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RESEARCH ARTICLE

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Valerian extract alters functional brain connectivity: A randomized double-blind placebo-controlled trial

Daeyoung Roh[1,2] | Jae Hoon Jung[1,2] | Kyung Hee Yoon[1] | Chang Hyun Lee[1,2] | Lee Young Kang[1,2] | Sang-Kyu Lee[1,2] | Kitack Shin[1] | Do Hoon Kim[1,2]

[1] Department of Psychiatry, Hallym University College of Medicine, Chuncheon, Korea

[2] Mind-neuromodulation Laboratory, Hallym University College of Medicine, Chuncheon, Korea

Correspondence
Do Hoon Kim, MD, PhD, Department of Psychiatry, Hallym University College of Medicine, Chuncheon Sacred Heart Hospital, 77 Sakju-ro, Chuncheon, Gangwon-Do 24253, Korea.
Email: dohkim@hallym.ac.kr

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Valerian root is the most commonly used herbal supplement for sedation and anxiolysis, but it is unknown whether it may affect functional brain connectivity. Our goal was to use electroencephalography (EEG) to investigate whether valerian root extract (VRE) affects resting-state connectivity changes and whether such changes are associated with clinical symptoms. This 4-week, double-blinded, randomized, placebo-controlled clinical trial was conducted with 64 nonclinical volunteers suffering psychological stress. The participants received VRE (100 mg) or a placebo thrice daily. We examined VRE's therapeutic effects on anxiety and stress-related psychological constructs. Functional brain connectivity changes were measured as EEG coherence in the alpha and theta frequency bands. The VRE and placebo groups both exhibited significant postintervention improvements on all clinical scales, but no significant between-group differences in these changes were noted. Compared with the placebo group, the VRE group exhibited significantly greater increases in frontal brain region alpha coherence across four electrode pairs, and these changes were significantly correlated with anxiolysis. The VRE group also exhibited significantly greater decreases in theta coherence across another four electrodes pairs. Our findings indicate that VRE alters functional brain connectivity in relation to anxiety. Further EEG studies are needed to confirm VRE's neurophysiological effects.

KEYWORDS

alpha band, brain connectivity, coherence, electroencephalography, herbal supplement, valerian

1 | INTRODUCTION

Anxiety is among the most common mental problems, currently affecting 7.3% of people worldwide (Baxter, Scott, Vos, & Whiteford, 2013). Conventional anxiolytic medications are considered efficacious and safe, but their use is still limited. Conventional drugs such as antidepressants and benzodiazepines do not alleviate all affective symptoms, and intolerable adverse effects may cause nonadherence (Kinrys, Coleman, & Rothstein, 2009). There is little evidence that conventional antidepressant drugs are effective, particularly for people with mild to moderate depression (Fournier et al., 2010). Herbal remedies could be an attractive option for patients as they are perceived as complementary and commonly have a more favorable side effects profile (Wachtel-Galor & Benzie, 2011) regardless of potential risks (Niggemann & Grüber, 2003). Therefore, in recent years, the use of over-the-counter psychotropic herbal medicines as self-treatment for various afflictions has been rapidly growing (Cavaliere, Rea, Lynch, & Blumenthal, 2009).

Valeriana officinalis, commonly known as valerian, has been used as a sedative–hypnotic herb for over 1,000 years. Valerian is the most commonly used herbal supplement (Blumenthal, Ferrier, & Cavaliere, 2006; Morris & Avorn, 2003). Valerian is listed by the US Food and Drug Administration as a food supplement and is approved as an over-the-counter medicine in Western Europe (Ross, 2014). There are no contraindications to its use (Blumenthal, 1998). It is most commonly utilized for its sedative–hypnotic effects, but it has been

suggested for several other uses, including alleviating anxiety, depression, and psychological stress (Kinrys et al., 2009). Although its effectiveness remains unconfirmed, valerian is considered a highly promising herbal agent (Baek, Nierenberg, & Kinrys, 2014).

Valerian's exact pharmacological mechanism remains undetermined, but some mechanisms have been identified. The valepotriates and valerenic acid in valerian root cause sedation and anxiolysis by enhancing γ-aminobutyric acid (GABA) transmission (Benke et al., 2009; Savage, Firth, Stough, & Sarris, 2018). Valerian compounds also act on the $GABA_A$ receptor, similarly to benzodiazepines (Hadley & Petry, 2003). Another core mechanism involves serotonergic effects via partial agonism of the 5-hydroxytryptamine-2A receptor (Dietz, Mahady, Pauli, & Farnsworth, 2005).

