Enhancing Brain Connectivity and Improving Anxiety, Depression, and Sleep through Computing Technology for Mental Health with a Convenient Head-Wearing Device Equipped with Bioceramic Material

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Abstract

Background: This pilot study aimed to investigate the potential efficacy of non-invasive Bioceramic brain stimulation (BMS) in improving brain connectivity and alleviating symptoms associated with anxiety, depression, and sleep disturbances.

Objective: The study enrolled 25 healthy participants who underwent BMS and completed anxiety, depression, and sleep quality questionnaires before and after the intervention. Standard preprocessing techniques were applied to the resting-state fMRI data collected from the participants.

Methods: Functional connectivity analyses were conducted to analyze the data and examine the effects of BMS on brain connectivity.

Results: Following the administration of BMS, significant improvements were observed in anxiety, depression, and sleep quality scores among the participants. Furthermore, enhanced functional connectivity was identified within the default mode network, as well as between different brain regions associated with emotional regulation, sensory processing, and cognitive control.

Conclusions: The findings of this study provide preliminary evidence supporting the potential efficacy of BMS as a non-invasive technique for brain stimulation. The observed improvements in symptoms and enhanced functional connectivity suggest that BMS may hold promise for the treatment of neurological and emotional disorders. Clinical Trial: The study was conducted at the Taoyuan General Hospital in Taiwan, and the research protocol involving human subjects was approved by the Medical Ethics and Institutional Review Board of the Taoyuan General Hospital, Ministry of Health and Welfare, Taiwan (Approval No.: TYGH106015).

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Original Manuscript

Enhancing Brain Connectivity and Improving Anxiety, Depression, and Sleep through Computing Technology for Mental Health with a Convenient Head-Wearing Device Equipped with Bioceramic Material

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Abstract

This pilot study aimed to investigate the potential efficacy of non-invasive Bioceramic brain stimulation (BMS) in improving brain connectivity and alleviating symptoms associated with anxiety, depression, and sleep disturbances.

The study enrolled 25 healthy participants who underwent BMS and completed anxiety, depression, and sleep quality questionnaires before and after the intervention. Standard preprocessing techniques were applied to the resting-state fMRI data collected from the participants.

Functional connectivity analyses were conducted to analyze the data and examine the effects of BMS on brain connectivity.

Following the administration of BMS, significant improvements were observed in anxiety, depression, and sleep quality scores among the participants. Furthermore, enhanced functional

connectivity was identified within the default mode network, as well as between different brain regions associated with emotional regulation, sensory processing, and cognitive control.

The findings of this study provide preliminary evidence supporting the potential efficacy of BMS as a non-invasive technique for brain stimulation. The observed improvements in symptoms and enhanced functional connectivity suggest that BMS may hold promise for the treatment of neurological and emotional disorders.

Key Words: Bioceramic Material; Brain Stimulation; Brain Connectivity; Anxiety; Depression; Sleep Quality;

Introduction

The human brain is a remarkably intricate and sophisticated organ, governing our thoughts, emotions, behaviors, and bodily functions. Neuroscience research has long been dedicated to unraveling its complexities, resulting in substantial advancements in understanding its structure and function. Despite this progress, many neurological and psychiatric disorders remain poorly comprehended and pose significant challenges for effective treatment. Psychiatric disorders, such as anxiety, depression, and sleep disturbances, are pervasive worldwide and have substantial consequences for individuals' well-being and productivity. Traditional treatment approaches often involve pharmacotherapy, including the use of antidepressants and anxiolytics. However, these medications can have associated side effects and potential dependency concerns. Consequently, non-pharmacological interventions have gained attention as potential alternatives for managing psychiatric disorders. The techniques of non-invasive brain stimulation have emerged as promising interventions for improving brain function and alleviating symptoms across various psychiatric disorders. Approaches like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown encouraging results in the treatment of conditions such as depression, anxiety, and chronic pain. However, these techniques come with limitations, including potential side effects and the need for trained personnel to administer the stimulation.

