Published in final edited form as:

Brain Stimul. 2010 October ; 3(4): 207–210. doi:10.1016/j.brs.2010.03.005.

Feasibility of Simultaneous Cognitive Behavioral Therapy (CBT) and Left Prefrontal rTMS for Treatment Resistant Depression

Andrei Vedeniapin, MD¹, Laura Cheng², and Mark S. George, MD^{1,3}

¹ Department of Psychiatry and Behavioral Sciences, MUSC, Charleston, South Carolina

² College of Medicine, MUSC, Charleston, South Carolina

³ Ralph H. Johnson VA Medical Center, Charleston, SC

Keywords

rTMS; CBT; treatment resistant depression; concept of control; prefrontal cortex

Introduction

Daily left prefrontal rTMS has emerged as a potentially useful treatment for acute major depression (1-3) and is now United States FDA approved. TMS was initially developed as a treatment based on the theory that in depression the prefrontal cortex was deficient in many tasks, including governing limbic activity (4). Repeated subconvulsive stimulation of the prefrontal cortex was theorized to reset the normal cortico-limbic regulatory circuit (5). Recent animal work supports this notion. Maier and colleagues (6) have studied the neurobiological basis of learned helplessness and resilience to repeated stressors (7-8). In this model of depression or PTSD, the animal with control over a stressor does not develop learned helplessness while being shocked, while the animal without control does. Both animals receive the same stress. Thus the 'concept' of being in control prevents the animal from developing learned helplessness. In a series of recent studies, Maier and colleagues have recently shown that the 'concept of control' is actually a signal from the prefrontal cortex to the dorsal raphe nucleus (7). Lesioning this circuit makes an animal who actually has behavioral control over a stressor still develop learned helplessness. Stimulating this circuit even while not providing a control lever protects from learned helplessness (8). They thus conclude that 'the concept of control is a regulatory circuit from the prefrontal cortex to the dorsal raphe nucleus (DRN).

These animal findings suggest that cortico-limbic and cortico-brainstem regulation during exposure to stress depends on a previously learned "sense of control" and that prefrontal stimulation during acute uncontrollable stress may "mimic" that learned experience and is

Correspondence to Dr. Vedeniapin: vedeniap@musc.edu, phone 843-792-0306, Address: 519 N, IOP, MUSC, 67 President St., Charleston, SC, 29425.

Financial Disclosures: Andrei Vedeniapin reports no biomedical financial interest or potential conflict of interest.

Laura Cheng reports no biomedical financial interests or potential conflicts of interest.

Mark George is an unpaid consultant to several TMS manufacturers (Neuronetics, Brainsway, Neostim, Neosync). Neuronetics loaned the TMS equipment for a recent NIH sponsored TMS trial in depression that Dr. George chaired. The brain stimulation laboratory is conducting a depression clinical trial funded by Brainsway. Dr. George is on the executive committee and is a site PI for a Veterans Affairs funded multisite cooperative studies trial of TMS to treat depressed veterans (VA CSP #556).

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protective against developing depression and, possibly, PTSD. Interestingly, most therapeutic TMS studies have not dictated what patients should do or think about while receiving therapy, other than to not fall asleep. This glaring omission is even more concerning as there is ample evidence with TMS that plasticity in the brain in response to stimulation depends on the state of the brain or the activation of the circuit during stimulation(14). Numerous studies in single cell recordings or circuit behavior have confirmed that a circuit is more 'plastic' or able to change its firing efficiency, if the circuit is active during stimulation. Hebb's rule postulated that cells that fire together, wire together. That is, their synaptic efficiency increases over time with conjoint firing (9).

Cognitive behavioral therapy (CBT) was originally developed based on the cognitive model of depression. However, it became clear that the cognitive predisposition to depression may be related to the impact of stress on neural functioning (10). There is increasing evidence that psychotherapy (11) and CBT in particular (12) affect brain function and even brain structure (13). At the same time, the effect of CBT on the function of prefrontal areas of the brain needs further study (11). If the animal data on the 'perception of control', provided by the stimulation of prefrontal cortex are correct, TMS stimulation of the left prefrontal cortex might synergistically reinforce the activity of CBT, bringing the regulatory circuit back on line faster and with more resilience.

However, there are practical issues involved in administering CBT to a patient in the TMS chair. We wondered whether one could actually perform CBT in the TMS chair, while a patient is receiving left prefrontal rTMS for treating depression. The present report demonstrates that it is feasible to perform modified CBT during TMS of the left prefrontal area in a depressed patient.