During the last 20 years, several clinical trials have investigated valerian's efficacy for psychological stress and anxiety, but few have been properly controlled. Valerian's stress-reducing effects have been shown in healthy volunteers in short-term care settings (Kennedy, Little, Haskell, & Scholey, 2006; Kohnen & Oswald, 1988), but not in long-term care settings. Moreover, systematic reviews of its anxiolytic effects have found inconsistent results due to a lack of standardization and quality controls (Kinrys et al., 2009; Nunes & Sousa, 2011). Recent animal studies have shown that valerian extracts have potent anxiolytic effects (Murphy, Kubin, Shepherd, & Ettinger, 2010) and reduce physical and psychological stress (Jung et al., 2015). However, rigorous studies involving objective measures are needed to confirm valerian's long-term efficacy in human subjects.

One particularly unfortunate lacuna in the literature on valerian is the lack of any studies examining valerian's effects on electroencephalography (EEG) rhythms or functional brain connectivity. Cerebral EEG rhythms reflect brain network activity (Steriade, 2006), and resting-state EEG can be used for serial examinations of psychological symptom changes (Kim et al., 2017; Roh et al., 2011). EEG measurements of brain wave coherence in particular reflect brain dynamics in terms of the coupling and functional association of paired regions (Shaw, 1984; Sklar, Hanley, & Simmons, 1972). EEG coherence measurements have been used to evaluate cortical functional connectivity (French & Beaumont, 1984) and are very sensitive to mental states (Chen & Rappelsberger, 1994). Pharmaco-EEG studies have proposed that administering psychotropic medications can affect EEG measurements in clinical populations (Aiyer, Novakovic, & Barkin, 2016). EEG studies of valerian are limited to a few sleep studies using crude EEG-based polysomnography measurements (Diaper & Hindmarch, 2004; Dimpfel & Suter, 2008).

Overall, few randomized controlled trials on valerian have been conducted, though those that were conducted have returned consistent results (Ahmadi, Khalili, Abbasian, & Ghaeli, 2017; Hassani et al., 2015). We, therefore, conducted a randomized, double-blinded, placebo-controlled, parallel-group trial to examine the therapeutic effects of valerian root extract (VRE) on anxiety and other psychological constructs including depression, cognitive deficits, perceived lack of social support, and occupational dysfunction in nonclinical volunteers suffering psychological stress. This study is the first to investigate VRE's effects on resting-state EEG changes. For functional connectivity, we investigated resting-state coherence values in the alpha (8–12 Hz) and theta (4–8 Hz) bands, as alpha and theta power activities are linked to decreased anxiety (Boutcher, 1993) and emotional arousal (Knyazev, 2007), respectively. Based on prior studies, we hypothesized that VRE would alter functional brain connectivity and that these changes would correlate with anxiolysis.

2 | METHODS

2.1 | Participants

This study was conducted in the psychiatry units at Chuncheon Sacred Heart Hospital, a teaching hospital affiliated with the Hallym University College of Medicine. It was retrospectively registered with the Clinical Trials Registry Korea (registration: KCT0002406). We used advertisements at the local university and in the community to recruit participants with stress that was not serious enough for a psychiatric diagnosis. The study protocols were approved by the hospital's Ethics and Medical Research Committee and conducted according to the principles of the Declaration of Helsinki. All subjects gave written informed consent.

The inclusion criteria were (a) a self-reported score above 4 on at least 1 of the 0-to-10 visual analogue scales separately administered for anxiety, depression, and insomnia; (b) being between 18 and 65 years old; and (c) being able to understand and follow the instructions and procedures. The exclusion criteria were (a) experiencing a current depressive episode or anxiety disorder, a current or past psychotic disorder or bipolar disorder, or a current alcohol or substance use disorder according to the Diagnostic and statistical manual of mental disorders - fifth edition (DSM-5) criteria (American Psychiatric Association, 2013); (b) having any history of serious liver or kidney disease; and (c) using relaxation techniques or herbal therapies. Face-to-face diagnostic interviews were performed to determine whether each participant had any functional impairment or major symptoms such as suicidal ideation related to anxiety disorders and affective disorders according to DSM-5 criteria.

The results of prior study (Ahmadi et al., 2017) indicated that the mean difference of HAM-A scores before and after treatment with valerian was 2.92 and the standard deviation of the difference between subjects was 4.70. Based on a standard sample size formula (Noordzij et al., 2010), we aimed for a sample size of 32 for each group, for a total sample size of 64, to cover an anticipated 10% loss to follow-up, for a two-sided type I error of 5% and 90% statistical power.

2.2 | Study procedures

The enrollees were randomly allocated to either the VRE group (n = 34, initially) or the placebo group (n = 30, initially) by a psychologist who was unaware of the study groups and saw only the participants' computer-generated identification numbers by simple randomization method.

