iCBT With TMS in Patients With MDD

NCT05988619 Study protocol with SAP

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Internet-based Cognitive Behavioral Therapy in Transcranial Magnetic Stimulation

Question: Does the addition of internet-delivered Cognitive Behavior Therapy (iCBT) to TMS improve immediate and long-term symptom, functioning and cognitive outcomes

Background and Significance:
Major Depressive Disorder (MDD) is a common diagnosis, with an estimated lifetime morbid risk of approximately 30% (Kessler et al., 2012). while there are many approaches to the treatment of MDD, Current treatments of MDD frequently fail to substantially reduce depressive symptoms among those in need of care, with individual interventions leading to remission in approximately one-third of patients (Trivedi et al., 2006, Rush et al., 2006). Prior research suggests that combining cognitive-behavioral therapy (CBT) and psychopharmacology can produce optimal treatment outcomes compared to the use of either treatment individually (March et al., 2004; Pampallona et al., 2004; Cuijpers et al., 2009).

Non-invasive brain stimulation presents an exciting alternative to these interventions. Transcranial Magnetic Stimulation (TMS) is one especially promising brain stimulation approach used to treat MDD, especially among patients with treatment-resistant symptoms (Diefenbach et al., 2016; Dilkov, et al., 2017). Like psychopharmacological interventions, TMS may produce optimal treatment outcomes when paired with CBT. However, standard TMS protocols are time-intensive, typically requiring daily doctor visits for one hour of six to eight weeks. Therefore, an internet-delivered CBT protocol may augment the effects of TMS without substantially increasing patient burden. To that end, the present study will assess if a combined TMS and internet-delivered CBT protocol may produce superior treatment outcomes compared with TMS alone.

Design:
Randomization to one of two treatments; primary outcomes assessed at
(a) Baseline
(b) Post-treatment (6 weeks, or 30 TMS session)
(c) 8 months after study entrance (~6 months post treatment)
(d) 11 months after study entrance (~9 months post treatment)

Other measures are collected at baseline, mid-treatment (3 weeks, or 15 TMS session) and post-treatment.

Participants: We will enroll 40 Subjects who will be assigned to iCBT or a mental health video series with 20 enrolled in each group. The same inclusion/exclusion criteria as the TMS clinic will be employed for eligibility. This involves a minimum score of 17 on HAM-D, evidence of treatment resistance, and evaluation by a study investigator. Participants must be right-handed and between 18-70 years of age.

Inclusions: Subjects with Major Depressive Disorder who are receiving a full course of TMS treatment in at the UCLA TMS Clinic. Participants must be willing to undergo 10-Hz TMS treatment at the outset of treatment.

Exclusions: Any indications of metal implants, pregnancy, psychosis, Obsessive compulsive disorder (OCD), autism spectrum disorders, complex regional pain syndromes, substance use dependence and comorbidities that would interfere with treatment response. The criteria are assessed using MINI interview and Hamilton Depression scale conducted by trained and certified interviewers. Participants may not participate if they are currently completing CBT outside of the study.

Eligibility will be determined by TMS physicians who are co-investigators on this study.

Interventions:

RANDOMIZATION	WEEK 1-6
TMS	TMS + Mental Health Television Episode
TMS + ICBT	TMS + ICBT

TMS:
We will evaluate standard of care for TMS, which involves some flexibility but typically includes 6 weeks, five days per week, followed by a weaning from 3 to 1 times per week for the next 3 weeks.

Some flexibility is permitted due to scheduling difficulties; require a minimum of 8 sessions within any given 14 day period during the first six weeks.

Post-treatment will be standardized at 6 weeks (after 30 TMS).

Mental Health Videos or iCBT will occur weekly, according to each participant's schedule. Participants will additionally schedule one weekly coaching session to discuss the viewed material. These coaching sessions will occur via HIPAA-compliant Zoom meetings arranced through the UCLA health system.

Qualitative Electroencephalograph: QEEG will be performed at the UCLA TMS Research area. Recordings will be performed while the subjects are resting in the eye-closed, maximally alert state. Electrodes will be attached to the subjects' scalps either with individual silver chloride electrodes, paste, and nylon electrode cap or net. All of these types of electrodes are non-invasive, apply easily and quickly with little or no discomfort to the subject, and are easily removed with minimal clean up. During the recordings, subjects will either sit in a comfortable chair while the electrodes are applied. The recording will then be performed and the technicians will alert subjects if any signs of drowsiness appear. A CPz-referential montage will be used with electrodes placed according to the 10-20 system (Leuchter et al., 1992; Dunkin et al, 1995). Signals will be digitally recorded (bandpass 0.3-70 Hz) and analyzed. The EEG procedure should not take more than ninety (90) minutes; generally speaking, the actual recording takes about twenty (40) minutes. QEEG studies may be repeated up to three (3) sessions under this protocol, depending upon subject's willingness to record.

