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CASE SERIES

Coupling Bio-Resonance Neurotechnology (BRNT) and Dual Hemispheric Repetitive Transcranial Magnetic Stimulation (rTMS) Reduces Comorbid Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) as Demonstrated by PHQ-9 and GAD-7: Pilot Case Series

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Video abstract

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Abstract: Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) are prevalent comorbidities related to a greater likelihood of poor treatment outcomes and prolonged treatment for Reward Deficiency Syndrome (RDS) behaviors. The current exploratory case study of a small cohort (n=3; f=2 m=1) used novel neurotechnology to treat co-occurring MDD and GAD with a multifaceted intervention that combines the novel bio-resonance neurotechnology (BRNT) referred to as NuCalm®, to restore autonomic nervous system balance and dual hemispheric repetitive transcranial magnetic stimulation (rTMS) of the ipsilateral Dorsal Lateral Prefrontal Cortex (DLPFC) to treat the disrupted structural components of the brain. Neuroacoustic brainwave entrainment, electromagnetic frequency bio-resonance, and light-blocking combine to place patients into a parasympathetic dominant state. The paired *t*-tests indicated a significant decrease in comparing before and after the intervention. The Patient Health Questionnaire PHQ-9 scores from the first to the last time-point (mean difference = 20, t(2) = 6.55, p = 0.0226), with a 95% confidence interval of mean difference ranging from 6.86 to 33.14. Similarly, there was a significant decrease in General Anxiety Disorder GAD-7 questionnaire scores from the first to the last time point (mean difference = 18.67, t(2) = 12.85, p = 0.0060), with a 95% confidence interval of the mean difference ranging from 12.42 to 24.92. After applying the Bonferroni correction, the corrected p-values for PHQ-9 and GAD-7 are 0.0452 and 0.0120, respectively. Cohen's d standardized effect size indicated that the main effect size was 5.47 and 13.8 times the

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noise (variability), respectively, for the initial versus final PHQ-9 and GAD-7. Further, more extensive, much larger sham-controlled and blinded studies are required to confirm these encouraging results and explore this multifaceted intervention.

Keywords: reward deficiency syndrome(RDS), RDS, parasympathetic and sympathetic nervous systems, repetitive transcranial magnetic stimulation(rTMS), rTMS, novel bio-résonance neurotechnology

Introduction

According to the Centers for Disease Control, mental illness is a condition that affects feeling, thinking, mood, or behavior. Individuals with an underlying mental disorder are frequently diagnosed with anxiety, mood, substance use, sleep disturbances, and antisocial personality disorders.[1,2]

Comorbidity, the coexistence of two or more medical conditions, is determined by the factors at play, genetic and biological characteristics, and environmental (epigenetic) influences. Comorbidity is associated with poor health outcomes, more complex clinical management, and increased health costs. The United States spends 80% of Medicare funding treating patients with four or more chronic medical conditions,[3] indicating the high prevalence of comorbidity. Comorbidity is a growing area of research, given that the coexistence of two or more medical conditions can make it difficult to isolate and identify the symptomology of the conditions separately, making treating the conditions quite difficult and sometimes ineffective.[4]

Solmi et al[5] evaluated comorbidity outcomes in people with mental disorder onset before age 14, 18, 25, at peak age at onset for any mental disorder and eleven diagnostic blocks across the International Classification of Diseases. They found that, in general, across 192 studies (n = 708,561), the proportion of individuals with the onset of any mental disorders before 14, 18, and 25 years of age were 34.6%, 48.4%, 62.5%, respectively, and peak onset age was 14.5 years, for anxiety/fear-related disorders, 38.1%, 51.8%, 73.3%, respectively, with peak onset 5.5 years, obsessive-compulsive /related disorders, 24.6%, 45.1%, 64.0%, with peak onset at 14.5 years, and stress disorders, 16.9%, 27.6%, 43.1%, with peak onset at 15.5 years, and mood disorders: 2.5%, 11.5%, 34.5%, respectively, with peak onset at 20.5 years.[5]

These results imply that early intervention in comorbid mental illness may improve health outcomes and reduce costs.

The Problem of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) Comorbidity

Major depressive disorder (MDD) and Generalized Anxiety Disorder (GAD) often co-exist and share core symptoms such as negative affect. Magnetic-resonance imaging (MRI) research suggests shared neuroanatomical/neurofunctional underpinnings.[6] Recently, a Sinderman et al study indicated that transdiagnostic structural/functional modifications occur in the orbitofrontal cortex/middle frontal cortex and limbic regions (amygdala, cingulum, hippocampus) in MDD and GAD. Specifically, they reported specific functional changes in the inferior frontal gyrus, dorsolateral prefrontal cortex, and limbic systems during emotional tasks for depression.[6] Moreover, pilot studies observed specific functional changes for anxiety- during emotional tasks in the insula and frontal regions, cognitive tasks in the inferior parietal lobule, the superior temporal gyrus, and frontal gyrus, and (para)limbic changes at rest.[6] Rumination is prominent in patients with MDD and GAD and encourages the use of "mood brightening", which might be effective with people experiencing internalizing symptoms in general.[7–9] However, the results are reportedly inconsistent, possibly due to impaired neurological circuits of at least the PFC, as seen in both MDD and GAD.[10,11]

Notably, anxiety disorders are the most diagnosed psychiatric disorders, with a prevalence between 4.8% and 10.9% worldwide,[12] and are often comorbid with other psychiatric problems such as depression and insomnia.[13] While pharmacological therapy, in addition to psychosocial intervention, is well-accepted,[14] there are questions about the long-term safety and adverse side effects of various medications.[15] Contrary to some positive aspects, two published drawbacks of psychosocial intervention include failure to achieve a complete response in a significant portion of individuals afflicted with anxiety and comorbid depression[15] and a high patient dropout rate.[16] Therefore, alternative treatments are frequently sought in these patients, especially for adolescents in whom MDD often arises comorbidly with anxiety.[17]

