic disorder (n=11), adjustment disorder (n=12), post-traumatic stress disorder (n=10). All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Symptom severity was assessed with the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), and the Beck Depression Inventory (BDI) (Beck et al., 1961). Subjective inattention was measured by the inattention sub-score of the Korean version of the Adult ADHD Scale (K-AADHDS), which was translated and validated (Kim, 2003) from the original adult ADHD scale developed by Murphy and Barkley (1996). The K-AADHDS consists of 18 items investigating behavior and 9 items related to inattention. Only the nine-item inattention scale (Cronbach alpha = .79) was used in our study (Table 1). We obtained written informed consent from all participants before study enrolment. The study was reviewed and approved by the Institutional Review Board of Inje University Ilsan-Paik Hospital.

2.2. EEG recordings and qEEG analyses

The subjects were seated in a dimly lit, sound-attenuated room, and asked to relax and stay still for 3 min with their eyes open and for 3 min with their eyes closed. Laboratory EEG recordings were collected using a NeuroScan SynAmps 2 amplifier (Compumedics, El Paso, TX) from 62 surface electrodes (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, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, POZ,

Table 1

Validated Inattention Scale with 9 items (K-AADHDS).

Scale items for ADHD inattention	Factor Loading
1. Fail to give close attention to details or make careless mistakes in my work or other activities	.528
2. Have difficulty sustaining my attention in tasks or fun activities	.686
3. Don't listen when spoken to directly	.416
4. Don't follow through on instructions and fail to finish work or chores	.615
5. Have difficulty organizing tasks and activities	.619
6. Avoid, dislike, or am reluctant to engage in tasks that require sustained mental effort	.509
7. Lose things necessary for tasks or activities	.411
8. Am easily distracted by extraneous stimuli or irrelevant thoughts	.614
9. Am forgetful in daily activities	.460

Note. K-AADHDS, the Korean version of the Adult ADHD Scale.

PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2) mounted on a Quik-Cap (Compumedics, El Paso, TX) according to the extended international 10–20 placement scheme. The ground electrode was placed on the forehead and the reference electrode was predefined in the cap and positioned at between Cz and CPz. The vertical electro-oculogram (EOG) was recorded using bipolar electrodes; one located above and one below the right eye. A horizontal EOG was recorded at the outer canthus of each eye. The impedance of the electrodes was maintained at less than 5 kΩ.

EEG data were recorded with a .1–100-Hz band-pass filter at a sampling rate of 1000 Hz and initially processed using Scan 4.3. Eye movements were visually screened and eliminated by an expert. Only the eyes closed resting state condition was retained for analyses. Signal was segmented using predefined time windows of 2.048 s each. Epoch with signal over the +80 μV or lower than –80 μV on any channel was rejected from the analysis. A total of 30 epochs (~60 s) were prepared for each subject. Spectral density was calculated in each epoch on 62 electrode channels, and averaged 30 epochs by the Fast Fourier Transform. After performing FFT, spectral density averaged into specific frequency ranges, and each frequency band range was composed as follows (Kim et al., 2012): delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and low gamma (30–50 Hz). Then, the relative power of each channel was calculated by dividing each band power by the total power of the channel. On the basis of previous literature, we considered 6 regions of interest (ROI), of three channels each, and the averaged signal within each region was considered for correlational analyses (Zion-Golumbic et al., 2008) (Fig. 1): 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). In addition, the relative global band powers were calculated over 62 electrode channels and then averaged (Gianotti et al., 2007; Jung et al., 2007).