In light of these considerations, the present study explores the potential of Bioceramic material stimulation (BMS) [1-11] as a non-invasive brain stimulation technique for enhancing brain connectivity and alleviating symptoms associated with anxiety, depression, and sleep disturbances. By investigating the effects of BMS on these conditions, we aim to contribute to the growing body of knowledge surrounding non-pharmacological interventions and their potential role in the treatment of neurological and psychiatric disorders.

Material and Methods

Bioceramic material and Brain stimulation by BMS

The utilization of Bioceramic material stimulation (BMS) in this investigation integrated cutting-edge technologies from the field of affective computing base on our previous studies[10-11]. The Bioceramic material used in this study came from the Bioenergy Laboratory in Taoyuan, Taiwan. It was made up of tiny particles from different types of elemental oxides [1-11]. This material could respond to both sound waves and visible light. Through the amalgamation of Bioceramic material powder with silicone rubber, a pliable, sound-transmitting membrane was synthesized. Two distinct modalities of BMS were employed for varied objectives in the study. For subjective assessment via questionnaires, participants donned a headset facilitating frontal-temporal contact, interfacing with a Bioceramic silicon rubber sheet(figure 1). Enhanced stimulation was achieved through integration with a tempo sound system, operating within frequencies of 1 to 12 Hz[12] and emitting sound at approximately 50 dB [13]. This setup enabled the nuanced evaluation of subjective experiences and symptomatology alterations. Conversely, during fMRI analysis, participants were positioned within the MRI scanner [14], with Bioceramic silicon rubber sheets placed bilaterally on their frontal-temporal scalp regions (figure 2). Stimulation intensity was further heightened by the acoustic noise generated by the pulse sequence, reaching sound levels nearing 90 dB. This configuration facilitated the exploration of brain activity and functional connectivity alterations via functional magnetic resonance imaging. All procedures and protocols strictly adhered to established guidelines and regulations, ensuring the safety and ethical integrity of the study participants. It is pertinent to underscore that while this study delved into the effects of BMS utilizing Bioceramic material stimulation, further investigations are imperative to elucidate the precise mechanisms underpinning its therapeutic efficacy and validate its effectiveness across larger and more diverse populations.

Subjects

For participant recruitment, the study utilized poster advertisements placed on bulletin boards near waiting rooms in Taoyuan Hospital. Potential participants were screened to ensure they did not have any neurological/psychiatric disorders, indications of drug abuse, or sleep deprivation. The study was conducted at the Taoyuan General Hospital in Taiwan, and the research protocol involving human subjects was approved by the Medical Ethics and Institutional Review Board of the Taoyuan General Hospital, Ministry of Health and Welfare, Taiwan (Approval No.: TYGH106015). Prior to participating in the study, all participants provided their informed consent by signing consent forms. A maximum of 25 participants were recruited for the study, although some may have been withdrawn at different stages. The participants completed the Becker's Anxiety questionnaire, Hamilton's Depression questionnaire, and the Pittsburgh Sleep Quality Index (PSQI) both at baseline and after undergoing BMS. The questionnaires were administered by trained researchers who ensured standardized administration and data collection procedures.

Resting-state functional magnetic resonance imaging (fMRI) data were collected and preprocessed using standard methods. The specific preprocessing steps may include motion correction, spatial normalization, smoothing, and removal of noise sources. Functional connectivity analyses, such as the calculation of regional pairwise correlation coefficients (RPCC), were performed to examine the patterns of functional connectivity between different brain regions. These analyses provide insights into the interactions and communication between brain regions during rest. By combining self-report questionnaires and fMRI data analysis, the study aimed to assess the effects of BMS on anxiety symptoms, depression symptoms, and sleep quality, as well as to investigate changes in functional connectivity within the brain.