Given the apparent connection between MDD and GAD, major depression presenting with high anxiety levels is also classified as "anxious depression".[18]

Previous studies have revealed that more than 70% of individuals who are diagnosed with depressive disorders tend to have symptoms of anxiety, and 40–70% of them meet the criteria for at least one type of anxiety disorder.[19] Depression comorbid with anxiety is often resistant to pharmacologic treatment.[20] Individuals with depression become more disabled and dysfunctional when anxiety symptoms occur.[21] Comorbid depression and anxiety are typically present in one of four clinical combinations. The exception is depression, not complicated by comorbidity. Anxiety disorders are the most common clinical risk factor for the development of depression. Significant life stressors such as interpersonal conflict, loss, or life-threatening events often lead to clinical anxiety levels. The experience of anxiety serves as a compounding stressor that facilitates further decompensation, leading to depression. The new onset of an anxiety disorder puts a patient at a significantly increased risk of developing major depression in the ensuing year.[22] Patients who suffer from comorbid depression and anxiety have higher severity of illness and chronicity and face a more significant impairment in work, psychological functioning, and quality of life when compared to those not suffering from comorbidity. Furthermore, the clinical implications of depression/anxiety comorbidity include increased risk of suicide, psychiatric hospitalization, disability, decreased compliance, and increased medical service use.[21]

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive Transcranial magnetic stimulation (rTMS) is pulsed magnetic field therapy using a rapidly changing magnetic field to stimulate cortical neurons—the FDA-cleared TMS for treatment-resistant depression. As well as depression, rTMS has been beneficial in therapy for many neuropsychiatric conditions, including anxiety disorder,[22] acute mania, bipolar disorders, hallucinations, obsessions/compulsions, schizophrenia, catatonia, posttraumatic stress disorder,[23,24] panic, and drug and alcohol cravings.[25,26] Lefaucheur et al reviewed the evidence and published guidelines for the therapeutic use of rTMS therapy and listed specific conditions for which current evidence is sufficient or insufficient to recommend treatment.[27] The use of rTMS in depression has been an accepted treatment, with 4145 articles published as of 4-26-24 in PubMed search using the words "repetitive Transcranial Magnetic Stimulation (rTMS.) and depression."

This study employed a novel explorative paradigm using a dual hemispheric approach, which, unlike standard utilization of approved TMS site stimulation, had received little attention. Multimodal stimulation studies that combined TMS with functional MRI or EEG found that different cortical areas are "tuned" to characteristic frequencies.[28] The literature search in PUBMED (4-28-23) revealed that this dual approach had been used off-label for anxiety comorbid with depression. Exploration of dual hemispheric rTMS combined with novel neuroacoustic brainwave entrainment and electromagnetic frequency BRNT to help treat anxiety with comorbid depression seems like a desirable next step.

Neuroacoustic Brainwave Entrainment, Electromagnetic Frequency Bio-Resonance, and Light-Blocking to Treat Stress and Anxiety

Stress is of fundamental concern when dealing with all neuropsychiatric disorders, particularly comorbid GAD and MDD. Therefore, addressing stress before treatment with rTMS therapy is crucial.[23] The goal of the present study is to describe and evaluate the hypothesis that the addition of brainwave entrainment and novel electromagnetic bio-resonance neurotechnology (BRNT) (Solace Lifescience NuCalm®, Wilmington, Delaware) to rTMS therapy can move patients from a sympathetic to a parasympathetic dominant state. The restoration of the autonomic nervous system balance creates a more receptive brain by activating the vagus nerve to down-regulate sympathetic tone and decrease cortisol and norepinephrine, which may work synergistically to prolong the benefits of rTMS. Since there is a paucity of literature related to this novel BRNT, we have taken the liberty herein to describe in some detail the putative working hypothesis of how this neurotherapeutic platform may accomplish attenuation of GAD.

What is Electromagnetic Frequency Bio-Resonance?

The Bio-signal Processing Disc neuro acoustic software stress management tool originated from an understanding that non-molecular, long-distance cellular communication occurs in parallel with biochemical and neurological

mechanisms.[29] Popp et al proposed that all living things absorb light energy from the sun or consumed plants, store it in the non-coding DNA, and release it as weak, coherent biophotons.[30] Research has shown that biophoton emissions may transmit information between disconnected cells without a molecular carrier.[30,31] Biophoton emissions radiate from cells in a spatial dynamic rhythmic pattern of electromagnetic frequencies.[30] Scientists have suggested that these frequencies may travel long distances through the body's Meridian system.[29,32,33]

Traditional Chinese Medicine considers meridians to be the pathways by which Qi energy (life force),[34] flows through living beings to ensure balance and homeostasis. Evidence shows that the Meridian system involves small vesicles carrying DNA granules.[33,35,36] Referred to as Bonghan system ducts or primo-vascular systems, these transparent rod-shaped vesicles are located throughout the body within the blood vessels, lymph vessels, and connective tissues. They can carry light with high efficiency.[33,35,37] The body's electromagnetic energy flow may be read through the acupoints along the Meridian lines, where the electrical impedance is lower and biophoton emissions are higher.[38] The emergence of Bio-resonance Medicine has brought a new understanding of how biophoton emissions flow throughout the body. Bio-resonance is a term given to the phenomenon that occurs when an oscillating endogenous system (like the body) responds to a matched exogenous driving frequency with maximum signal amplitude. Although controversial, evidence suggests that bio-resonance is effective for diagnosing and correcting abnormal biological frequencies in human disease.[25,32,39,40]

The theory is that when biophoton emissions and electromagnetic frequencies of cells are incoherent, cellular communication and homeostasis are not maintained, leading to illness and disease. Delivering coherent frequencies to the body in a specific manner may restore optimal biophoton emissions so that the body can heal itself. Well-regarded tools in this field include Pulsed Electromagnetic Frequency (PEMF) therapy, which delivers high-powered energy waves to injured tissues, and varying forms of acupuncture, which involve inserting needles, applying pressure, using magnets, or delivering electricity to points along the meridian system to heal physical, mental and emotional conditions.[25] The Biosignal Processing Disc provided for this study is like a non-electric version of PEMF that acts on an acupoint of the body's meridian system.

