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Case Report

Combining Mindfulness Based Cognitive Therapy (MBCT) with Brain Stimulation Using Concurrent Repetitive Transcranial Magnetic Stimulation (rTMS) and Focused Attention Meditation During the rTMS Session for Refractory Depression: A Case Report

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Abstract

Importance: Current pharmacological and psychotherapeutic treatment strategies for treatment resistant depression (TRD) are limited in effectiveness; so, new interventions are direly needed. Both transcranial magnetic stimulation (TMS) and mindfulness based cognitive therapy (MBCT) are evidence based treatments for TRD with minimal side effects. Combining MBCT with concurrent TMS therapy and focused attention meditation during the TMS session is a unique approach for TRD but hasn't been studied yet to the best of our knowledge.

Objective: To present a case report along with literature review and methodology of this novel intervention.

Methods: For literature review, we searched PubMed, PsycINFO, Web of Science, Cochrane Central, PILOTS, Google Scholar and clinicaltrials.gov from 1990 to 2017. In this combined approach used for this 68 years old White female suffering from chronic depression of more than 30 years, 5-times a week TMS sessions (total 30 sessions) and 20 MBCT sessions were applied concurrently over a 6-week period. Outcome measures included pre-, intra- and post- treatment scores on Hamilton Depression Scale (Ham-D17), Assessment Scale for Mindfulness Interventions (ASMI), and real-time EEG data during meditation practice and TMS administration. Throughout the course of this combined treatment, patient's medications (90 mg/day Duloxetine and 20 mg/day Escitalopram, Alprazolam 0.5 mg twice daily) were kept at same dose.

Results: This patient required 30 sessions of TMS (compared to the usual 36 sessions needed) and 20 sessions of MBCT for remission of her chronic depression. There was progressive decline in Ham-D scores and progressive increase in ASMI scores during the course of this treatment. Pre-treatment HAM-D scores and ASMI scores were 36 and 20 respectively, as compared to post-treatment scores of 6 and 80 respectively. Currently, at 8-months follow up, the patient's depression is still in remission (latest HAM-D17 scores are 5), her functioning has improved from baseline GAF scores of 35 to current scores of 60 and she has been able to discontinue Escitalopram and Alprazolam.

Conclusion: Although results of this novel approach needs to be confirmed in future trials, this approach suggests its feasibility as well as therapeutic utility for TRD. This multi-modal approach has the advantages of optimizing two treatment approaches during the same time course of TMS therapy. In this, patient's depression did remit with fewer number of TMS sessions, and relapse has been prevented for at least 8 months even with less number of medications. Future studies can shed further light on the possible brain mechanisms to explain these results.

Keywords: *Brain Stimulation; Refractory Depression; Meditation; Mindfulness Based Cognitive Therapy; Dorsolateral Prefrontal Cortex*

Abbreviations

TRD: Treatment Resistant Depression; MBCT: Mindfulness Based Cognitive Therapy; TMS: Transcranial Magnetic Stimulation; EEG: Electroencephalogram; HAM-D: Hamilton Depression Rating Scale; ASMI: Assessment Scale for Mindfulness Intervention

Introduction

Treatment Resistant Depression: Costs and Challenges

Depression is a highly prevalent condition that results in substantial functional impairment and leads to extensive healthcare utilization and expenses. It is the leading cause of disability in the U.S. for ages 15 to 45, affects more than 16.1 million American adults, or about 6.7% of the U.S. population age 18 and older in a given year, and its prevalence is on the rise from 2005 onwards [1]. The impact of depression is associated with an enormous personal, economic and societal burden. In the United States alone, research more than a decade back estimates the cost of depression around $83.1 billion dollars in terms of its cost of treatment, associated utilization of healthcare systems, loss of worker productivity, and cost of the associated morbidity and mortality [2,3]. Findings of more recent research are even more bothersome: total cost (direct as well as indirect) of depression for the American society is about $210 billion per year. Direct cost of depression is 98.9 billion a year, which is a hike of 27.5%, compared to that a decade ago. For every dollar spent treating depression, an additional $4.70 is spent on direct and indirect costs of related illnesses, and another $1.90 is spent on a combination of reduced workplace productivity and the economic costs associated with suicide directly linked to depression [1].