Data acquisition and preprocessing of resting state-fMRI study and analysis for functional connectivity

Our study followed a methodology inspired by a previous investigation on resting-state fMRI [15]. The protocol encompassed three primary steps: (1) MRI data acquisition and preprocessing, (2) network construction and functional module parcellation graph construction, and (3) assessment of functional connectivity variations with and without Bioceramic material stimulation (BMS). For MRI data acquisition, we utilized a 1.5T Philips MRI/MRS system equipped with a 20-channel array head coil. The resting-state fMRI data were collected during this phase. Subsequently, we employed SPM12 and REST software packages for data preprocessing. To analyze the fMRI activity, we performed regional pairwise correlation coefficient (RPCC) analysis between regions of interest (ROIs) that were selected based on the Automated Anatomical Labeling (AAL) map template [16-17]. All data analysis and presentation of results were conducted using MATLAB, ensuring a comprehensive assessment of the effects of BMS on functional connectivity during resting-state fMRI.

Clinical evaluation and brain functional change by BMS

To evaluate the relationship between clinical evaluation and brain functional change by BMS, we conducted a literature search using PUBMED. The search included publications containing the keywords "anxiety," "depression," and "sleep" to match the concept of ‘brain stimulation’ and the brain locations of functional connectivity identified in our study. We specifically focused on reports published in English and reviewed the abstracts and then full-test to gather information.

Data Analysis:

In this study, the participants were administered three questionnaires: the Becker's Anxiety questionnaire, Hamilton's Depression questionnaire, and the Pittsburgh Sleep Quality Index (PSQI). These questionnaires were administered both before and after the Bioceramic material stimulation (BMS) study. To analyze the collected data, we utilized Statistix 8.0 (Analytical Software, Tallahassee, Florida, USA). Descriptive statistics were employed to provide an overview of the data, including mean values and a 95% confidence interval with a 5% error range. To determine if there were significant differences in the mean values of the questionnaire scores before and after the study, we conducted paired t-tests. The paired t-test allowed us to compare the pre-test and post-test scores for each questionnaire. Significance levels were indicated as follows: $p \leq 0.05$*; $p \leq 0.01$**; and $p \leq 0.001$***.

Results

The results of the self-report questionnaires demonstrated significant improvements in anxiety symptoms, depression symptoms, and sleep quality following Bioceramic material stimulation (BMS), with statistical significance indicated as $p<0.05$ (Table 1). The Becker's Anxiety questionnaire revealed improvements in various symptoms, including the inability to relax, fear of the worst happening, heart pounding/racing, nervousness, trembling hands, difficulty breathing, indigestion, suicidal ideation, psychic anxiety, and somatic anxiety symptoms. Hamilton's Depression questionnaire demonstrated improvements in symptoms such as feelings of guilt, dizziness or light-headedness, fear of losing control, and difficulty with work and activities (Table 2). The Pittsburgh Sleep Quality questionnaire indicated improvements in items such as difficulty falling asleep, feeling too cold, experiencing pain, overall sleep quality, and daytime sleepiness (Table 3).

In addition to the questionnaire analysis, the resting-state fMRI data were analyzed using the regional pairwise correlation coefficients (RPCC) method to investigate the variation in brain connectivity networks between the absence and presence of BMS in the 18 participants. A threshold value of '$p<0.001$' was set, revealing enhanced connections between the parahippocampal gyrus and cerebellar lobule V, as well as between the angular gyrus and precuneus. Conversely, a decreased connection was observed between the caudate nucleus and cerebellar lobule VIIb (Table 4).

According to the literature search conducted using PUBMED to evaluate the correlation between the clinical improvements of anxiety, depression, and sleep with changes in brain functional connectivity and the concept of 'brain stimulation,' we selected relevant references for discussion (Table 5).

Discussion:

Brain Connectivity Networks

The findings from our study indicate that Bioceramic material stimulation has a positive effect on brain connectivity. The increased connectivity between the parahippocampal gyrus and cerebellar lobule V, as well as between the angular gyrus and precuneus, suggests that Bioceramic material stimulation may enhance the integration of sensory and cognitive information within the brain [18]. This enhanced connectivity could potentially contribute to improved cognitive processes and information processing. Furthermore, the decreased connectivity observed between the caudate nucleus and cerebellar lobule VIIb suggests that Bioceramic material stimulation may have a modulatory effect on reward processing and motor coordination [19]. This modulation could potentially impact the brain's ability to regulate reward-related behaviors and motor functions. Overall, these results suggest that Bioceramic material stimulation has the potential to positively impact brain connectivity and symptom severity related to anxiety, depression, and sleep quality. However, it is important to note that further research is necessary to fully understand the underlying mechanisms and to validate these findings.