2.3. Statistical analysis

Spearman's correlation analysis was performed to evaluate the relationship between the qEEG and scores on the selected scales in patients with MDD. The bootstrap resampling technique (n=5000) was used to correct multiple correlations. To explore the predicting factors of inattention in patients with MDD, a two-step regression procedure was used. In the first stage, we controlled significant effects of demographic variables on inattention in the regression model. In the second stage, we input HAM-A, HAM-D, and BDI as predictor variables and analyzed the result. To verify the path involved when depression and anxiety affect

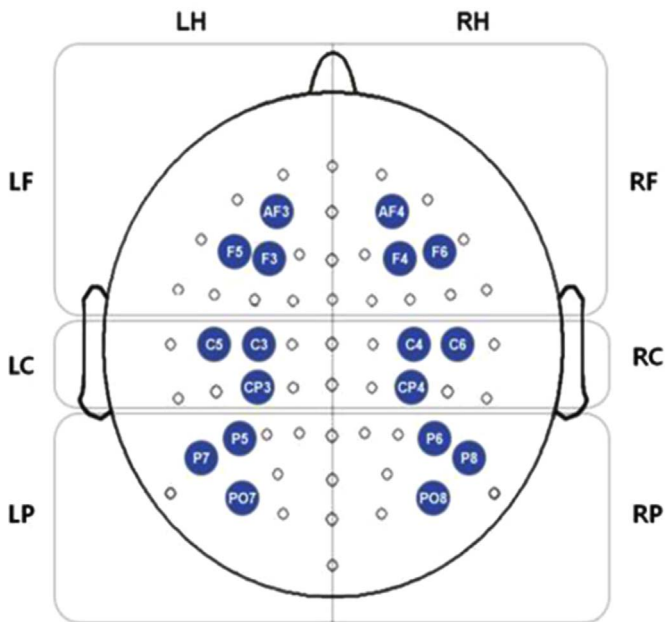


Fig. 1. Electrodes map and regions of interest (ROI). Note. LH, Left Hemisphere; RH, Right Hemisphere; LF, Left Frontal; RF, Right Frontal; LC, Left Central; RC, Right Central; LP, Left Parieto-occipital; RP, Right Parieto-occipital.

inattention, we used Hayes and Preacher’s (Hayes and Preacher, 2014) bootstrapping macro designed for SPSS to run a mediation model. Following the recommendations made by MacKinnon et al. (2004), when directly examining mediation in small samples, we used a nonparametric, resampling method (bias-corrected bootstrap) with 5000 resamples to derive the 95% confidence intervals (CI) for the indirect effect of symptom scores (Preacher and Hayes, 2008). We did not attempt to strictly correct the issue of multiple testing given the exploratory nature of the study. The significance level was set at $p < .05$. Statistical analyses were performed using SPSS software (version 18; IBM Inc. NY, USA).

3. Results

3.1. Symptom severity of participants

Symptom severity ranged from mild to severe (HAM-A mean \pm SD = 21.31 \pm 7.65, HAM-D mean \pm SD = 23.27 \pm 10.34, BDI mean \pm SD = 21.21 \pm 10.23, Inattention mean \pm SD = 15.40 \pm 7.54). Demographic and clinical variables are presented in Table 2.

3.2. qEEG and its correlation with symptom severity scores

Table 3 shows the pattern of correlation between EEG relative power over the six regions of interest (ROI) and the clinical variables in patients with MDD, as measured by the HAM-A, HAM-D, BDI, and the K-AADHD inattention sub-scale. Significant correlations were mainly found in the power of the beta band in patients with MDD. EEG beta power was negatively correlated to the inattention score in the left frontal ($r = -.328, p = .005$), the right frontal ($r = -.303, p = .009$), the left central ($r = -.307, p = .008$), and the right central ($r = -.317, p = .006$) regions. EEG low gamma power was also negatively correlated to the inattention scores in the left frontal ($r = -.243, p = .038$), the right frontal ($r = -.257, p = .028$), the left central ($r = -.245, p = .038$), and the right central ($r = -.256, p = .029$) regions. Figs. 2 and 3 illustrate the relationship between beta and low gamma power, respectively, and inattention over frontal and central regions. However, there were no

Table 2
Demographics and psychiatric rating scales’ descriptive statistics for MDD patients (N=73).