There are many patients with major depressive disorder (MDD) who, despite adequate trial of treatments, do not achieve remission; also, there are many who, despite their initial remission, relapse soon enough. Treatment Resistant Depression (TRD) is a term broadly used to denote this kind of depression in these individuals account for 12 - 20% of patients with MDD [4,5]. Patients with TRD have a substantially lower quality of life than patients with treatment responsive depression, and may represent an added societal cost of $29 - $48 billions [6]. Being a more severe illness, patients with TRD also suffer from greater functional impairments, and melancholia [7].

Repetitive transcranial magnetic stimulation (rTMS) and mindfulness based cognitive therapy (MBCT) for Depression

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and focal brain stimulation method currently being used for TRD with fair amount of efficacy [8]. Usually rTMS for depression involves administration of high frequency (activating) pulses to the left dorso-lateral pre-frontal cortex (DLPFC) [9]. A 2014 meta-analysis pooled the data of seven randomly controlled trials that investigated the efficacy of rTMS when used as an augmentative strategy along with antidepressants in TRD, and calculated a number needed to treat (NNT) of 3.4. The study also noted the minimal dropout rate and favorable side effect profile, with the most commonly reported side effect being mild headache [10]. In addition to its therapeutic effects on depression, rTMS in a recent study has been found to improve cognitive functions as well [11]. In this pilot study involving patients with TRD, in addition to improvement of depression, researchers also found an increase in the Modified Concept Shifting Task (mCST) scores, a test of strategy and attention that is used to assess higher cognitive processes involving the DLPFC [11].

Although helpful in depression, unfortunately many patients with TRD may not respond to a course of rTMS therapy and among patients who respond, many are prone to relapse. While acute antidepressant benefits of rTMS in TRD have been replicated in many studies including in an NIMH-sponsored RCT with a validated active sham technique [12], there are a very few studies on the durability of benefit following rTMS therapy: it is encouraging to see some long-term efficacy studies emerging in recent years. In a recent study by Mantovani., *et al*. a cohort of patients (N = 61) who remitted following their acute course of TMS therapy, were tapered off TMS and transitioned to maintenance medications; then they were followed up for 3 months more [13]. At 3 months, 58% patients were classified as in remission (Ham-D-24 score ≤ 10), 4% were classified as partial responders (Ham-D-24 scores reduction < 50% from baseline), 13.5% met criteria for relapse and average time to relapse was 7.2 ± 3.3 weeks [13]. In another naturalistic multisite observational study without any concurrent control population, 205 patients with TRD who received acute rTMS therapy were followed up long-term over 52 weeks [14]. In this cohort, at 52 weeks follow up, 62.5% patients continued to meet response criteria. However, many of them needed to continue their antidepressant medications and also re-introduction of rTMS therapy. Among patients who remitted, 42.1% patients relapsed and needed re-introduction of rTMS along with antidepressant medications [14]. Authors concluded that after 52-weeks, approximately two-thirds of those who were responders to treatment maintained that level of benefit under conditions of continuation pharmacotherapy with general access to TMS reintroduction as needed [14].

As described by Kabat-Zinn, mindfulness involves being aware of the present moment without judgement and can thus reduce stress while promoting balance [15]. In the past decade, there has been considerable progress and recognition of mindfulness-based therapies (MBT) that includes yoga and meditation interventions, mindfulness based stress reduction (MBSR), dialectic behavior therapy (DBT), acceptance and commitment therapy (ACT) and mindfulness based cognitive therapy (MBCT). These therapies fall under the spectrum of Complementary and Alternative Medicine (CAM), and are being more frequently used for ameliorating the distress associated with psychiatric illnesses including depression and anxiety [16,17]. Focusing on the reduction of mood and anxiety symptoms in clinical populations, a quantitative meta-analysis of 39 studies evaluated the effect of mindfulness-based therapies (MBT) [18] and found out that the MBT were most effective for reducing anxiety symptoms in patients with anxiety disorders, followed by patients with cancer, and then pain disorder. MBT was also effective in reducing depressive symptoms in patients with depression, followed by anxiety disorders, pain disorders, and then cancer [18].