The drug capsule was made in a Korean health supplement company (Natural F&P Inc., Seoul, Korea). Valerian roots were extracted with 70% ethanol solvents, and each capsule was standardized to contain 100 mg of VRE with 0.8% valerenic acids using high pressure liquid chromatography. Only one lot of valerian (EA142003)

was used in the study. The placebo and VRE capsules were visually similar and were similarly packaged so that only the pharmacist could distinguish them. This kept the research staff and the participants blinded to group assignments. The participants were instructed to take the capsules orally thrice daily for 4 weeks.

Each participant underwent a screening assessment, a baseline assessment, and an end-of-study assessment. At each screening, the subjects underwent a structured interview with a senior psychiatrist and an experienced psychologist. At the baseline and end-of-study assessments, we conducted EEG recordings, various stress-related psychological assessments, routine blood cell counts, and hepatorenal function tests. Safety was evaluated at each visit through history-taking, clinical examinations, and the noting of participants' complaints and adverse events. Compliance with the study medication was evaluated by counting pills at the study's end.

2.3 | Psychological measures

Clinical psychologists assessed the severities of depression and anxiety in the participants with validated Korean translations (Kim, 2000; Yi et al., 2005) of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959; Hamilton, 1960). The HAM-D and HAM-A have 17 and 14 items, respectively, and higher scores indicate greater symptom severity. We also used reliable and valid Korean translations (Lee et al., 1995; Yook & Kim, 1997) of the Beck Depression Inventory and Beck Anxiety Inventory, which are both 21-item self-rating scales (Beck & Steer, 1990; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Higher scores in those scales mean more serious symptoms. To measure sleep quality, we used a validated Korean translation (Sohn, Kim, Lee, & Cho, 2012) of the Pittsburgh Sleep Quality Index, which is a 19-item self-rating scale on which higher scores mean lower sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). We used the Korean version of the 5-item World Health Organization Well-Being Index (WHO-5) to measure levels of positive well-being (Moon, Kim, & Kim, 2014; WHO, 1998). The WHO-5 uses 6-point Likert scales, and higher level of this scale indicate more positive well-being level. To assess the levels of stress and social and occupational functioning, we used Korean translations of the Brief Encounter Psychosocial Instrument (Frank & Zyzanski, 1988; Yim et al., 1996), which is a 5-item scale based on 5-point Likert scales, and the Social and Occupational Functioning Assessment Scale (Frances, 1994; Lee, Cho, & Kwon, 2006), which is scored from 0 (the lowest functional level) to 100 (the highest functional level). We used validated Korean translations (Park & Kim, 2010; Yun et al., 2005) of the 9-item Brief Fatigue Inventory and the 3-item Sheehan Disability Scale to measure fatigue and functional impairment, respectively (Mendoza et al., 1999; Sheehan, 1983). Higher scores in these scale be interpreted as they experience more fatigue and functional impairment.

2.4 | EEG acquisition and recording

To derive measures of EEG alpha and theta band coherence, we recorded electrical brain activity with a 64-channel geodesic electrode net of Ag/AgCl electrodes encased in saline-dampened sponges (Electrical Geodesics, Eugene, OR). Electrode impedances were reduced to less than 50 kΩ, and analog EEG signals were amplified and sampled at a 1,000-Hz rate with bandpass filtering at 0.1–100 Hz. We achieved 16-bit precision with an online vertex (Cz) reference.

Before recording sessions, participants were instructed to rest for 10 min. Participants had the net placed on their heads and were then escorted into a semidarkened, sound-attenuated booth and seated in front of a computer screen. A computer outside the booth recorded the EEG signals. We conducted recordings in an initial 3-min period in which the participants were asked to keep their eyes open and in a further 3-min periods in which they were asked to keep their eyes closed. However, we only used data from the eyes-closed periods because previous studies have found no differences between eyes-open and eyes-closed recordings (Henriques & Davidson, 1991; Stewart, Bismark, Towers, Coan, & Allen, 2010).

2.4.1 | EEG processing

The 32-channel resting-state EEG data, which included recording artifacts from eye movements, muscle movements, and cardiac activity, were imported into NeuroGuide 2.3.5 software (Applied Neuroscience, St. Petersburg, FL). The EEG data were re-referenced to averaged linked ears from both mastoid channels in subsequent analyses. Artifact removal was performed off-line by an experienced physician. The data were submitted to an automated cleaning algorithm that removed all movement artifacts and blinks with amplitudes exceeding ±75 mV. The data were then reedited by visual inspection for any remaining artifacts. We selected 30 artifact-free epochs of 2-s durations. The split-half reliability and test–retest reliability were at least 0.95 for the cephalic electrodes. Each digitized epoch of eye-closed EEG data was quantified with a fast Fourier transform algorithm (Cooley & Tukey, 1965) to calculate spectral power (μV^2).