Anxiety

Our study demonstrated a significant improvement in anxiety symptoms following Bioceramic material stimulation (BMS), as indicated by the Becker's Anxiety questionnaire. This finding aligns with previous research on non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which have shown a reduction in anxiety symptoms post-stimulation [20-21]. Moreover, our study revealed alterations in resting state functional connectivity (RSFC) in the brain after BMS. Specifically, we observed an increase in positive RSFC between the para-hippocampal gyrus and cerebellar lobule V, as well as between the angular gyrus and precuneus. The para-hippocampal gyrus is involved in emotional and spatial processing, while the angular gyrus and precuneus are associated with emotion and cognition regulation and self-referential processing, respectively [22-24]. The modulation of RSFC between these brain regions suggests that BMS may impact emotional and cognitive processes related to anxiety symptoms. Additionally, we found a significant decrease in RSFC between the caudate nucleus and cerebellar lobule VIIb. The caudate nucleus is implicated in reward processing and decision-making, while the cerebellum plays a role in cognitive and emotional processing. Altered RSFC between the caudate nucleus and other brain regions has been reported in various neuropsychiatric disorders, including anxiety disorders [25-26]. The observed changes in RSFC may contribute to the therapeutic effects of BMS on anxiety symptoms.

Depression

In our study, we examined the effects of Bioceramic material stimulation (BMS) on depression symptoms using Hamilton's Depression questionnaire. The observed increase in resting-state functional connectivity (RSFC) between the para-hippocampal gyrus and cerebellar lobule V, as well as between the angular gyrus and precuneus, aligns with previous research highlighting the importance of these brain regions in emotion regulation and self-referential processing [27-28]. BMS may enhance communication and coordination between these regions, potentially contributing to its therapeutic effects on depression symptoms. However, our study also revealed a significant decrease in RSFC between the caudate nucleus and cerebellar lobule VIIb. The caudate nucleus is a part of the brain's reward system and is involved in motivation and goal-directed behavior, while the cerebellum plays a role in cognitive and emotional processing [29]. The observed decrease in RSFC between these regions suggests that BMS may modulate the connectivity within the reward and cognitive-emotional processing networks, which could be implicated in the therapeutic effects of BMS on depression symptoms. Additionally, BMS was found to improve specific symptoms of depression, such as feelings of guilt, difficulties with work and activities, fear of losing control, and feeling dizzy or lightheaded. These findings are consistent with previous research demonstrating the positive impact of non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), on depression symptoms [30-31].

Sleep

In our study, we investigated the effects of Bioceramic material stimulation (BMS) on sleep quality using the Pittsburgh Sleep Quality questionnaire and observed changes in functional connectivity within the brain. We found a positive functional connectivity between the parahippocampal gyrus and cerebellar lobule V, as well as between the angular gyrus and precuneus. These regions have been implicated in cognitive processing and memory consolidation [32-33]. The observed increase in functional connectivity suggests that BMS may enhance communication and coordination between these regions, which could potentially contribute to improved sleep quality. On the other hand, we observed a decreased functional connectivity between the caudate nucleus and cerebellar lobule VIIb. The caudate nucleus is involved in reward processing, while the cerebellum plays a role in motor coordination [34-35]. The decreased functional connectivity between these regions may indicate a shift in the balance between reward processing and motor coordination, potentially influencing sleep quality. Furthermore, our study demonstrated significant improvements in various aspects of sleep quality, including sleep latency, sleep quality, and daytime functioning, following BMS [36]. While the exact mechanisms underlying the effects of BMS on sleep quality are not fully understood, previous research suggests that similar types of stimulation can modulate neuronal activity and affect functional connectivity within the brain [37-38].