The theory is that the disc restores the electromagnetic frequencies of the neurotransmitter L-Theanine and the inhibitory neurotransmitter GABA (Gamma-Aminobutyric Acid) and its chemical precursors, as well as those found in the GABAergic system.[41] The Chinese name Pericardium (PC 6) Meridian acupoint is Neiguan; the English translation is Inner Gate. The Pericardium 6 acupoint is located (three fingers up from the inside base of the wrist joint) where the electrical impedance is low; the disc releases the EM frequencies and stimulates the Pericardium Meridian, which is frequently used in Traditional Chinese Medicine for its sedative effect. The EM frequencies also activate autonomic nerve fibers, which, in turn, increase brain parasympathetic and vagal nerve activity. Research shows that electroacupuncture or magneto-acupuncture at PC6 can reduce heart rate variability.[42–46]

Although the mechanism of action of acupuncture is still undecided, a somatic-autonomic theory, in which somatic nerves below meridian systems interact with autonomic nerves, has been proposed.[44,45] Another theory is that biophoton emissions travel through meridian pathways and, like optical channels, transfer information to the autonomic nervous system.[33,35,37]

In addition, basic research continues into the effect of acupuncture on Substance Use Disorder. Acupuncture may inhibit extracellular dopamine in the accumbens by activating GABA (B).[41,47] This acute effect could prepare the mind for calm and relaxation. The purpose of the Biosignal Processing Disc is to stimulate the GABAergic system to reduce anxiety by initiating a stress response negative feedback loop.

What is Neuroacoustic Brainwave Entrainment?

Over the last two decades, an interest in the psychological and physiological effects of brain wave stimulation with instrumental music, mostly comprised of entrainment beats, has prompted the development of neuroacoustic brainwave entrainment. Electroencephalogram (EEG) studies have examined and categorized how musical beats affect brainwaves. Brainwave entrainment focuses on binaural beats, two tones at different frequencies presented separately to each ear that elicit the sensation of a third tone. The third tone is the Binaural beat measured in HZ, which is the difference in the frequencies between the binaural beats. The brainwave entrainment hypothesis is that external binaural beat stimulation

at specific frequencies leads to brain electrocortical activity oscillating at the same frequency, which is the basis for research about the possible effects on cognitive and affective states.[48]

Neuroacoustic Software

The novel BRNT neuro-acoustic software is designed to help the body enter parasympathetic dominance, where breathing and heart rate slow. Binaural beats can entrain brain waves and cause neurons to fire synchronously with the frequency of the beat. A binaural beat can change the brain's state and activity to help reduce anxiety.[49,50] Traditional binaural beats sometimes fail to overcome the brain's tolerance to repeated stimuli.[51] The neuroacoustic software presents varying frequencies to the brain in a non-linear and binaural fashion to create auditory-evoked potentials in the theta brainwave range (4–8Hz) to overcome this tolerance. The Theta frequency range is situated on the verge of sleep and is associated with sustained periods of deep meditation.[52,53] Light blocking eliminates visual distractions and stimulates slower brain wave formation.

Study Objective

The goal of using the novel BRNT), which combines neuroacoustic brainwave entrainment, electromagnetic frequency bio-resonance, and light-blocking, is to restore autonomic nervous system balance and move patients into a parasympathetic-dominant state, allowing users to respond better to stress.

The present case series describes the treatment of comorbid Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) with a combination of novel BRNT and dual hemispheric repetitive Transcranial Magnetic Stimulation (rTMS). This descriptive paper elucidates a novel combination of therapies used in a small pilot case series to evaluate the feasibility and the potential for clinical benefit from this unique bio-resonance therapy and rTMS configuration.

Materials and Methods

Device and Approach

Solace Lifesciences, Inc., of Wilmington, Delaware, USA, provided the BRNT and the dual hemispheric rTMS devices. The manufacturer designed the Bio-signal Processing Disc to activate the GABAergic system and stimulate the negative feedback loop of the stress response system in a biomimetic fashion. This study employed a novel explorative paradigm using a dual hemispheric approach, which, unlike standard utilization of approved TMS site stimulation, had received little attention. The literature search in PUBMED (4-28-23) revealed that this dual approach had been used off-label for anxiety comorbid with depression.[54–57]

Methodology

This retrospective study took place (12/14/2021 to 4/15/2022) following the recruitment of a convenience sample of three adults with comorbid anxiety and depression. The study was carried out in compliance with the Declaration of Helsinki. Each participant was informed about the research goal and protocol and provided written informed consent to have their de-identified data used in a research report. The initial psychiatric screening was a non-structured interview that followed the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Participants then provided written informed consent to have their de-identified data used in this research report. Each participant stated their understanding that this combination of NuCalm and rTMS was an off-label intervention (not approved by the FDA).

Prior approval for human subject research was obtained from Advarra, they offer IRB Services for Private Research Sites like Brisas Recovery and Wellness Center of Riverside (IRB #: 2019-0019-BRWC). The study title is A Novel Stress Management Tool for Patients with Substance Use and Psychiatric Disorders—a Pilot Randomized Controlled Trial of the NU Calm Device. In addition, approval from WCG, an independent ethical review company (wcgclinical.com), study number 1254094, tracking number 20190239, for A Retrospective Review of Personalized Repetitive Magnetic Stimulation (PrTMS®). The study was deferred due to the COVID-19 epidemic.