2.4.2 | EEG coherence

We computed absolute power spectra in the alpha and theta frequency ranges from the 19 scalp electrodes (i.e., FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). We then used the power calculation outputs to compute the alpha and theta band coherence values for all 171 interhemispheric and intrahemispheric pairings of these 19 electrodes with a previously defined method (Thatcher, Krause, & Hrybyk, 1986). We defined coherence as follows:

$$r^2_{xy}(f) = \frac{\left(G_{xy}(f)^2\right)}{(G_{xx}(f)G_{yy}(f))}, \quad (1)$$

where $G_{xy}(f)$ is the cross-power spectral density and $G_{xx}(f)$ and $G_{yy}(f)$ are the auto-power spectral densities. Applying this equation involved complex analyses, which produced a real cospectrum ("r") and an imaginary quad-spectrum ("q"). Applying r and q to Equation (1) produces the following result:

$$r_{xy}^2 = \frac{r_{xy}^2 + q_{xy}^2}{G_{xx}G_{yy}}. \quad (2)$$

2.5 | Statistical analysis

The Kolmogorov–Smirnov test revealed that some data were not normally distributed, so we used nonparametric tests for further data analysis. We used Wilcoxon's test to compare the baseline and follow-up values of variables. We conducted between-group comparisons with the Mann–Whitney U test and the χ^2 test. We calculated Spearman correlation coefficients for correlations between electrophysiological changes and clinical variable changes. All analyses were two-tailed, and we defined statistical significance as $p < 0.05$. We used SPSS version 16.0 (IBM, Armonk, NY) for all statistical analyses.

3 | RESULTS

3.1 | Study participants

Of the 80 participants approached, 16 were excluded for not meeting the inclusion criteria (seven were older than 65 years, three had physical diseases, and four were diagnosed with major affective or anxiety disorders) and two declined to participate. Ultimately, 64 participants were enrolled, all of whom were ethnically Korean.

Figure 1 depicts the flow of study participants. From the VRE and placebo groups' initial sizes of 34 and 30 patients, respectively, they lost five and seven patients, respectively, to follow-up, which translates into withdrawal rates of 14.7% and 23.3%, respectively. These withdrawal rates are comparable with those of similar studies (e.g., Ahmadi et al., 2017). However, the two groups were still well-balanced and nonsignificantly different in their baseline characteristics and psychometric scale changes (Tables 1 and 2).

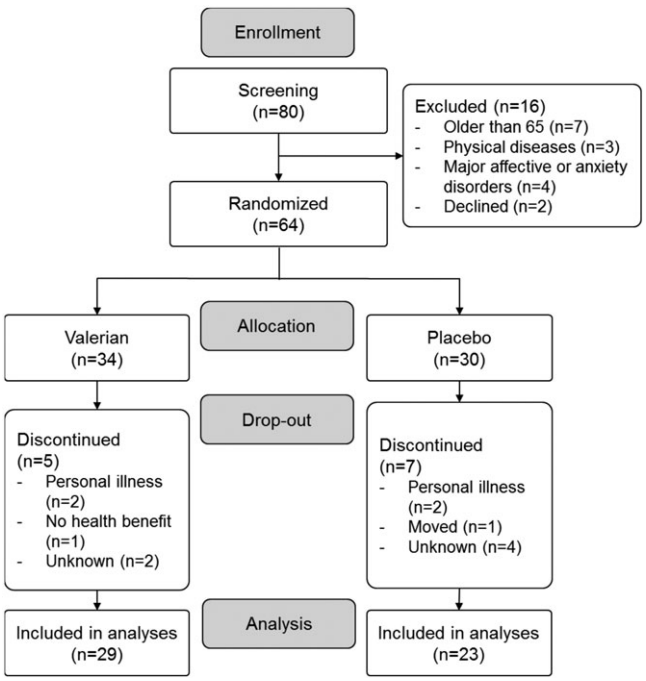

FIGURE 1 Flowchart of study progress

3.2 | Effects of VRE on symptom changes

We observed significant improvements in all psychiatric variables between the baseline and follow-up assessments in both groups (Table 2). This meant significantly decreased scores on the HAM-D, HAM-A, Beck Depression Inventory, Beck Anxiety Inventory, Pittsburgh Sleep Quality Index, Brief Encounter Psychosocial Instrument, Brief Fatigue Inventory, and Sheehan Disability Scale and significantly increased scores on the WHO-5 and Social and Occupational Functioning Assessment Scale. However, we found no significant between-group differences in the changes for any psychiatric variable (Table 2). There were no significant correlations in the VRE group between alpha coherence changes and other psychiatric variables.