	Mean	SD
Age (years)	38.71	13.85
HAM-A	21.31	7.65
HAM-D	23.27	10.34
BDI	21.21	10.23
Inattention sub-score of Adult ADHD Scale	15.40	7.54
	<i>n</i>	Percent
Sex		
Male	33	45.2
Female	40	54.8

Note. HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; ADHD, Attention Deficit Hyperactivity Disorder.

Table 3
Spearman’s correlation (*rho*) with bootstrapping (n=5000) between EEG beta and low gamma bands power and HAM-A, HAM-D, BDI and Inattention in six cortical regions in MDD patients. Significant differences are indicated with asterisks (N=73).

	1	2	3	4
1. HAM-A	–			
2. HAM-D	.782***	–		
3. BDI	.539***	.703***	–	
4. Inattention	.298**	.327**	.522**	–
LF_Beta	–.080	–.178	–.107	–.328**
LF_Low Gamma	.053	–.035	.039	–.243*
RF_Beta	–.032	–.116	–.101	–.303**
RF_Low Gamma	.078	–.038	–.004	–.257*
LC_Beta	–.039	–.134	–.113	–.307**
LC_Low Gamma	.064	–.033	.037	–.245*
RC_Beta	.050	–.081	–.099	–.317**
RC_Low Gamma	.136	.023	.018	–.256*
LP_Beta	.107	–.013	–.046	–.181
LP_Low Gamma	.142	.014	.014	–.153
RP_Beta	.105	.039	–.023	–.185
RP_Low Gamma	.144	.097	.073	–.114

Note. EEG, Electroencephalography; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; LF, Left Frontal; RF, Right Frontal; LC, Left Central; RC, Right Central; LP, Left Parieto-occipital; RP, Right Parieto-occipital.

* $p < .05$.
** $p < .01$.
*** $p < .001$.

significant correlations in delta, theta, and alpha frequency bands.

3.3. Inattention score predicted by depression and anxiety scores

Table 4 presents that, among the demographic variables, only age regressed on inattention at step 1 ($b = -.407, p = .000$). With demographic variables controlled at step 2, the HAM-A main effect accounted for 10.9% of the variance ($b = .344, p = .002$); the HAM-D main effect accounted for 8.7% of the variance ($b = .299, p = .006$); and the BDI main effect accounted for 23.9% of the variance ($b = .495, p = .000$).