Table 1 Detailed Demographics of the Three Participants Examined in This Study

Patient	Age	Gender	Ethnicity	Primary Diagnosis	Elapsed Time Since Onset of Symptoms
1	47	Female	Caucasian	Major Depressive Disorder without Psychotic Features (Severe, Recurrent), Generalized Anxiety Disorder	20 years
2	32	Female	Caucasian	Major Depressive Disorder (Severe, Recurrent), Generalized Anxiety Disorder	13 Years
3	45	Male	Caucasian	Major Depressive Disorder (Severe, Recurrent), Generalized Anxiety Disorder, Post Traumatic Stress Disorder	15 Years

Participants selected for the study had been diagnosed by the psychiatrist using the DSM5 criterion for symptoms with both Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). The scales used to measure their scores were the Patient Health Questionnaire-9 (PHQ-9) for patients with MDD[58,59] and the Generalized Anxiety Disorder Scale (GAD-7)[60–62] (see demographics Table 1).

The exclusion criteria for this case series were that the patients did not have a prior brain injury, neurodegenerative disorder, or cancer, and they were included only if they were 18 years or older.

Procedure

The informational consultation, consent, and enrollment with the psychiatrist were followed by head mapping to mark the treatment area and determine the participants' resting motor threshold to establish the treatment intensity required for the electromagnetic coil before administration of the rTMS according to the DASH Protocol, which was cleared by the FDA in 2016.[63] The bio-signal processing disc was placed three fingers up from the inside base of the wrist joint at the Pericardium Meridian Acupoint (PC6) on the inside of the left wrist. The participants sat comfortably in a reclining chair and wore a light-blocking mask, and the neuro-acoustic brainwave entrainment software track 2.0 Relax II (ST2003_Music by Sound Tonics, written, performed, and produced by the Sound Tonics program) was played through noise-canceling Bluetooth headphones placed over the participants' ears. Each subject listened to the entire soundtrack, with the volume adjusted for comfort for 30 minutes before and during the entire administration of the rTMS DASH protocol.

Data Collection and Statistical Analysis

A trained professional administered and recorded the PHQ-9 and GAD-7 assessments before and after each treatment, and the results were compared statistically.

A paired *t*-test assessed the statistical differences between the before and after the intervention PHQ-9 and GAD-7 scores. The Bonferroni correction was applied to the p-values obtained from the *t*-test to account for multiple comparisons and to control the overall Type I error rate. Analytically based data visualization was attained via scatterplots for GAD-7 and PHQ-9 scores, depicting the distribution of individual participant scores across assessment numbers. The scatterplots were enhanced with Locally Weighted Scatterplot Smoothing (LOESS) curves to highlight the overall trends in the data. Cohens d standardized was applied and yielded a result of 5.47 and 13.8 for the initial versus final PHQ9 and GAD 7 scores, respectively, suggesting that the effect size was much larger than the "noise factor."

Data Storage and Confidentiality

The principal investigator, Dr. Keerthy Sunder, gave each subject a study ID number. This information has been stored in a locked room on a password-protected computer. Only the investigator and research staff on site had access to the file pertaining to the subject identifiers to ensure participant confidentiality. Moreover, pre-screening and experiments were run in a private room to protect the confidentiality of subjects. Some sensitive data was collected for this experiment. However, all demographics, questionnaire responses, and other data were saved to a secure Dropbox account coded by

subject IDs only. The data monitor, sponsor, data analysts, and on-site research team had access to the de-identified data saved on the Dropbox folder by invitation only. Members of the research team with access to the de-identified data were required to access it only under secure servers. No one on the research team had any access to the patient's identity. The data is held within this closed system and not shared with others.

Study Participant Reports & Results

Patient 1: (60 TMS Sessions)

A 47-year-old female patient with a 20-year history of severe recurrent MDD without Psychotic Features and GAD stated that familial situations, including ten years of her husband's multiple deployments, exacerbated her symptoms. The patient had numerous trials of medications (Paxil, Zoloft, Wellbutrin, and Xanax), and psychotherapy failed to relieve her symptoms. Due to the severity of her depression and anxiety, it took almost double the number of sessions to reduce her PHQ-9 and GAD-7 scores.

Treatment

Patient 1 started on Standard DASH protocol (Left side, 3000 Pulses, 10 pulses per second, with 120% Motor Threshold (MT)) for MDD with the following parameters:

Standard Motor Threshold (SMT) – 1.48
Stimulus Onset Asynchrony (SOA) – 34
Anterior/Posterior (A/P) – 10.4
Coil Angle: +20
Anxiety Protocol: Right side, 600 pulses, one pulse per second, 100% MT.[63]

Result

The patient presented to the program with a PHQ-9 score of 27 and a GAD-7 score of 21. After 60 TMS sessions, the patient had a PHQ-9 score of 1 and a GAD score of 0, with complete remission of her Depression and Anxiety (Figure 1 and Table 2). Due to the severity of her depression and anxiety, it took almost double the number of sessions to reduce her PHQ-9 and GAD-7 scores.

The graph shows PHQ-9 and GAD-7 scores. The first data point indicates the pretreatment value in each graph. Subsequent treatments and assessments are plotted according to the date after the onset of treatment.