3.3 | Alpha coherence changes and anxiety levels

Compared with the placebo group, the VRE group showed significantly greater increases in alpha coherence across the F3-C4 (VRE: 3.20 [6.39]; placebo: −0.07 [7.37]; $p = 0.025$), C3-F8 (VRE: 4.61 [10.63]; placebo: −2.28 [14.75]; $p = 0.038$), C3-T4 (VRE: 6.93 [12.67]; placebo: −0.69 [16.30]; $p = 0.038$), and F7-Fz (VRE: 4.26 [13.7]; placebo: −3.89 [13.92]; $p = 0.028$) electrode pairs. We also found significant negative correlations in the VRE group between HAM-A score changes and alpha coherence changes across all four of those electrode pairs (F3-C4: $r = -0.408$, $p = 0.028$; C3-F8: $r = -0.372$, $p = 0.047$; C3-T4: $r = -0.429$, $p = 0.020$; and F7-Fz: $r = -0.442$, $p = 0.016$; Figure 2).

3.4 | Theta coherence changes

Compared with the placebo group, the VRE group exhibited significantly greater decreases in theta coherence across the Fz-C4 (VRE: −6.27 [9.89]; placebo: −2.42 [14.9]; $p = 0.015$), P4-Fz (VRE: −3.10 [13.06]; placebo: 3.75 [12.53]; $p = 0.033$), O2-Fz (VRE: −4.92 [17.28]; placebo: 7.28 [16.93]; $p = 0.026$), and F7-Fz (VRE: −7.34 [16.57]; placebo: 4.88 [16.54]; $p = 0.013$) electrode pairs (Figure 3). There were no significant correlations in the VRE group between theta coherence changes and psychiatric variables.

TABLE 1 Demographic characteristics of the participants

	Valerian group (n = 29)	Placebo group (n = 23)	χ^2	p value
Sex, female (%)	26 (89.7)	17 (73.9)	$\chi^2 = 2.221$	0.136
Age (year)	37.0 ± 15.6	34.6 ± 16.5	U = 304.000	0.585
Education (years)	12.93 ± 2.7	12.87 ± 2.3	U = 323.000	0.842

Values are mean ± standard deviation or n (%). U: Mann–Whitney U test.

TABLE 2 Changes and comparison of psychiatric variables between the valerian and placebo groups

		Valerian group (n = 29)			Placebo group (n = 23)			p value for between-group comparison of difference**
Variables	Time	mean ± *SD*	p value*	Mean difference	mean ± *SD*	p value*	Mean difference	
HAM-D	Baseline Posttreatment	13.21 ± 3.98 5.07 ± 4.11	0.000	−8.14 ± 4.38	12.70 ± 4.00 4.74 ± 4.61	0.000	−7.96 ± 3.65	0.746
HAM-A	Baseline Posttreatment	13.38 ± 5.04 4.69 ± 3.52	0.000	−8.69 ± 4.74	13.00 ± 6.09 3.91 ± .95	0.000	−9.09 ± 3.36	0.584
BDI	Baseline Posttreatment	20.24 ± 7.58 11.86 ± 9.01	0.000	−8.38 ± 7.25	17.30 ± 8.42 9.35 ± 8.45	0.000	−7.96 ± 7.66	0.427
BAI	Baseline Posttreatment	17.34 ± 8.96 12.66 ± 11.02	0.001	−4.69 ± 6.61	16.22 ± 10.38 10.39 ± 9.10	0.001	−5.83 ± 6.94	0.904
PSQI	Baseline Posttreatment	11.41 ± 3.75 7.86 ± 3.75	0.000	−3.55 ± 2.95	10.13 ± 3.92 6.74 ± 3.41	0.000	−3.39 ± 3.46	0.875
WHO-5	Baseline Posttreatment	6.52 ± 3.47 8.97 ± 4.47	0.010	2.45 ± 4.28	5.65 ± 3.77 8.87 ± 5.35	0.002	3.22 ± 4.26	0.941
BEPSI	Baseline Posttreatment	13.86 ± 3.59 10.03 ± 2.81	0.000	−3.83 ± 3.51	13.52 ± 4.11 9.87 ± 3.81	0.000	−3.65 ± 3.79	0.535
SOFAS	Baseline Posttreatment	72.48 ± 11.69 78.45 ± 12.70	0.004	5.97 ± 11.19	71.00 ± 10.60 77.52 ± 11.68	0.004	6.52 ± 9.42	0.794
BFI	Baseline Posttreatment	26.08 ± 4.96 19.78 ± 7.83	0.000	−6.30 ± 7.70	25.55 ± 5.90 19.74 ± 6.82	0.009	−5.81 ± 7.77	0.692
SDS	Baseline Posttreatment	16.66 ± 3.79 11.41 ± 7.02	0.002	−5.24 ± 7.33	16.43 ± 5.78 11.35 ± 7.21	0.013	−5.09 ± 8.61	0.897

Note. BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BEPSI: Brief Encounter Psychosocial Instrument; BFI: Brief Fatigue Inventory; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; PSQI: Pittsburgh Sleep Quality Index; SDS: Sheehan Disability Scale; SOFAS: Social and Occupational Functioning Assessment Scale; WHO-5: 5-item World Health Organization Well-Being Index.