MBCT is a structured and time limited therapy that integrates mindfulness meditation training with cognitive behavior therapy (CBT) and was specifically developed as a relapse prevention intervention for individuals with histories of recurrent Major Depressive Disorder (MDD) [19]. Like cognitive behavioral therapy (CBT), MBCT functions on the theory that when individuals who have historically had depression become distressed they return to automatic cognitive processes that can trigger a depressive episode. The goal of MBCT is to interrupt these automatic processes and teach the participants to focus less on reacting to incoming stimuli and instead focus more on accepting and observing them without judgment. The mindfulness practice allows the participant to notice when automatic processes are occurring and helps them to alter their reaction in reflective and non-reactive ways [20,21]. In a preliminary study without controls, Kenney and Williams found that MBCT further reduced the scores on Beck's Depression Inventory for patients who continued with depression symptoms despite having tried CBT or antidepressant medications [22]. Specifically considering depression, a study found that an MBCT course significantly decreased the time to onset of recurrence for recovered depressed patients who had at least 3 depressive episodes previously [23]. Furthermore, a 2011 meta-analysis that examined MBCT for depression found that MBCT significantly reduced the risk of relapse/recurrence [24]. However, despite these efficacy data, mindfulness-based therapies, more often than not, remain under-utilized.

Benefits of combining rTMS and MBCT

MBCT and rTMS are both promising and evolving therapies for TRD in their own right, and there are potential benefits of combining the two treatment modalities. As described earlier, rTMS has been shown to be a cost-effective treatment for TRD and has the advantage of less side effects compared to medications, electro-convulsive therapies and other treatment modalities used for TRD [25]. MBCT is an evidence-based treatment for depression, can be conveniently combined with medications or with rTMS therapy, can be practiced at home and can be incorporated into a patient's daily life, thus not only placing a small financial burden on the patient but also promotes-self-efficacy. The rTMS therapy sessions are daily sessions for 36 sessions and during which the patient is fully conscious to participate in talk therapy, cognitive behavioral therapy (CBT), or meditation practice. Thus, apart from the advantage of daily therapeutic sessions, the rTMS has the unique advantage of being combined in a rigorous way (i.e. once daily frequency) with other therapeutic modalities like MBCT within the same schedule without demanding extra-time from the patient or from the provider as described previously [20,21]. The favorable safety profile of rTMS can increase the number of patients who can undergo both modalities of treatment within the same time schedule of rTMS therapy. Most medical comorbidities (except in health conditions in which a ferro-magnetic substance is present in the head and neck region) will not exclude a patient from receiving rTMS. Of note, a select patient population like patients with cochlear implants, skull and brain implants, and implanted electrodes of the central or peripheral nervous system may not be able to undergo rTMS [26].

Recent research from neuroimaging and cognitive neuroscience has shown that meditation, in controlled studies, apart from increasing cortical blood flow and inducing functional changes, has also been shown to affect structural changes in the brain, e.g. can increase the thickness of many structures in the brain, especially the pre-frontal cortex and anterior cingulate cortex areas, right anterior insula, and right middle and superior frontal sulci corresponding approximately to Brodmann areas (BA) 9 and 10 [17,27]. Many of these effects have been found not only in long-term meditators but also in short-term meditation practice as well [28]. In another study using high resolution MRI and voxel-based morphometry analysis, it was shown that there were larger gray matter volumes in active long-term meditators in the right orbito-frontal cortex, as well as in the right thalamus and left inferior temporal gyrus. As stated by the authors "Both orbito-frontal and hippocampal regions have been implicated in emotional regulation and response control. Thus, larger volumes in these regions might account for meditators' singular abilities and habits to cultivate positive emotions, retain emotional stability, and engage in mindful behavior" [29].

Using meditative techniques during sessions of rTMS can synergistically benefit patients by targeting the areas of the brain implicated in depression while simultaneously obtaining the benefits of MBCT, potentially targeting anatomical areas correlated with emotional regulation, and thus having patients improve from both modalities in a shorter period of time. Using a concurrent augmentative strategy as done in this case report (described later), the activating frequencies (10 Hz) of rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) can work in conjunction with focused attention meditation practice during the rTMS session to concurrently stimulate the prefrontal cortex to improve attention, cognitive function and to reduce the effects of negative ruminations. This augmentation strategy also helps to keep the brain stimulation parameters (e.g. motor threshold level) low so that the common side effects like headache, increased heat under the rTMS coil, seizures (rare side effect of rTMS) which happen due to delivery of high energy are prevented. After focused attention is established, subsequent use of depression specific cognitive behavioral therapy (CBT) interventions can help to alter the dysfunctional thought patterns, negative automatic thoughts and improve mood and coping. These authors find that if a patient can be trained on these on daily basis to build the necessary meditation and CBT skills and daily home practice of meditation and CBT is established to maintain the therapeutic benefits, not only remission of depression becomes possible but also time to relapse becomes longer.