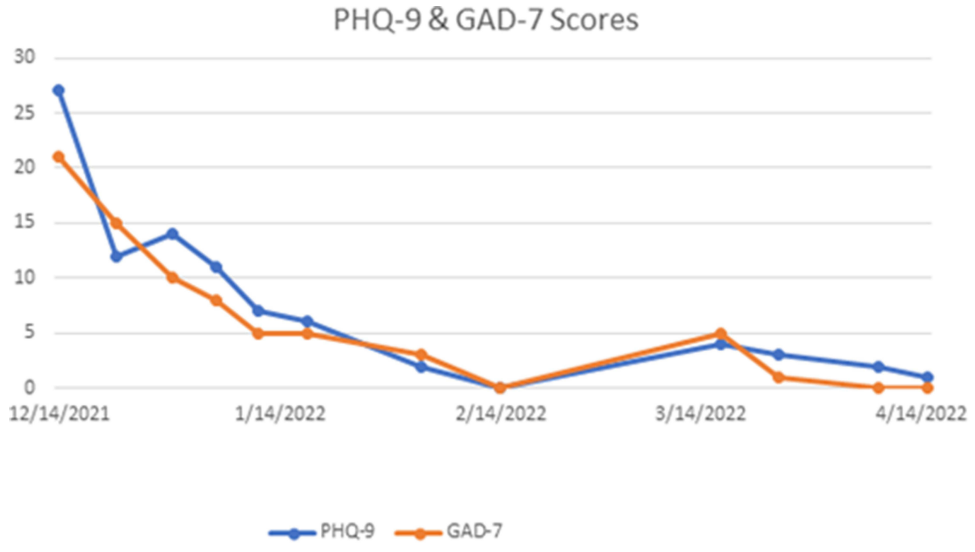

Figure 1 Neuropsychology test battery scores for patients one before and after the intervention. The graph illustrates the PHQ-9 and GAD-7 scores. The first data point indicates the pretreatment value in each graph. The second data point indicates subsequent treatments and assessments plotted according to the date after the onset of treatment.

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Table 2 Raw PHQ=9 and GAD-7 Scores for Patient 1

Date	PHQ-9	GAD-7
12/14/2021	27	21
12/22/2021	12	15
12/30/2021	14	10
1/5/2022	11	8
1/11/2022	7	5
1/18/2022	6	5
2/3/2022	2	3
2/14/2022	0	0
3/17/2022	4	5
3/25/2022	3	1
4/8/2022	2	0
4/15/2022	1	0

Patient 2: (36 TMS Sessions)

A 32-year-old patient presented with a history of severe recurrent MDD and GAD beginning in 2007 and reported that her symptoms worsened after tremendous feelings of guilt during the postpartum period. The patient also presented with low mood and anhedonia, insomnia, lack of energy, and lack of concentration. All of this contributed to her guilt regarding the care of her children. The patient had several medication trials (Sertraline, Bupropion, Citalopram, Fluoxetine, and Venlafaxine) and psychotherapy without relief from her symptoms.

Treatment

The patient started on Standard DASH protocol (Left side, 3000 Pulses, ten pulses per second, with 120% MT) for MDD with the following parameters:

S.M.T.- 1.45
SOA – 32
A/P – 12.5
Coil Angle - +15
Anxiety Protocol: On the right side, 600 pulses, one pulse per second, 100% MT.[63]

Result

The patient presented for treatment with a PHQ-9 score of 20 and a GAD-7 score of 21 (Figure 2 and Table 3). After 36 TMS sessions, the patient had a PHQ-9 score of 2 and a GAD-7 score of 2, with total remission of her Depression and Anxiety.

Patient 3: (36 TMS Sessions)

A 45-year-old male patient with symptoms of severe recurrent MDD, GAD, and Post Traumatic Stress Disorder (PTSD) stated that his symptoms started in 2007 after returning from his military deployment. The patient reported insomnia, anhedonia, feelings of guilt associated with being unable to spend time with family, and difficulty concentrating, significantly contributing to impairment in daily functioning. The Physician's Clinical List-Military (PCL-M) score

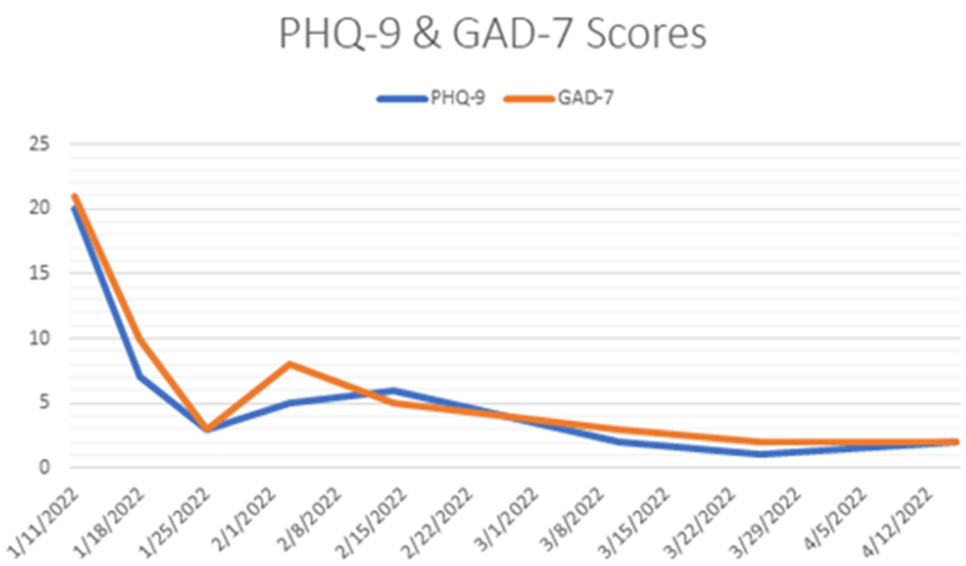

Figure 2 Neuropsychology test battery scores for patients 1–3 before and after intervention. The PHQ-9 and GAD-7 scores for patient 2 are shown in the graph. The first data point indicates the pretreatment value. Subsequent treatments and assessments are plotted according to the date after the onset of treatment.

assessed his PTSD symptoms. The patient had several medication trials (Zoloft, Cymbalta, Abilify), which did not lead to the remission of his symptoms.

Treatment

The patient started on Standard DASH protocol (Left side, 3000 Pulses, ten pulses per second, with 120% MT) for MDD with the following parameters:

S.M.T. – 0.93
SOA – 30
A/P – 8.4
Coil Angle - 0
Anxiety Protocol: On the right side, 600 pulses, one pulse per second, 100% MT.[63]

Result

The patient presented with a PHQ-9 score of 17, a GAD-7 score of 19, and a PTSD PCL-M score of 79 (out of 85). After 36 TMS sessions, the patient had a PHQ-9 score of 1, a GAD-7 score of 3, and a PTSD PCL-M score of 25 (Figure 3 and Table 4).