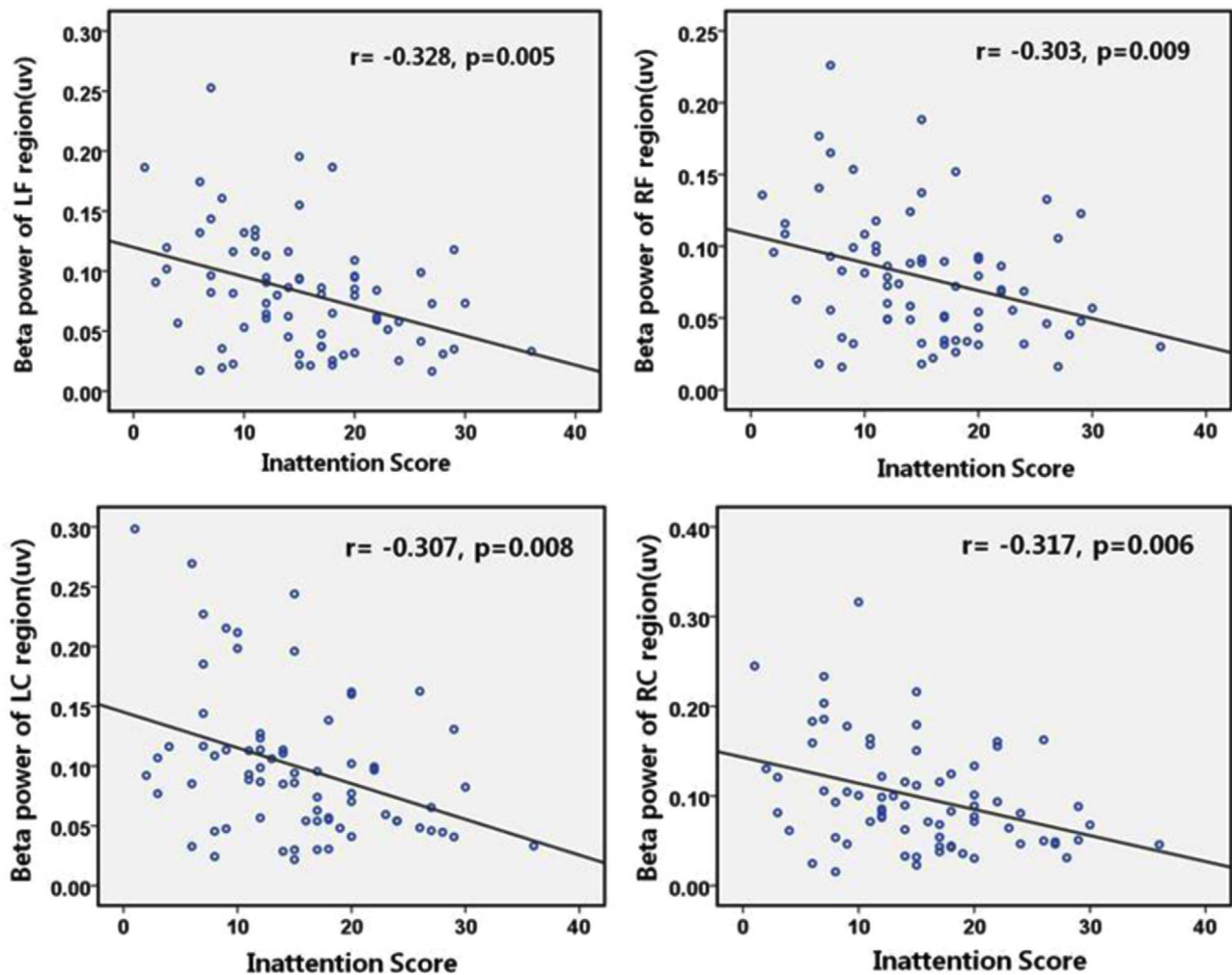


Fig. 2. Correlations between beta power and inattention score in 4 regions of interest (ROI). Note. LF, Left Frontal; RF, Right Frontal; LC, Left Central; RC, Right Central.

In the mediation analysis, Fig. 4 shows that the direct effect of HAM-A on inattention was not significant ($c' = .004$). Table 5 illustrates that the indirect effect of HAM-A on inattention through the BDI was significant at .268; zero does not appear in the 95% CI that lies between .139 and .432. The ratio of indirect to total effect of HAM-A on inattention was 98.4%, which implies the BDI fully mediated the effect of anxiety on inattention.

4. Discussion

Our study was designed to explore the relationship between qEEG power of specific bands and the severity of inattention in patients with MDD. The research revealed that (1) beta and low gamma power bands in the frontal and central regions of the brain were significantly negatively correlated with the inattention score; (2) The symptom severity scores, such as HAM-A, HAM-D and BDI, strongly predicted inattention; in particular, BDI accounted for 23.9% of the variance; (3) BDI fully mediated the path from anxiety to inattention.

The significant negative correlations in beta and low gamma bands with the inattention scores are in line with those of previous studies. Beta band was traditionally used as an EEG correlate of attention and arousal in neuro-feedback training (Egner and Gruzelier, 2004). MacLean et al. (2012) suggested that decreased beta power during rest was associated with the deficit in performance of the attentional blink test. EEG beta activity has been

repeatedly reported to be associated with inattention in ADHD patients, although results to date are partially contradictory (Kim et al., 2015; Markovska-Simoska and Pop-Jordanova, 2016; Roh et al., 2015). In addition, Herrmann et al. (2010) and Howard et al. (2003) suggested that gamma band is involved in cognitive processes, memory and spatial/temporal integration. Velasques et al. (2007) also found that gamma activities in the frontal areas were observed due to their involvement in attention, planning, and selection of movement while performing a reaching motor task (catching a ball in free fall).