Use of real-time EEG neurofeedback (rt-EEG-nf) for customization as well as quality enhancement of rTMS and meditation interventions in TRD

Neurofeedback is a type of biofeedback that is focused specifically on brain wave activity using electroencephalogram (EEG). People who engage in neurofeedback can respond to real-time EEG information about their brain wave activity in order to produce a desired brain wave shift. Neurofeedback, since its inception around 1950's as an aid for epileptic adults, has come a long way, both in diagnostic as well as therapeutic realms. More recently neurofeedback became utilized in the conduction of research on meditation practitioners in order to better understand the brain wave changes occurring during meditation sessions. The results have been an enhanced understanding of the positive physiological effects of alpha brain waves, and the general health benefits of meditation. Gaining insight into one's brain activity in real time during a meditation session can help both in standardizing as well as personalizing the meditation in a customized manner and is possible through the process of neurofeedback. Technological advances in EEG diagnostics has enabled neurofeedback to provide information in real time that is valuable to enabling people suffering from a range of conditions to increase their alpha wave prevalence and decrease the typical beta wave level that is characteristic of wakefulness [30]. Consequently, the clinical management of such disparate disorders as childhood ADHD, sleep apnea, brain injuries, depression and PTSD may all incorporate teaching neurofeedback techniques to afflicted patients in tandem with (or instead of) medication treatments. As described later, in this case report, we incorporated the real-time EEG neurofeedback (rt-EEG-nf) using the MUSE meditation headband [30] in order to customize as well as standardize the meditation interventions during this treatment protocol using the combined rTMS and MBCT interventions.

Case Report

The patient is a 68 years old White female, college educated but unemployed since a decade due to worsening depression, and currently living alone although with good support from her 3 children and their families who live nearby in the same city. Her depression dates back to her early 30's and more recent worsening was when she was around 57 and had taken a treatment resistant course by not responding to many trials of 5 antidepressant medications at adequate dosages and durations (Fluoxetine 60 mg/day, Escitalopram 20 mg/day, Bupropion 450 mg/day, Duloxetine 90 mg/day, Mirtazapine 30 mg/day: all verified by her antidepressant treatment record (ATR) along with more than 3 years of cognitive behavioral and supportive psychotherapy. Her most recent worsening was after the death of her father (due to prostate cancer) that happened 2 years prior to her enrollment in the neuromodulation center at the Cooper University Healthcare, New Jersey. This worsening was persistent despite she being on 3 medications in adequate dose (Duloxetine 90 mg/day, Escitalopram 20 mg/day and Alprazolam 1 mg twice daily). Her presenting complaints were feeling 'empty from inside' which she described as 'dark feelings' and 'brain fog'; persistent loss of interest, avoiding social gatherings due to loss of interest and anxiety, persistent hopelessness and worthlessness, poor frustration tolerance and frequent crying spells, negative ruminations, intermittent suicidal

thoughts without any suicidal behavior, forgetfulness and poor concentration to the extent of needing to have a journal for keeping track of daily activities and doctor appointments (neuropsychological testing negative for dementia), poor sleep with delayed sleep onset and also early morning insomnia (waking up around 3am and not able to fall asleep) due to depressive ruminations, and an increased appetite with an associated 8 pounds weight gain over 6 months. Additionally, she reported generalized anxiety symptoms, irritability, muscle tension, and many somatic symptoms like headaches and intermittent constipation and diarrhea for which medical work up was negative.

There were no manic/hypomanic/psychotic features but there was early morning worsening of her depression symptoms. There was no history of substance abuse currently or in the past. Her medical history was unremarkable except hypertension that was well-controlled on Amlodipine 10 mg a day. Her family psychiatric history was significant for depression in her mother and maternal grandmother, but their treatment history was unknown to her. At our outpatient center, the patient was diagnosed with Major Depressive Disorder with co-morbid Generalized Anxiety Disorder and her basic lab work including serum TSH was unremarkable. In the past, she had 5 episodes of severe non-psychotic depression without any seasonal pattern and she had been hospitalized twice (at age 57, and at age 66) in psychiatric hospitals for suicide attempts by overdosing with medications (antihistamine and fluoxetine). The fear of post ECT cognitive deficits made her and her family reluctant to seek ECT during her most recent depressive episode and led her to choose this combined approach with rTMS therapy and MBCT instead.

She had history of partial response to thyroid (T4) augmentation when she was 58 years old but the improvements were temporary (about 6 months) and so she didn't continue it.