Table 3 Raw PHQ-9 and GAD-7 Scores for Patient 2

Dates	PHQ-9	GAD-7
1/11/2022	20	21
1/18/2022	7	10
1/25/2022	3	3
2/3/2022	5	8
2/14/2022	6	5
3/10/2022	2	3
3/25/2022	1	2
4/15/2022	2	2

https://doi.org/10.2147/PRBM.S482960

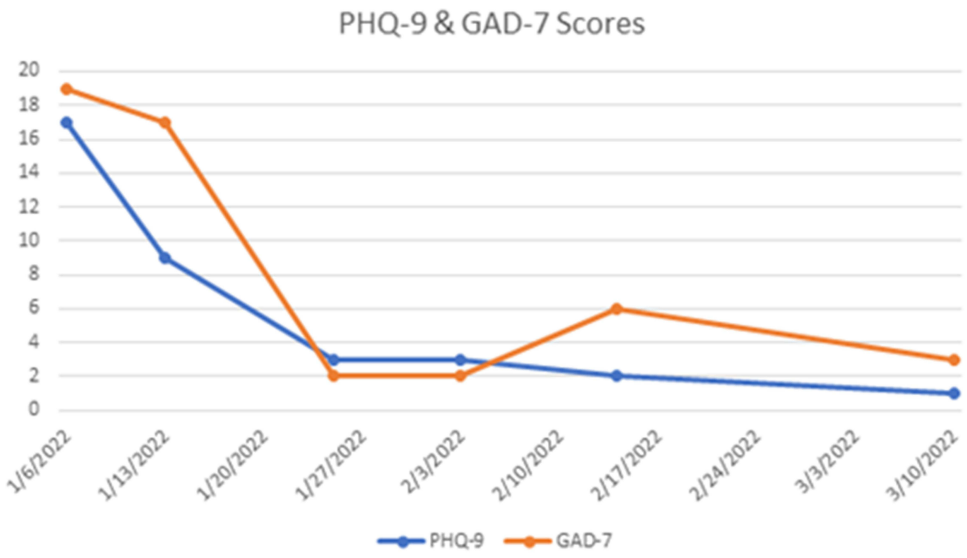

Figure 3 Neuropsychology test battery scores for patient three before and after intervention. The PHQ-9 and GAD-7 scores for patient 3 are shown in the graph. The first data point indicates the pretreatment value in each graph. Subsequent treatments and assessments are plotted according to the date after the onset of treatment.

Statistical Analysis

The paired parametric *t*-tests compared the three participants' first and last PHQ-9 and GAD-7 scores (Table 5 and Figure 4). Figures 5 and 6 show the PHQ-9 and GAD-7 scores over time with a locally smoothed scatterplot line and 95% confidence intervals. The paired *t*-tests showed that there was a significant decrease in PHQ-9 scores from the first to the last time point (mean difference = 20, t(2) = 6.55, p = 0.0226), with a 95% confidence interval of the mean difference ranging from 6.86 to 33.14. Similarly, there was a significant decrease in GAD-7 scores from the first to the last time point (mean difference = 18.67, t(2) = 12.85, p = 0.0060), with a 95% confidence interval of the mean difference ranging from 12.42 to 24.92. After applying the Bonferroni correction, the corrected p-values for PHQ-9 and GAD-7 are

Table 4 Raw PHQ-9 and GAD-7 Scores for Patient 3

Dates	PHQ-9	GAD-7
1/6/2022	17	19
1/13/2022	9	17
1/25/2022	3	2
2/3/2022	3	2
2/14/2022	2	6
3/10/2022	1	3

Table 5 Paired *T*-Test Results for PHQ-9 and GAD-7 Scores of the Participants

Test Type	t-value	Degrees of Freedom (df)	p-value	Bonferroni Corrected p-value	95% Confidence Interval	Mean Difference
PHQ-9	6.5465	2	0.023	0.045	[6.855179, 33.144821]	20
GAD-7	12.847	2	0.006	0.012	[12.41506, 24.91828]	18.66667

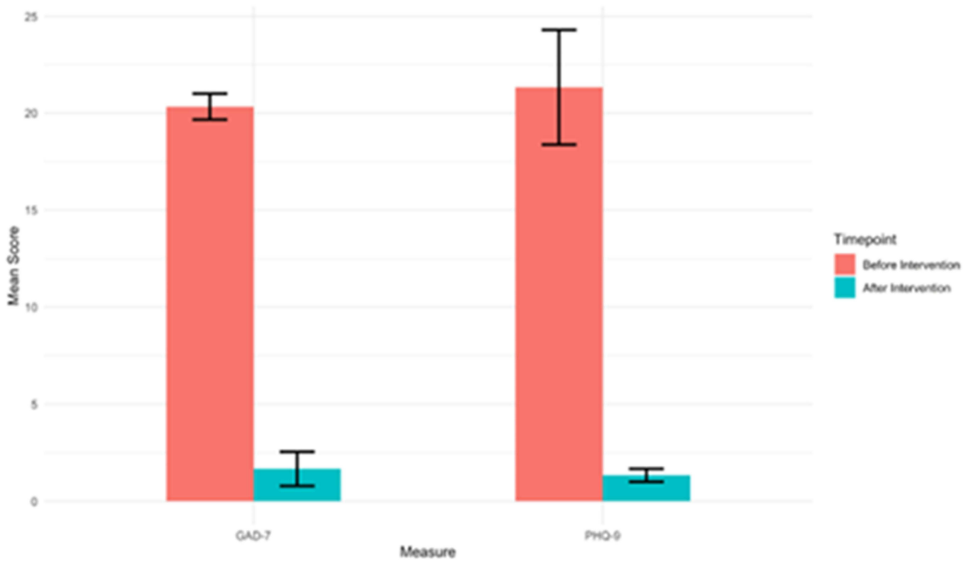

Figure 4 Grouped Bar Graph of PHQ-9 and GAD-7 Scores Before and After Intervention. This figure illustrates the aggregate data acquired for the participants. The black bars indicate the standard error of the mean (SEM).