Frontal lobe dysfunction has been repeatedly reported in patients with MDD (Baxter et al., 1989; Liao et al., 2013). Attention and executive functions are impaired in MDD patients (Paelecke-Habermann et al., 2005), and this suggests a fronto-subcortical dysfunction. These deficits seem to persist to some extent after the resolution of depressive episodes, during euthymic phases. However, these findings are still debated in the literature (Clark et al., 2005; Smith et al., 2006). It has also been found that depression in the elderly is associated with a significant degree of deficit in tests sensitive to frontostriatal dysfunction (Beats et al., 1996). Even though sensor level results could not be generalized to source level activity, our results also support the notion that frontal lobes might be impaired in MDD. Moreover, results reveal that the central lobes also might have certain involvement in the impairment with MDD.

Many previous studies have shown a moderate effect size of neurocognitive deficit in patients with MDD in the domains of

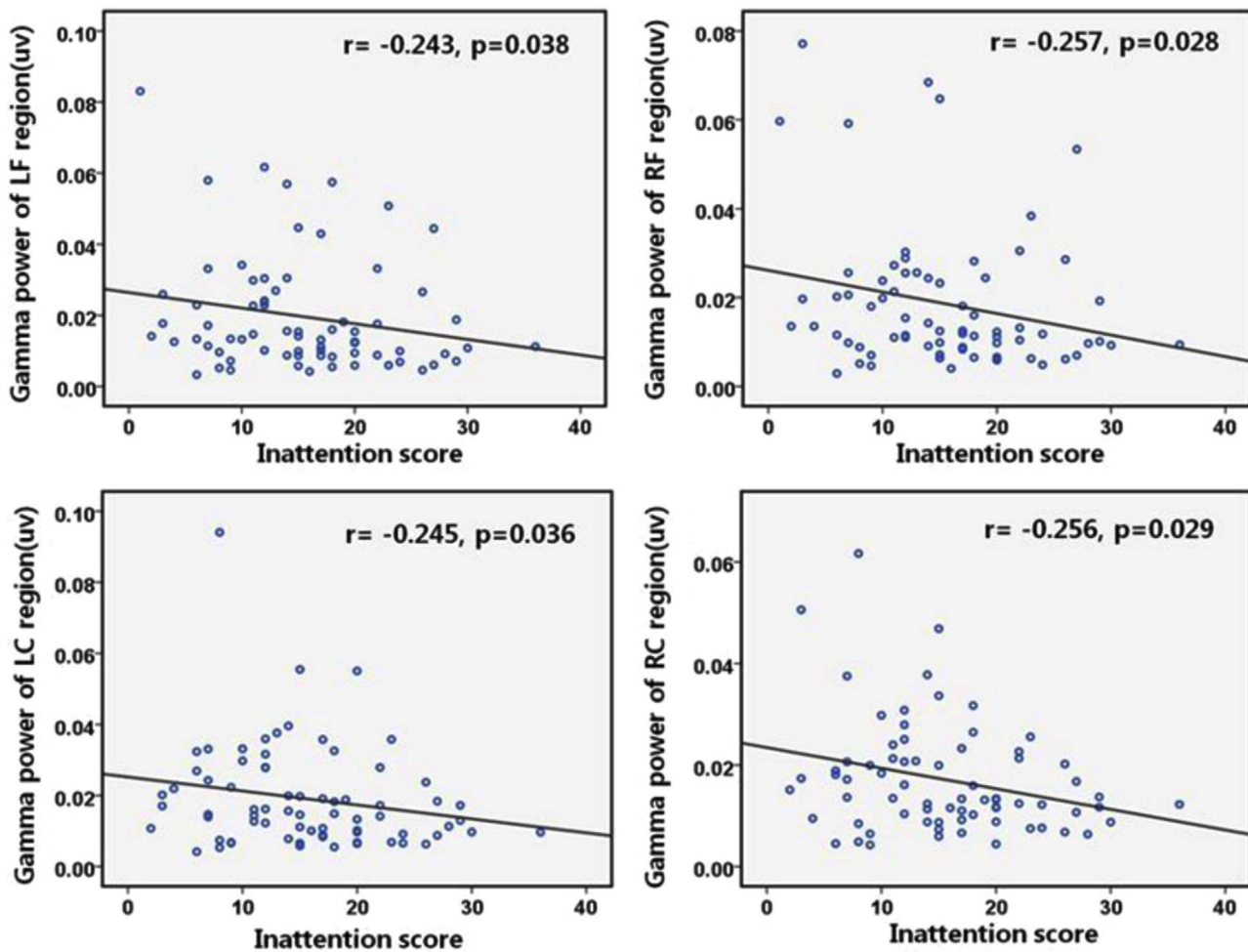


Fig. 3. Correlations between low gamma power and inattention score in 4 regions of interest (ROI). Note. LF, Left Frontal; RF, Right Frontal; LC, Left Central; RC, Right Central.

Table 4
Hierarchical regression analysis predicting inattention by HAM-A, HAM-D and BDI in all participants (N=73).

Predictor	Standardized β	Standard error	t	p	ΔR^2
Constant		4.547	5.708	.000	.169**
Sex	-.030	1.711	-.265	.792	
Age	-.407	.060	-3.685	.000	
Smoking	-.042	1.974	-.370	.713	
HAM-A	.344	.106	3.195	.002	.109**
HAM-D	.299	.077	2.820	.006	.087**
BDI	.495	.070	5.234	.000	.239***

Note. HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory. * $p < .05$.

** $p < .01$.

*** $p < .001$.