*Wilcoxon's test.

**Mann–Whitney U test.

3.5 | Adverse effects

No complaints of moderate or serious adverse reactions were registered, and no abnormal laboratory changes were detected. Only *two* adverse effects were reported, *one* each from the VRE and placebo groups. The VRE-treated subject complained of atypical chest pain. We assessed the symptom severity as mild and the symptom as unrelated to the medication. The placebo-treated subject complained of mild gastrointestinal problems. Although both subjects' symptoms resolved spontaneously, they withdrew from the study.

4 | DISCUSSION

This was the first study that evaluated valerian's neurophysiological effects on brain connectivity in nonclinical individuals. We hypothesized that VRE would alter functional brain connectivity and that these changes would correlate with anxiolysis over 4 weeks of treatment, VRE significantly improved anxiety and other various psychiatric symptoms, but these effects were not significantly greater than the placebo effect. Regarding coherence, which reflects brain connectivity, the VRE group exhibited significantly greater alpha coherence increases than the placebo group did across four electrode pairs covering frontal brain regions. The increases across all four pairs were significantly correlated with anxiolysis. Lastly, the VRE group exhibited significantly greater theta coherence decreases than the placebo group did. We regard these findings as confirming our initial hypothesis.

A meta-analytic review of previous randomized, placebo-controlled trials of valerian found unconvincing evidence of efficacy (Miyasaka, Atallah, & Soares, 2006), though higher valerian doses might produce greater effects. Previous studies with valerian extracts used dosages in the range of 400 to 900 mg/day (Stevinson & Ernst, 2000). We chose a 300-mg/day extract dose for this study because all of our participants were short, nonclinical, Asian patients. Hence, the similar responses to VRE and placebo treatment could be partly explained by the relatively small valerian dose. Second, intervention-independent influences might have had an impact on anxiety measures as we observed a decrease in both groups. The Sewol ferry disasters that happened on April 16, 2014, severely shocked Korean society and induced negative emotional reaction of the general population (Woo, Cho, Shim, Lee, & Song, 2015). The gradual attenuation has been showed over the course of a few months in stress reactions among members of the general population who indirectly exposed to the traumatic event through media reports (Neria & Sullivan, 2011; Perlman et al., 2011). This changes in the public mood might have influenced the results, as all assessments took place after May 1, 2014. Recent studies have suggested that valerian is less promising as a sleep aid than earlier studies suggested (Leach & Page, 2015), but other clinical benefits of valerian are still supported by recent randomized, placebo-controlled trials (Ahmadi et al., 2017; Hassani et al., 2015; Jenabi, Shobeiri, Hazavehei, & Roshanaei, 2017). Further studies are needed to confirm valerian's efficacy in various clinical populations and determine the optimal dose.