In summary, our findings suggest that BMS may impact functional connectivity in regions associated with cognitive processing, reward processing, and motor coordination, and it may have a positive effect on sleep quality. These findings have important implications for the development of non-invasive therapies for neurological and psychiatric conditions. However, further research is needed to fully understand the neural mechanisms underlying the effects of BMS on sleep quality and to validate these findings in larger and more diverse populations.

The Advantage of BMS as a Non-Invasive Therapeutic Method

One advantage of Bioceramic material stimulation (BMS) as a therapeutic method is its non-invasive nature and absence of electrical stimulation. BMS utilizes audible sound and visible light stimulation, which are considered safe and harmless to the brain. In contrast, techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) involve the use of electrical currents and are considered minor invasive treatments that carry potential risks. There has been case reports documenting certain side effects associated with TMS and tDCS. These side effects can include scalp redness, headaches, tingling sensations, and in rare cases, seizures [39-41]. Although these side effects are generally considered to be uncommon and mild, they highlight the potential risks associated with electrical brain stimulation techniques.

In comparison, BMS offers a safer and more comfortable alternative for individuals who may have concerns about the potential risks associated with TMS and tDCS. BMS does not involve the direct application of electrical currents to the brain, reducing the likelihood of adverse effects. The use of audible sound and visible light stimulation in BMS makes it a non-invasive and well-tolerated approach for brain stimulation. However, it is important to note that further research is needed to fully understand the safety and efficacy of BMS. While it appears to be a promising alternative to electrical brain stimulation techniques, larger studies and long-term follow-up assessments are necessary to evaluate its effectiveness and potential side effects in a broader population.

Conclusion

In conclusion, the results of our study indicate that Bioceramic material stimulation (BMS) has the potential to positively impact neural networks associated with cognitive processing, reward and motivation, and sensorimotor control. These effects may contribute to the improvements observed in symptoms of anxiety, depression, and sleep quality. However, it is important to note that further research is necessary to gain a deeper understanding of the underlying mechanisms and to validate these findings in larger and more diverse populations. Nonetheless, our study provides promising preliminary evidence for the potential of BMS as a non-invasive brain stimulation technique. The non-invasiveness and absence of electrical stimulation in BMS offer advantages in terms of safety and comfort compared to other techniques. The positive outcomes observed in this study support the exploration of BMS as a potential therapeutic option for individuals with neurological and psychiatric conditions. It is important to continue advancing our understanding of BMS and conducting rigorous research to establish its efficacy, optimal protocols, and long-term effects. This will pave the way for the development of safe and effective non-invasive brain stimulation interventions that can improve the lives of individuals affected by neurological and psychiatric disorders.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

TKL designed the research and performed the device processing. TKL and IWW performed the research. IWW and CHC work as clinical assistance to help data collection, statistical calculation and data analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work).

Ethics Approval and Consent to Participate

Research protocol involving human subjects was approved by the Medical Ethics and Institutional Review Board of the Taoyuan General Hospital, Ministry of Health and Welfare, Taiwan (Approval No.: TYGH106015). All participants signed a written informed consent form according to the Helsinki Declaration.

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Conflict of Interest

The authors declare no conflict of interest.