Methodology of Combined rTMS and Mindfulness Based Cognitive Therapy Model

At the neuromodulation center in outpatient clinic of the Cooper University Hospital, New Jersey, the patient was initially continued on Duloxetine 90 mg/day, Escitalopram 20 mg/day and Alprazolam 1 mg twice daily and the combined sessions with rTMS, meditation practice during the rTMS session and combination with MBCT sessions were applied using methodology described below. The methodology of this combined approach was adapted from a previous study by Pradhan., *et al* [20,21]. In this combined approach, 30 TMS sessions (daily sessions, 5 times a week over 6 weeks) and 20 MBCT sessions (5 skill building sessions in first week followed by every other day over next 5-weeks were applied concurrently). The TMS parameters were 5 times a week, 4 seconds stimulation/cycle with 26 second rest period, 3000 pulse trains, 10 Hz to left pre-frontal cortex applied over 45-minute duration. Immediately before starting TMS session, patient was first trained on a standardized focused attention meditation for 5 minutes and level of brain activity (calm, neutral and active; level of distraction; level of non-reactivity) was measured by real-time EEG (MUSE headband) while meditating. Then TMS session was started and patient continued the focused attention practice for first 30 minutes of the TMS session. Then MBCT interventions were incorporated during the last 10 - 15 minutes of the TMS session and focused on decreasing negative ruminations by enhancing focused attention, establishing non-reactivity to negative thoughts by establishing mindfulness and relaxation and decreasing the impact of negative automatic thoughts and cognitive distortions by generating alternatives and enhancing coping respectively. Outcome measures included Hamilton Depression Scale (Ham-D17) [31] scores for depression and Assessment Scale for Mindfulness Interventions [17] scores for level of mindfulness. The severity level of depression was measured using Ham-D17 scale that was administered at baseline and after completion of each 5 sessions of TMS until the end of the course of TMS; level of mindfulness was measured by using ASMI scale which was administered at baseline and after completion of each 10 sessions of TMS until end of the course of TMS. Throughout the course of TMS, patient's medications were kept at the same doses (Duloxetine 90 mg a day, Escitalopram 20 mg a day and Alprazolam 1 mg twice daily). Of note, prior to trying the combined rTMS and MBCT approach, her depression had not responded to these medications.

Results and Discussion

The scores on depression scale (Ham-D17) and mindfulness scale (ASMI) were serially measured and results are depicted in tables 1, 2 and also in the figures 1 to 4. The pre-treatment and post-treatment mental status examination findings have been contrasted in table 3. As demonstrated below, her pre-treatment Ham-D17 scores were 32 (very severe depression) compared to scores of 6 (remission) at session#30. Similarly, pretreatment ASMI scores (reflecting level of mindfulness) were 20 (max scores 90) as compared to post-treatment scores of 80. With the combined approach using rTMS, meditation practice and MBCT, this patient needed 30 sessions of TMS and 20

sessions of MBCT for remission of her chronic depression of more than 30 years and there was significantly enhanced level of mindfulness as measured by the ASMI scale. Of note, TMS when used alone, many times TRD doesn't remit and if remits, takes 36 sessions or more. At 8-month follow up after last session of rTMS, patient's depression is still in remission (latest Ham-D17 scores 6) and she is needing only one antidepressant (i.e. Cymbalta 90 mg a day). Her Escitalopram 20 mg/day and Alprazolam 1mg twice daily have been discontinued after a taper over 3-month period.

Session #	HAM – D17 (max. score 50)
Baseline/Pre-treatment	32
Session 5	28
Session 9	18
Session 13	15
Session 17	15
Session 21	12
Session 25	9
Session 30	6

Table 1: *HAM- D17 Rating scale for Depression (Rated every 5th session of TMS until 30th session).*

Session #	**ASMI** Scores (Max. scores 90)
Baseline/Pre-treatment	20
10th session of MBCT	30
20th session of MBCT	80

Table 2: *ASMI Rating Scale (Rated every 10th session of MBCT until 20th session).*