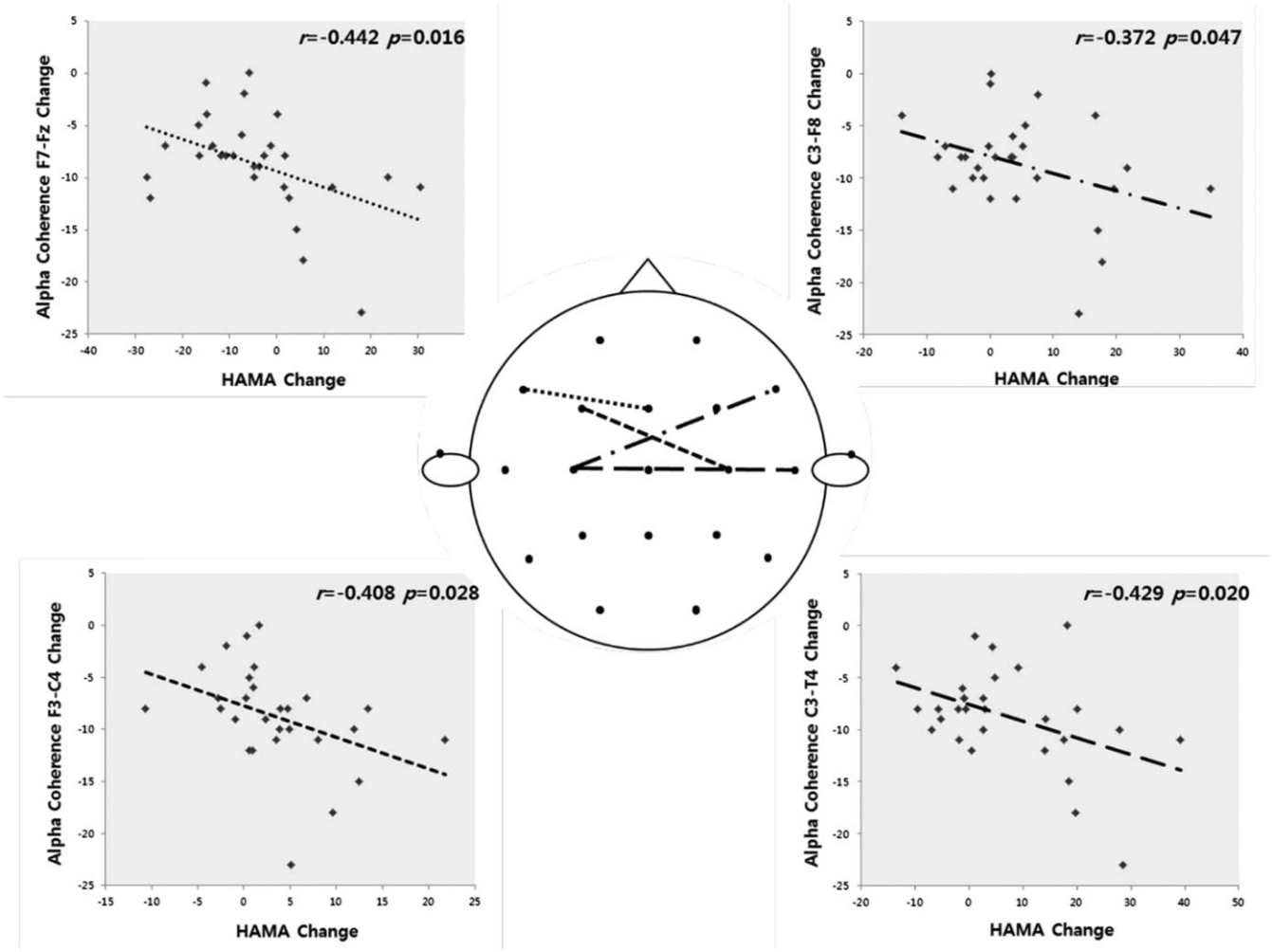

FIGURE 2 Summarized topography of alpha coherence pairs with significantly greater increases in the VRE group than in the placebo group. All such increases in the VRE group were significantly correlated with HAM-A score changes. HAM-A: Hamilton Anxiety Rating Scale; VRE: valerian root extract

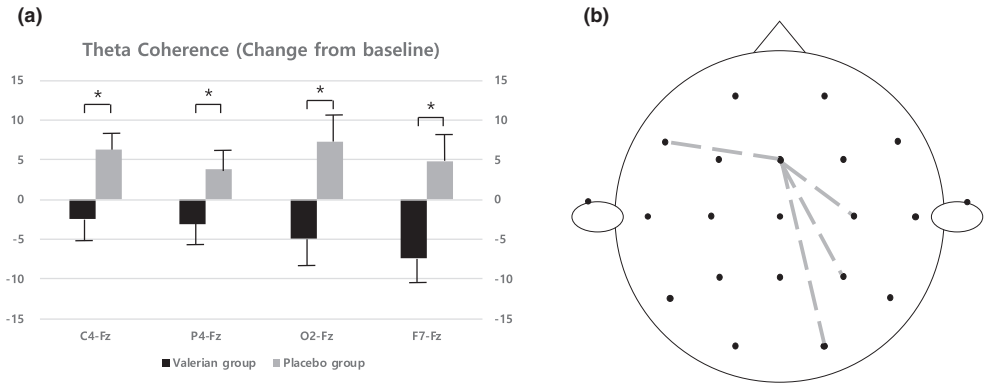

FIGURE 3 (a) Theta coherence changes in electrode pairs with significant differences between the VRE and placebo groups ($^{*}p < 0.05$; error bars indicate the standard error). (b) Summarized topography of theta coherence pairs with significantly greater decreases in the VRE group than in the placebo group. VRE: valerian root extract