processing speed, attention, executive functions, learning, and memory (Hasselbalch et al., 2012; Murrough et al., 2011) as well as in cognitive affective bias (Lam et al., 2014). These cognitive complaints are known to remain in remitted MDD patients at rates ranging between 30% and 50% (Conradi et al., 2011; Fava et al., 2006; Snyder, 2013), which may explain persistent psychosocial impairment in patients with MDD. Recently, cognitive dysfunction, including attention, memory, and processing deficits, was suggested as a primary mediator of functional impairment in patients with MDD (McIntyre et al., 2013).

Using regression analysis, we found that BDI scores accounted for 25% of the variance to explain inattention, which is greater than our expectation, while HAM-D scores accounted for 8.7% of the variance. The observer-rated HAM-D and the self-report BDI are among the most commonly used symptom rating scales for depression, and both have well demonstrated reliability and validity. However, many depressed subjects have discrepant scores on these two assessment instruments. Enns et al. (2000) suggested that depression ratings obtained with the BDI and HAM-D are frequently discordant. A number of patients' characteristics predict the discrepancy between these two rating methods; the BDI scores psychological symptoms of depression, whereas the HAM-D scores somatic symptoms of depression. From this perspective, our results suggest that subjective symptom severity (as measured by the BDI) more reliably reflected patients' inattention and changes in EEG spectral density.

Path analysis revealed no direct effect of anxiety on inattention. Anxiety explained inattention only through depression, and specifically through BDI scores. This finding was in line with those of several previous studies. Gorman et al. (2002) suggested that GAD is a chronic disorder that often precedes the development of depression. Wittchen et al. (2000) examined the relationship between anxiety and depressive disorders in 4–5-year prospective-longitudinal community study and concluded that most anxiety disorders are almost always primary disorders that substantially increase the risk for secondary depression. Patients with comorbid anxiety and depressive disorder usually have a more severe level of cognitive dysfunction compared to patients with anxiety