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Figures and Tables

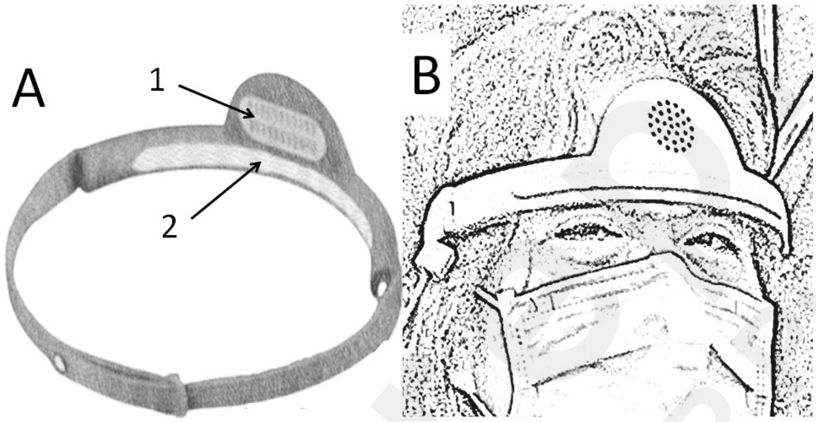

Figure 1: (A) The components of the headset device include: (1) tempo sound output ; (2) Silicon rubber sheet mixing Bioceramic material (B) A sketch drawing illustrating frontal-temporal head contact during operation.

Figure 2: The participant was positioned in the MRI scanner, and a Bioceramic silicon rubber sheet was placed on the bilateral frontal-temporal scalp regions. The stimulation was intensified by the acoustic noise generated by the pulse sequence.

Table 1. Becker’s Anxiety questionnaire

Items	Treatment	No. of People	Average	Standard deviation	Statistical significant （*P* value）
Numbness or tingling	Before	25	1.1154	0.9089	0.1749
	After	25	0.76	0.7234	
Feeling hot	Before	25	0.3077	0.6794	0.0588
	After	25	0.68	0.8021	
Wobbliness in legs	Before	25	0.2308	0.5144	0.1034
	After	25	0.04	0.2	
Unable to relax	Before	25	1.5769	0.8086	<0.0001
	After	25	0.4	0.5774	
Fear of worst Happening	Before	25	1.0385	0.9584	0.0053
	After	25	0.32	0.5568	

Dizzy or lightheaded	Before	25	1.0769	1.0168	0.0311
	After	25	0.64	0.7572	
Heart pounding/racing	Before	25	0.5385	0.8593	0.0111
	After	25	0.04	0.2	
Unsteady	Before	25	0.8077	0.8494	0.0245
	After	25	0.36	0.5686	
Terrified or afraid	Before	25	0.4615	0.706	0.0429
	After	25	0.12	0.3317	
Nervous	Before	25	1.2692	0.9616	<0.0001
	After	25	0.16	0.3742	
Feeling or choking	Before	25	0.5	0.9487	0.0317
	After	25	0.2	0.7071	
Hands trembling	Before	25	0.8462	0.7317	0.0047
	After	25	0.36	0.4899	
Shaky/unsteady	Before	25	0.2692	0.6668	0.0500
	After	25	0	0	
Fear of losing control	Before	25	0.5769	0.8086	0.0075
	After	25	0.08	0.2769	
Difficulty in breathing	Before	25	0.6154	0.9829	0.0093
	After	25	0.2	0.6455	
Fear of dying	Before	25	0.2308	0.6516	0.1344
	After	25	0	0	
Scared	Before	25	0.6154	0.9414	0.0252
	After	25	0.08	0.2769	
Indigestion	Before	25	1.4615	1.067	0.0003
	After	25	0.64	0.7	
Faint/lightheaded	Before	25	0.3846	0.7524	0.2326

	After	25	0.16	0.3742	
Face flushed	Before	25	0.2692	0.6038	0.5381
	After	25	0.2	0.5	
Hot/cold sweats	Before	25	0.0769	0.2717	0.1615
	After	25	0	0	
Total score	Before	25	14.269	8.6836	<0.0001
	After	25	5.44	3.5716	

Table 2: Hamilton’s Depression questionnaire

Items	Treatment	No. of People	Average	Standard deviation	Statistical significant (*P* value)
Depressed mood	Before	23	1.52	0.9472	0.3075
	After	23	1.25	0.794	
Feelings of guilt	Before	23	1.13	0.8689	0.0308
	After	23	0.63	0.6469	
Suicide	Before	23	0.43	0.6624	0.0047
	After	23	0.00	0	
Insomnia early in the night	Before	23	1.04	0.7674	1.0000
	After	23	1.00	0.7802	
Insomnia: middle of the night	Before	23	0.83	0.7777	0.7143
	After	23	0.75	0.7372	
Insomnia: early hours of the morning	Before	23	1.26	0.8643	0.7469
	After	23	1.25	0.847	
Work and activities	Before	23	1.13	0.6255	0.2660
	After	23	0.96	0.4643	
Retardation	Before	23	0.39	0.7223	0.0172
	After	23	0.04	0.2041	