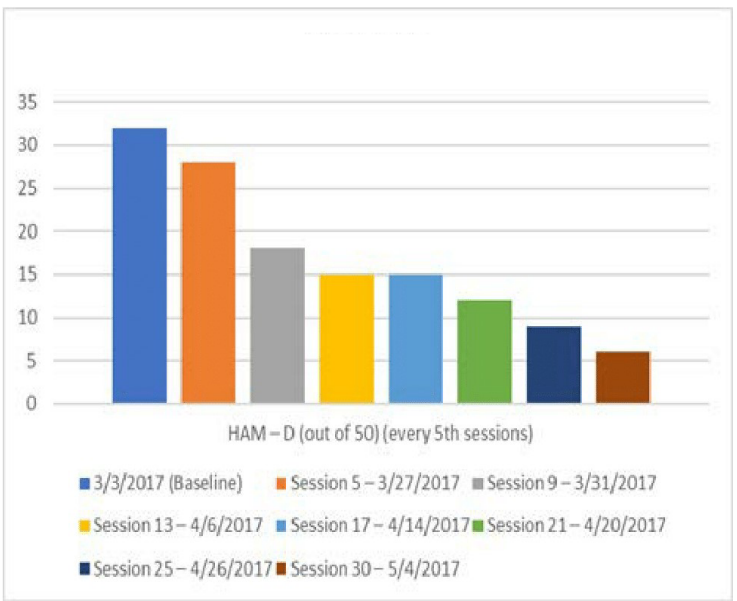

Figure 1

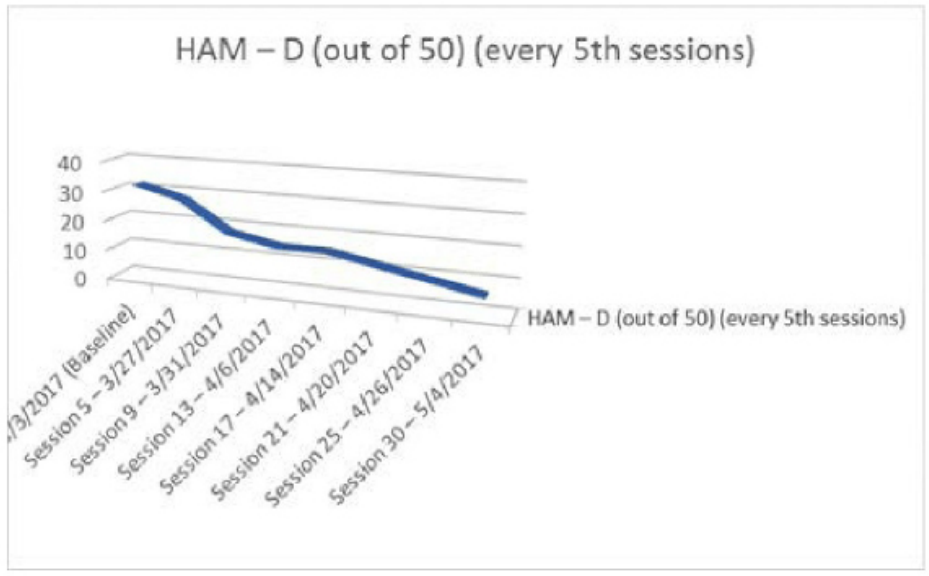

Figure 2

Figure 1 and 2: *Depicting the trend of reductions in the depression (Ham-D17 scale) scores during combined rTMS and MBCT treatment.*