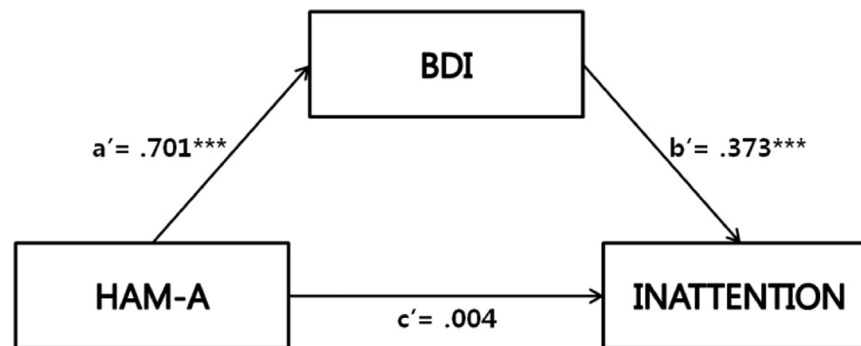


Fig. 4. Conceptual mediation diagram of HAM-A on Inattention through BDI. Note. HAM-A, Hamilton Anxiety Rating Scale; BDI, Beck Depression Inventory. a' = Direct effect of HAM-A on BDI, b' = Direct effect of BDI on Inattention, c' = Direct effect of HAM-A on Inattention, *** $p < .001$.

Table 5
Indirect effect of anxiety on inattention (Mediation effect through BDI).

Variable	Effect	Boot S.E.	95% confidence intervals	
			LLCI	ULCI
BDI	.261	.072	.139	.432

Note. Bootstrap sample size: 5000. The indirect effect is significant where the confidence intervals does not contain zero. LLCI = Lower Level of the 95% bootstrap percentile Confidence Interval; SE = Standard Error; ULCI = Upper Level of the 95% boot-strap percentile Confidence Interval. BDI, Beck Depression Inventory.

disorder alone (Dupuy and Ladouceur, 2008). In addition, patients with MDD have more difficulty in recognizing facial emotional tasks compared to patients with anxiety disorders (Yoon et al., 2016). Following this pathogenesis, our results suggested that inattention observed in patients with MDD is not directly influenced by anxiety but is instead fully mediated by depressive symptoms. However, before a conclusion can be made on this pathway, more research is required.

There are strengths and limitations of this study that are worth discussing, as they affect the interpretation of our results. A central strength of this study included the use of 64 channel EEG, which allowed for a regional analysis of neural activity and which was not possible with traditional low density EEG studies. One major limitation was that we could not fully control the medication effect in our participants. Studying patients who are not taking medication might help explain more clearly the relationship between inattention and qEEG change. Second, we did not use neuropsychological tests to measure inattention, and therefore relied on subjective measures. It cannot be excluded that cognitive distortions about the self, which has long been reported in depression (Beck, 1973, 2008), might have influenced patients' self-assessment on the adult ADHD scale. Third, 38 out of 72 MDD participants had a comorbid anxiety disorder. Although MDD is often found in overlap with several anxiety disorders (Clayton, 1990), a single diagnosis is a preferable choice to explore disease-specific patterns. Fourth, it was difficult to contextualize the findings within the context of a comparison analysis with no presence of a control group of healthy individuals. With those limitations, the reported results represent an important starting point for future MDD research to build upon, through investigation that examines local dysregulation in specific brain regions using EEG, and its correlation to clinical variables.

5. Conclusion

Patients with MDD had inattention symptoms that showed a

significant negative correlation with beta and low gamma band power in the frontal and the central regions. Subjective depressive symptom severity (as indicated by the BDI score) showed more variance to explain the inattention compared to objective symptom severity (indicated by the HAM-D score). In addition, anxiety, as measured by our study, did not have a direct effect on inattention, but was fully mediated by depressive symptoms. Overall, our results suggest that beta and low gamma power of the fronto-central regions might be a reliable measure of attention deficits in patients with MDD, which seem to be related to the severity of subjective depressive symptoms. Further work is needed to confirm this finding on larger, drug and comorbidity-free samples, and to test the clinical utility.

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