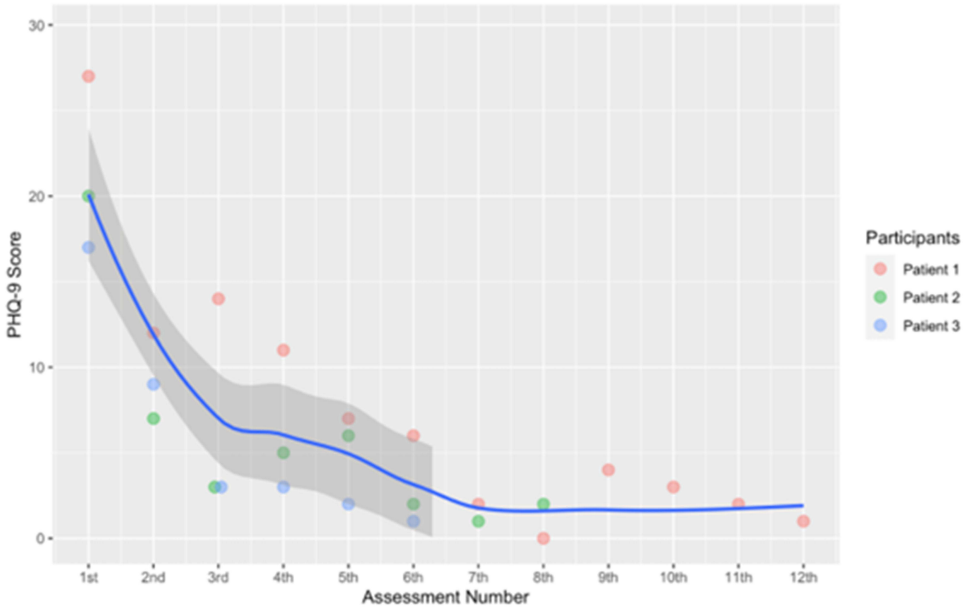

Figure 5 Scatterplot of PHQ-9 Scores. The graph shows Locally Weighted Scatterplot Smoothing (LOESS) for the Participants. The 95% confidence interval, denoted by the grey shading, ends at the sixth treatment as the number of subjects declined. A unique color represents each participant to facilitate the interpretation of the results.

0.0452 and 0.0120, respectively. These findings suggest that the participants experienced a significant reduction in their depression (PHQ-9) and anxiety (GAD-7) symptoms throughout the study.

This pilot investigation (n=3; f=2 m=1) coupled novel BRNT and dual hemispheric repetitive (r) transcranial magnetic stimulation (rTMS). Interestingly, a significant attenuation of both ongoing depression and anxiety utilizing pre- and post-PHQ −9 ($P< 0.023$) and GAD −7 scores ($P< 0.006$) occurred. Surprisingly, using the Bonferroni correction, the corrected p-values for PHQ-9 and GAD-7 are 0.0452 and 0.0120, respectively. Cohen's d standardized was applied and yielded 5.47 and 13.8 for the initial versus final PHQ9 and GAD 7 scores, respectively, suggesting that the effect size was much larger than the "noise factor."

https://doi.org/10.2147/PRBM.S482960

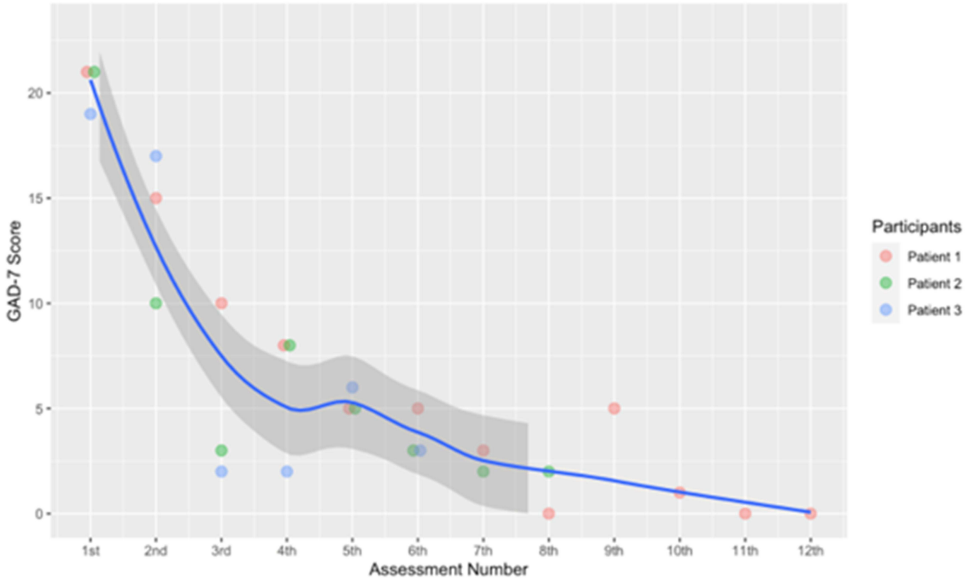

Figure 6 Scatterplot of GAD-7 Scores. The graph shows Locally Weighted Scatterplot Smoothing (LOESS) for the Participants. The 95% confidence interval, delineated by the grey shading, ends at the seventh treatment as the number of subjects declined. A unique color represented each participant in the case series to facilitate interpreting the results.

These findings suggest that the participants experienced a significant reduction in their depression (PHQ-9) and anxiety (GAD-7) symptoms throughout the study.