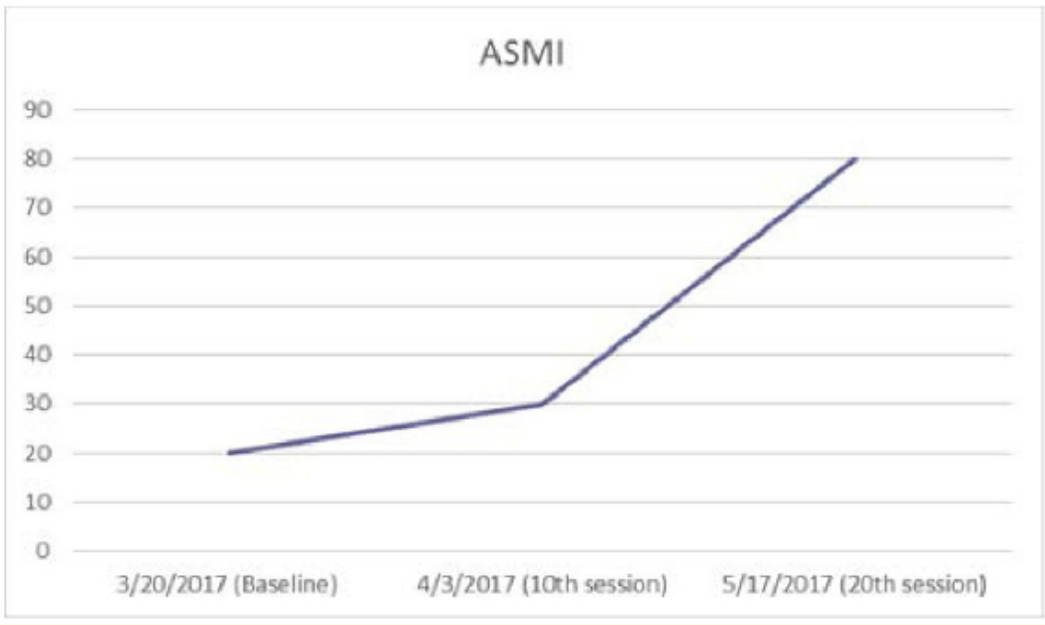

Figure 3

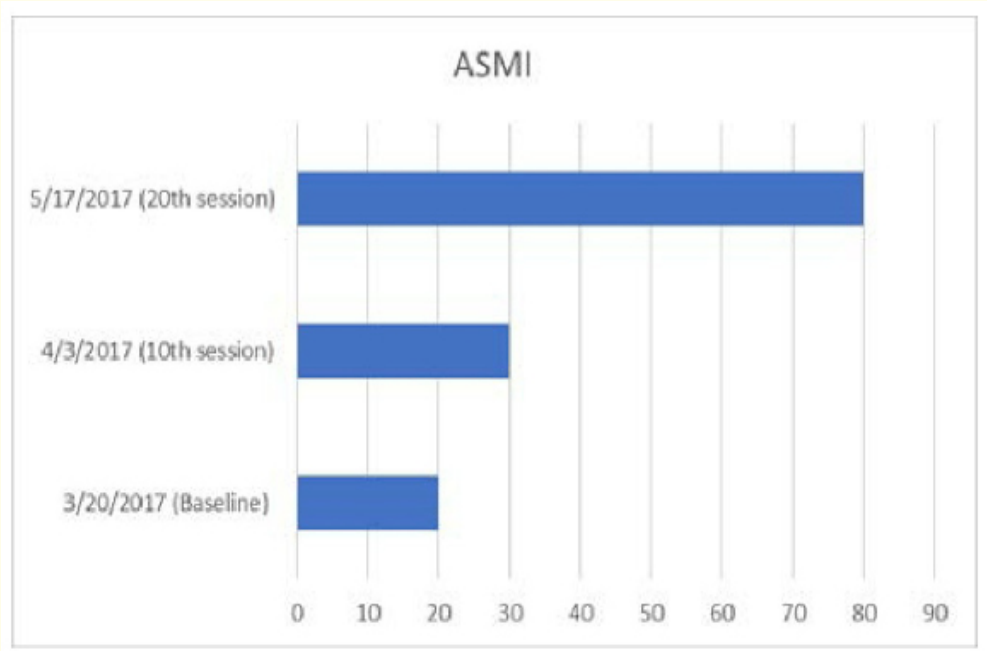

Figure 4

Figure 3 and 4: *Depicting the trend of increase in the mindfulness (ASMI scale) scores during combined rTMS and MBCT treatment.*

	Baseline -3/3/2017	At last visit – 5/5/2017
General/Appearance	68 y.o., female. Appears stated age, alert, very anxious and depressed.	68 y.o., female. Appears stated age, alert, less anxious and depressed
Attitude/Behavior	Cooperative, appears very sad with downcast gaze; tearful when talking about mother	Cooperative, much better energy, better attention as well. No longer expresses self-criticality when speaks. Not tearful when talking about mother
Mood	Depressed and 'feel so sad'	'Not depressed, not anxious as well'
Affect	Range restricted towards sadness, hopelessness	Range broad today. Still calm and feels hopeful
Thought Content	Has passive death wish but denied Suicidal or Homicidal ideas. No evidence of delusions or paranoia at this time. Significant thoughts/worries: depression and hopelessness and 'almost giving up'. Able to contract for safety at this time	Denied Suicidal or Homicidal ideas. No evidence of delusions or paranoia at this time Able to contract for safety at this time
Functioning Status	Severely impaired due to current symptoms or dysfunctions	Mildly impaired (symptoms have begun to remit)

Table 3: *Contrast between Mental Status Examinations: Pre-treatment Vs Post-treatment.*