Case Report

The patient M. was a 26 year old married college graduate student with a history of recurrent unipolar major depressive disorder without psychotic features. M. became clinically depressed the first time in her life during her first year of undergraduate college. She reported having good mood and energy level and interest in many activities before entering college. Her pre-college social history was largely unremarkable, but her family history was positive for depressive disorder. M. stated that school and personal life stressors were contributory factors to her first depressive episode. She denied use of alcohol, tobacco or any substances at that time or ever after. She was physically healthy. The first depressive episode was ameliorated by a combination of fluoxetine and counseling. Subsequent episodes of major depression, which became less related to acute stressors, also became more treatment resistant. Over a period of the last six years, SSRIs, SNRIs with lithium augmentation, bupropion and tricyclic antidepressant trials lead to minimal mood improvement, and her depression became more chronic. She was entered into a medication-free TMS treatment trial two years ago where 59 treatment sessions lead to an initially slow clinical response but later significant and lasting improvement. She relapsed a year later with a reappearance of a minor depressive episode despite continuing her medication and weekly supportive psychotherapy. This relapse was successfully treated with 14 TMS sessions as an adjunct to her medication (tranylcypromine 30 mg daily). The patient was also engaged in CBT-based therapy with a counselor at the Student Behavioral Health Center with weekly sessions over a period of one year prior to the present TMS-CBT treatment. Recognition and replacement of negative thoughts with positive ones was a dominant therapeutic intervention. She stated that psychotherapy helped her to hold her mood relatively steady between her depressive episodes, but could not prevent worsening of her depression. After her depression deepened from mild - moderate to severe, the therapy stopped working, the patient said. She also had monthly visits with a psychiatrist for medication management. Her mood was stable for about five months. Additional life and school stressors

lead to a return of depressive symptoms in emotional, cognitive, and sleep-wake domains. Her BDI scores as a function of time and treatment are depicted in Figure 1. She suffered from low mood and energy, lack of interest in activities, hypersomnolence and prominent feelings of guilt, worthlessness, and low self-esteem. She denied suicidal ideations. Her current medication was tranylcypromine 30 mg daily. The medication and the dose were not changed over a period of the last 6 months before beginning this TMS course.

Prior to beginning TMS, we educated the patient on the theory of CBT. She readily accepted the use of CBT during the TMS sessions, and was actively engaged in the therapy. We initially used her responses to the Beck Depression Inventory, completed weekly, as a template of her negative thoughts. The patient had 39 TMS sessions in total over a period of 14 weeks. During her first 8 weeks of treatment, we combined TMS and CBT approximately three times a week. 14 combined TMS-CBT sessions were provided, along with 25 sessions with TMS alone without CBT (see Figure 1). The TMS treatment employed left prefrontal cortex stimulation with rTMS trains of 120% MT, 10Hz, 5 sec on, 10 sec off, for 6000 stimuli total delivered over 30 minutes. The TMS treatment parameters were identical for all TMS treatment courses, provided to the patient. During the combined TMS - CBT sessions the patient wore an earplug only in her right ear and the therapist sat on her left, but in view of the patient. The therapist did not wear earplugs. Sentences were paused for the 5 sec on periods when the TMS was actively stimulating, but then resumed, sometimes in mid-sentence.

During the first 8 combined TMS-CBT sessions we divided each 30 minute TMS treatment session into two parts. During the first 15 minutes, we discussed the negative thoughts related to guilt, feelings of failure and self-deprecation (the areas most highly rated on her BDI). For example, the therapist asked: 'Explain to me what is behind the thoughts of yourself as a "failure"?' The patient's responses often induced tears and other negative emotions. During the second half (15 minutes) of each session, the therapist asked her to rephrase and restructure her answers and provide alternative understanding of various personal situations. For example, in response to the failure question she provided information that she overslept and did not attend classes. During the reframing she would offer the explanation that she was ill, and that despite her illness she could catch up with her missed class later. This half of the session generally resulted in improved mood with an occasional smile. The therapist frequently used the word 'control' to highlight her ability to reframe and modify her emotions.

In the second 6 TMS-CBT sessions the patient was given more control over which thoughts she would like to work on during the session. This often involved taking events from daily life that had negatively triggered emotions. Prior to starting a TMS session, she would describe what had happened, and her reaction. Then during the active TMS session, she would try to reinterpret and reprocess the events and her response in a more controlling and therapeutic manner. Sensory cues were used to more acutely remember the events. Guided imagery was used to visualize different outcomes which involved more cognitive control of her emotions. The patient reflected on the CBT during TMS as successful in relation to her ability to recognize and process her negative thoughts and thought-evoked emotions; and to actively "work" to change them.

The patient had a gradual reduction in symptoms and remitted. She required fewer overall sessions to reach remission during this TMS course compared to her first and initial TMS course of a major depressive episode treatment two years ago, although there were also differences in medication (on medication this course, medication free the first course).

After completing therapy she moved to a different state and was depression free for at least three months.

Conclusions and Discussion

We conclude that structured and guided CBT with a therapist present in the room is possible with patients while they are actually receiving prefrontal TMS. In our case it may have facilitated the speed of improvement (the total of 39 rTMS sessions instead of initial 59 rTMS sessions to treat her previous depressive episode), and tentatively suggest a synergetic effect, although this cannot be proven with a single case. If TMS works to increase cortico-limbic regulation, and if Maier's work in learned helplessness and "sense of control" as resilience factor is correct, then combined CBT and TMS might prove to be an effective treatment, and more effective than either alone. Controlled trials of these hypotheses are warranted.

Acknowledgments

Partial funding to Dr. Vedeniapiin was provided by National Institute on Drug Abuse grant R25 DA020537 (PI: Brady, KT)

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Figure 1. Beck Depression Inventory (BDI) Scores Reflect the Dynamic of the TMS-CBT Treatment
 The squares on the TMS-CBT scale represent the TMS-CBT sessions. The triangles represent the TMS only sessions. The circles on the BDI scale represent the BDI values on days when the BDI was completed.