Discussion

Depression and anxiety are of fundamental concern for people today overwhelmed by psychosocial-economic and spiritual problems. Comorbid MDD and GAD are associated with poor treatment outcomes, prolonged resistance to treatment, and a greater likelihood of relapse to substance misuse. Reward Deficiency Syndrome (RDS)[1,64–69] felt as dissatisfaction and lack of well-being based on hypodopaminergia results in seeking behaviors that require more effective treatment options. The MDD and GAD comorbidity is more prevalent than not[57–66] and related to a greater likelihood of treatment resistance and poor outcomes.

Therefore, it is vital to identify multifaceted interventions to treat the co-occurrence of MDD and GAD, which target the neurological systems[65,69–72] and the central, Sympathetic, and Parasympathetic nervous systems.[72–74] Moreover, controlled clinical trials of ipsilateral DLPFC (Dorso-lateral prefrontal cortex) left and right hemispheric stimulation with rTMS are needed, especially in comorbid MDD and GAD patients.

While more research is required that utilizes the novel BRNT in larger studies, these positive results may be due to the downregulation of sympathetic tone and activation of the vagus nerve, thus decreasing cortisol and norepinephrine, increasing the brain's receptivity and prolonging the benefits of rTMS.

Additionally, there is indeed much support for the comorbid presence of physical symptoms caused by mental or emotional disturbance (psychosomatic disorders) with anxiety and depression.[71] Patients with mood disorders demonstrate abnormalities in the morphology of cortico-limbic areas involved in emotional responses and autonomic regulation, including the ventral medial prefrontal cortex (vmPFC), amygdala, insula, and hippocampus.[75] Until recently, this bidirectional communication between body and mind was largely overlooked. However, neuroscience research on stress and trauma tends to confirm the ancient wisdom traditions of Chinese and Ayurvedic Medicine that the body accumulates the effects of stress and trauma.[76] Therefore, the effective treatment of major depression comorbidity with anxiety may be accomplished and sustained when a bidirectional paradigm involves the simultaneous treatment of the structural components of the brain and the dysregulated autonomic nervous system.

Importantly, as far as is known, this is the first study to ever combine the novel BRNT system with dual-hemispheric rTMS in comorbid MDD and GAD patients. A PUBMED search using "TMS in comorbid MDD and GAD" as 8/13/23

resulted in three studies. None involved this combination. However, Marino et al reported on the beneficial effect of reducing anxiety using the novel BRNT system.[77] Specifically, 25 patients undergoing office dental procedures reported that preoperative anxiety (2.00/5.00) was significantly higher than postoperative anxiety (1.25/5.00) on a 5-point scale ($p = 0.005$). Based on their observation, the authors suggested that various office-based rhinological procedures are technically feasible and can be performed with adequate patient comfort using novel BRNT and without oral analgesics.[77]

The hypothesis is that personalized repetitive transcranial magnetic stimulation (PrTMS) may be a novel way to help overcome the treatment refractoriness of these unwanted comorbidities.[78] The basis of this methodology is the individual's spectral EEG characteristics and neuropathophysiological findings about MDD and GAD. Studies that involve this novel, non-addicting, well-tolerated, and potentially effective therapeutic intervention using personalized (P)rTMS and brain wave entrainment are necessary and anticipated. The interventions used in this case series accomplished and sustained a bidirectional paradigm that involves simultaneous treatment of both the structural components of the brain and the dysregulated autonomic nervous system for patients with MDD and GAD.

Limitations

The results of this exploratory study require caution due to the small number of participants. Based on this investigation, although a small cohort, with the potential for bias due to self-reporting and lack of cohort diversity.

The authors encourage the clinical and basic scientific field to recognize the importance of adding dual hemispheric stimulation, which synergistically affects both hemispheres of the brain, together with the novel adoption of the novel BRNT added 30 minutes before each session.

Simple *t*-test statistics and scatter plots revealed significant differences between pre- and post-analyses for MDD and GAD. A much larger population is required to confirm these promising results. After applying the conservative Bonferroni correction, the results have statistical significance but limited generalizability. It is also very encouraging that we found a significant effect size despite only three subjects.

Another limitation is the lack of controls and comparison groups in the study. The development of a consistent and reliable sham for control for comparison purposes will require engineering acumen. However, it could address some of the caveats noted above.

More basic research on the biophysics and neurobiology of TMS is needed to get further basic insight into its mechanisms of action. The brain's response to TMS provides a challenge for the interpretation of its (neuro)physiological and behavioral effects. Advancing TMS as a therapeutic tool requires a deeper understanding of how electromagnetic pulses stimulate brain networks from microcircuits to single cell types, link the physiological and behavioral changes, and how TMS may be tailored to individual brains.[28] Experiments designed to test the theories about the mechanisms involved in the novel BRNT device are needed. Additional large double-blind studies that test the interpretation of the results of treatment with the brainwave entrainment hypothesis,[79] and restoration of frequencies of the molecular elements in the inhibitory neurotransmitter GABA, attributed to the bio-resonance disc, are encouraged. Specific future studies that look at treatment with rTMS and the novel BRNT could incorporate genetic testing and mRNA profiling to determine objective clinical outcomes and neurotransmitter function pre- and post-treatment.[80]

Conclusion

This protocol for patients having treatment-resistant anxiety and depression comorbidities resulted in a significant reduction in GAD and MDD for the participants. This study demonstrated the feasibility and success of this treatment for this well-known comorbid (epigenetic) state and/or possibly trait (DNA) and provides a clear rationale to continue combining rTMS with BRNT.

The hope is that investigators in Bio-resonance Medicine, which incorporates novel and ancient knowledge, will welcome these exploratory findings and be inspired to perform more extensive studies to confirm these results and better understand how these therapies may alleviate the symptoms of depression and anxiety. Validation of the effectiveness of this multifaceted intervention requires more extensive studies that include sham controls, other treatment groups, more diverse cohorts to make more robust comparisons, and a personalized approach, tailoring rTMS to individual brains.

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Disclosure

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