Discussion, Conclusion and Future Directions

As seen in this case report, although this combined approach was effective, there are some challenges for patients as well as providers in implementing meditation practice and MBCT interventions during the rTMS session when patient is receiving the brain stimulation using rTMS. First of all, using both MBCT and rTMS concurrently during the session needs specialized expertise of the provider. Also, rTMS is a time intensive modality, as it requires 5 sessions a week for 30 - 36 sessions which can be quite burdensome for patients. The noise coming from the magnetic coil during rTMS administration can be distracting while patient is practicing meditation during the rTMS ses-

sion. The literature is not quite clear on a possible dose response relationship between mindfulness practice and symptomatic improvements. Studies don't find significant correlations between the amount of practice time at home and the changes experienced by patients in their physical and medical symptoms. However, findings of a study did suggest that practice time for formal meditation (body scan, yoga, sitting) was significantly related to increases in the mindfulness facets of observing and non-reactivity to inner experience, increases in psychological well-being, and decreases in interpersonal sensitivity and anxiety [16]. With ample research from neuroimaging and cognitive neuroscience, it is evident that in patients with depression, many different parts of the brain and neural circuits are affected. These include the reciprocal connections between the pre-frontal tri-circuit, amygdala, insula and thalamus [17,32]. The pre-frontal tri-circuit includes the dorsolateral prefrontal cortex (DLPFC) which regulates working memory, attention, initiation of cognitive control; the ventromedial prefrontal cortex (vmPFC) which along with the Anterior Cingulate Cortex (ACC) is known for its role in motivation, emotional regulation, decision making and via its connection with amygdala and insula regulates one's empathy. The Amygdala has a crucial role in regulation of emotions, in memory consolidation, and formation and storage of memory associated with emotional events. The insula helps in regulating sense of somatic state through its representation of bodily/visceral sensation (interoception) [33].

The rTMS at activating frequencies (i.e. 10 Hz as used in most TRD protocols) has direct stimulatory and regulatory effects of the pre-frontal tri-circuit (mostly on the DLPFC) and through this tri-circuit indirectly regulates the thalamus. Focused attention meditation stimulates the DLPFC whereas mindfulness meditation enhances activation of ACC as well as the vmPFC which has reciprocal connection with amygdala, the band-master of the emotional orchestra. Thus, both meditations when used in a balanced in combination (as done in this case study) can enhance one's attention as well awareness and reduces the reactivity to stressful events as well as to the negative ruminations, both of which are commonly seen in chronic depression. The focused attention through activation of the prefrontal cortex enhances one's breath and body awareness, and improves cognitive functions including the executive and regulatory functions whereas mindfulness meditation by decreasing one's reactivity to the stimuli in one's awareness (e.g. internal triggers like negative thoughts, hopelessness and external triggering situations in one's day to day environment, interpersonal stress etc.). This promotes calmness, enhances emotional regulation and empathy as well as promotes one's openness and acceptance to alternative possibilities, all of which are deranged in chronic depression. This also paves the way for enhancing patient's participation in the subsequent application of CBT techniques as well as coping and thus completes the implementation of the whole clinical package of MBCT for chronic depression. From neurobiological stand point, mindfulness meditation, by activating the anterior-cingulate cortex (ACC) and the ventro-medial pre-frontal cortex (vmPFC) circuits, helps to reduce activation of amygdala and improves motivation, and decreases the storage of memory associated with negative emotions and helps in formation of new memory. With enhanced insular activity, somatization tends to lessen [34].

The brief review and this case report provides a good rationale for combining the rTMS, meditation practice and MBCT interventions for patients with TRD. Because of ethical reasons and patient's preference, the patient's medications were kept at the same doses (Duloxetine 90mg a day, Escitalopram 20 mg a day and Alprazolam 1mg twice daily). Of note, prior to trying the combined rTMS and MBCT approach, her depression has not had responded to these medications. Although this needs to be confirmed in future studies, this case report suggests the feasibility as well as the therapeutic possibility of using combined novel approach using MBCT and brain stimulation by use of concurrent rTMS therapy and focused attention meditation during the rTMS session for refractory depression. As seen in this case, this approach is unique, multi-modal, optimizes the available therapeutic interventions during the same time course of rTMS therapy and helped patient's depression not only remit but also in less number of rTMS sessions and needed less number of medications. Currently we are testing efficacy of this approach in a larger cohort of 20 patients with TRD using this combied approach with rTMS and MBCT guided by real-time EEG neurofeedback (rt-EEG-nf) using the MUSE meditation headband [30]. Studies in the future can shed more light on replicability of this combined innovative approach and hopefully can clarify more on the possible brain mechanisms that may help explain these results.

Acknowledgements

None.

Conflict of Interest

None.

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