Agitation	Before	23	0.17	0.491	0.0829
	After	23	0.04	0.2041	
Anxiety psychic	Before	23	1.09	1.0835	0.0295
	After	23	0.63	1.0135	
Anxiety Somatic	Before	23	1.48	0.7305	0.0248
	After	23	0.92	0.5836	
Somatic Symptoms - Gastrointestinal	Before	23	0.65	0.487	0.2660
	After	23	0.54	0.509	
General Somatic symptoms	Before	23	1.13	0.6255	0.0557
	After	23	0.88	0.5367	
Genital symptoms	Before	23	1.39	0.8913	0.2571
	After	23	1.25	0.847	
Hypochondriasi s	Before	23	1.04	1.2961	0.2660
	After	23	0.88	0.8502	
Loss of weight A	Before	23	0.39	0.7827	0.0557
	After	23	0.13	0.4484	
Loss of weight B	Before	23	0.09	0.417	0.3282
	After	23	0.04	0.2041	
Insight	Before	23	0.09	0.2881	0.3282
	After	23	0.13	0.4484	
Total score	Before	23	15.26	6.38	0.0004
	After	23	11.29	4.73	

Table 3: Pittsburgh Sleep Quality questionnaire

Items		Groups	No. of People	Average	Standard deviation	Statistical significant (*P* value)
The reason of not sleeping well	cannot get to sleep within 30 minutes	Con 1	20	1.75	1.118	0.0174
		Con 2	20	1.20	1.105	
	wake up in the middle of the night or early morning	Con 1	20	1.45	0.9987	0.0828
		Con 2	20	1.15	0.8127	
	have to get up to use the bathroom	Con 1	20	1.15	1.04	0.0563
		Con 2	20	0.90	0.9119	
	cannot breathe comfortably	Con 1	20	0.70	0.8013	0.2044
		Con 2	20	0.45	0.6863	
	cough or snore loudly	Con 1	20	0.70	0.6569	0.3299
		Con 2	20	0.60	0.6806	
	feel too cold	Con 1	20	0.30	0.5712	0.0421
		Con 2	20	0.10	0.3078	
	feel too hot	Con 1	20	0.30	0.7327	0.2141
		Con 2	20	0.10	0.3078	
	have bad dreams	Con 1	20	1.05	0.887	0.2967
		Con 2	20	0.85	0.7452	
	have pain	Con 1	20	0.50	0.6882	0.0421
		Con 2	20	0.30	0.6569	
	other reason(s),	Con 1	20	0.00	0	M

	please describe	Con 2	20	0.00	0	
During the past month, how would you rate your sleep quality overall?		Con 1	20	1.75	0.6387	0.0035
		Con 2	20	1.30	0.7327	

During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	Con 1	20	0.20	0.6156	M
	Con 2	20	0.20	0.6156	
During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	Con 1	20	2.25	0.9105	0.0020
	Con 2	20	1.70	0.7327	
During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	Con 1	20	1.65	0.9881	0.0047
	Con 2	20	1.30	0.8645	
Total score	Con 1	20	13.75	5.5524	0.0022
	Con 2	20	10.15	5.2942	

Table 4: Resting state-fMRI for functional connectivity analyses

Functional	Brain locations

connectivity		
Increased Connectivity	parahippocampal gyrus	cerebellar lobule V
	angular gyrus	precuneus
Decreased Connectivity	caudate nucleus	cerebellar lobule VIIb

Table 5: References for discussion base on PUBMED searching results

Clinical manifestation	Selected references for discussion were chosen under the concept of 'brain stimulation' and the brain locations of functional connectivity identified in our study
Anxiety	[20-26]
Depression	[27-31]
Sleep	[32-38]