Although no significant differences between the VRE and placebo groups were seen on any psychiatric scale, our neurophysiological experiments showed significant effects of VRE. Strengthened frontal EEG alpha coherence following VRE ingestion appears to be associated with anxiolysis. Alpha oscillatory activity is thought to reflect decreased cortical activity associated with states of relaxation and decreased anxiety (Boutcher, 1993). If alpha oscillators are regarded as a united "global" brain system, then stronger coherence

within this system would result in greater synchrony or connectivity between the system's different parts (Knyazev, Savostyanov, & Levin, 2005). In our findings, increased alpha coherence was prominent in frontal region of brain as shown in Figure 2. There is evidence that increased frontal EEG coherence is positively associated with neurophysiological integration (Wallace, Mills, Orme-Johnson, Dillbeck, & Jacobe, 1983), cognitive flexibility (Dillbeck & Bronson, 1981), and information processing (Petsche, Kaplan, von Stein, & Filz, 1997; Pfurtscheller & Andrew, 1999) between different parts of brain, whereas weakened EEG coherence is associated with aging (Duffy, Mcanulty, & Albert, 1996), white matter lesions (Nunez, Srinivasan, & Fields, 2015), decreased cerebral blood flow (Leuchter et al., 1997), depression (Leuchter et al., 1997), and schizophrenia (Wada et al., 1998). Intervention studies using mindfulness-based techniques have similarly reported increased frontal region alpha coherence (Ivanovski & Malhi, 2007; Murata et al., 2004). Consistent with our findings, frontal EEG coherence is reportedly inversely correlated with both state and trait anxiety (Travis & Arenander, 2006) and somatic anxiety (Lee, Yu, Chen, & Chen, 2011). The relationship between strengthened connectivity and anxiolysis implies that valerian-induced increases in cortical information exchange can relieve anxiety in stressed individuals.

In contrast to benzodiazepines, which bind the γ subunit of $GABA_A$ receptors, valerian binds the β subunit and creates hyperpolarization by facilitating chloride influx (Khom et al., 2007). This receptor modulation mediates valerian's anxiolytic effects (Benke et al., 2009). Furthermore, the alpha band synchronization of large neuronal populations during rest has been attributed to GABAergic inhibition (Fingelkurts et al., 2004). $GABA_A$ potentiating agents induce thalamic and cortical synchronization that is characterized by coherent frontal alpha oscillations (Cimenser et al., 2011). It is therefore expected that valerian will enhance coherent frontal alpha activity concurrently with its anxiolytic effect as we observed.

Despite using different methods, other studies have reported that increased theta power and connectivity is related to dysfunctions in affective disorders such as depression, obsessive–compulsive disorder, and posttraumatic stress disorder (Imperatori et al., 2014; Kopřivová et al., 2011; Leuchter, Cook, Hunter, Cai, & Horvath, 2012). Whole-brain resting-state theta-based connectivity is stronger in patients with social anxiety disorders than in healthy controls and is positively associated with state anxiety levels (Xing et al., 2017). Theta power and coherence increase when an individual engages in personal rumination (Andersen, Moore, Venables, & Corr, 2009), and increased theta coherence represents attention to negative thoughts or emotions (Xing et al., 2017). Especially, significantly decreased theta coherences were observed over medial frontal electrodes centered on Fz (Figure 3b). The anterior cingulate is the source of the frontal midline theta rhythm and with maximal amplitude near Fz (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999). Anterior cingulate cortex is involved in cognitive processing (Roh, Chang, Yoo, Shin, & Kim, 2017) and regulating the emotional state of anxiety and relaxation (Kropotov, 2016). Therefore, the VRE group's decreased theta coherence may reflect VRE's therapeutic effects related with emotional processing, although this needs to be confirmed in studies using therapeutically effective VRE doses.

4.1 | Limitations

Our findings should be interpreted in the context of several limitations. First, our sensor-based connectivity analyses may be hindered by volume conduction problems that caused pseudo-correlation recordings from neighboring electrodes (Stam, Nolte, & Daffertshofer, 2007). High-resolution EEG recordings combined with source localization methods could minimize this problem in future studies. Second, our small sample may have lacked the statistical power necessary to detect some modest but meaningful differences in psychological variables. Third, as mentioned above, the negative findings on psychological scales might be related to the relatively small VRE dose. Valerian's effects might be too modest to detect with multidimensional scales. Additional measures of cognitive function (Hassani et al., 2015) could help identify valerian's clinical benefits in future studies. In addition, study period might be insufficient to produce improvement in anxiety, and low dose-VRE might require extended treatment course lasting longer than 4 weeks.

5 | CONCLUSIONS

Despite the negative psychological scale findings, VRE affected alpha and theta band EEG coherence, and the alpha coherence changes were related to anxiolysis. These findings suggest that although no VRE effect could be detectable by psychological measures, neurophysiological measures might capture Valerian's beneficial effect on the brain. EEG coherence, which reflects functional brain connectivity, appears to be a promising biological index of VRE's effects. Further neurophysiological studies with various methods such as resting-state EEG or event-related potential measurements are needed to confirm valerian's benefits.

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CONFLICTS OF INTEREST

The authors have declared that there is no conflict of interest.

ORCID

Daeyoung Roh https://orcid.org/0000-0001-7242-9496

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