Neuropsychological testing: This testing involves completing specific tests measuring cognitive functioning, such as concentration, ability to think, and memory. In addition, subjects may be

asked about their feelings, thoughts, activities, or emotional well-being. Our neuropsychological testing battery may require up to two (2) hours of participation.

iCBT:
Existing standard program (ThisWayUp)

Once per week for weeks 1 through 6.

Plus access to iCBT at other times.

Keep track of usage.
Orientation to program by research staff at first occasion, who will also be available to answer questions (research staff at TMS clinic, who are trained by DGC team- Madison Schmidt)

The protocol for "This Way Up" utilizes the following lesson plan:

Lesson number	***Content***	***Homework exercise***
1	Psychoeducation about anxiety and depression, the fight or flight response, controlled breathing, and physical exercise	Controlled breathing, physical exercise
2	Cognitive therapy components: education about the cognitive model, cognitive distortions, and introduction to thought monitoring; activity planning	Thought monitoring, activity planning
3	Thought challenging/cognitive restructuring; challenging positive and negative metacognitive beliefs about repetitive negative thinking; shifting attention, hunt for positives	Thought challenging, hunt for positives
4	Education about avoidance and safety behaviors; graded exposure and structured problem solving	Graded exposure and structured problem solving
5	Advanced graded exposure (imaginal exposure, interoceptive exposure); troubleshooting difficulties with graded exposure	Graded exposure
6	Relapse prevention	Relapse prevention plan

Lesson content is presented in the form of an illustrated story about two fictional characters who are anxious and depressed, but who gain mastery over their problems using CBT techniques. Following each lesson, participants download a document that summarizes the key information in each lesson, and includes practical homework exercises that reinforce the content of the lesson. Participants are encouraged to practice their lesson homework for at least 2 hours in the 3-4 days before starting the next lesson.

Participants also have access to:
1) frequently asked questions about each lesson
2) "Patient Recovery Stories" from former patients, and
3) extra resources on a range of topics such as sleep hygiene, medications and panic attacks.

Once participants download their homework, they will be considered to have completed the lesson. Lessons will be completed sequentially. "This Way Up" will be hosted locally on our secure server and can be directly accessed via the website https://ucla.thiswayupclinic.com/.

The "This Way Up" program is hosted on the Semel-NPI server architecture. After being registered by a study clinician, participants log-in to access lesson content only, no identifiable e-mail other than name and e-mail are stored in the system.

Mental Health Television Episodes

The existing program, Stories of the Mind, was originally developed for the Public Broadcast Service (PBS) and affiliated broadcasts. It is freely available at http://mentalhealthchannel.tv/series/stories-of-the-mind.

Participants will view a video once per week for weeks 1 through 6. Although they have access to all videos of the program, they will be specifically instructed to view materials according to the following schedule:

Lesson number	***Episode Title***	***Episode Description***
1	Overcoming Depression	A writer, a musician and a video blogger find three surprising paths to recovery, with powerful takeaways for all viewers.
2	Beating Anxiety	Three characters in different times of their lives use different tactics to manage their anxiety, the most common type of mental health disorder for Americans.

3	Get your Sleep	Sleep deprivation affects everything, from memory to mood to decision making. In our 36-hour No Sleep Challenge, researchers track 4 participants to see just how vital sleep is to your mental health.
4	Coping with Illness	When your physical health suffers, your mental state may too. Meet three people who practice good mental health despite physical conditions.
5	A Place to Belong	Being part of a strong community is good for anyone's mental health.
6	Ways to Wellness	Five ways for every viewer to achieve optimum mental fitness, told through the personal experiences of fascinating, diverse characters.

Study Schedule:

TMS + iCBT Group	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Weeks 7-9	6 Month F/U	9 Month F/U
Consent	X									
TMS		5x	5x	5x	5x	5x	5x	1-5x per week		
iCBT Access and Coaching		1x	1x	1x	1x	1x	1x			
EEG	X			1x			1x			
Stroop	X									
HAMD	X								X	X
IDS	X								X	X
DARS	X								X	X
GAD-7	X								X	X
Sheehan	X								X	X
Pt Attitude and Expectancy Form	X									
Demographics	X									
Medical Status	X	X	X	X	X	X	X	X	X	X

TMS + Mental Health Videos	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Weeks 7-9	6 Month F/U	9 Month F/U
Consent	X									
TMS		5x	5x	5x	5x	5x	5x	1-5x per week		
Video Access and Coaching		1x	1x	1x	1x	1x	1x			
EEG	X			1x			1x			
Stroop	X									
HAMD	X								X	X
IDS	X								X	X
DARS	X								X	X
GAD-7	X								X	X
Sheehan	X								X	X
Pt Attitude and Expectancy Form	X									
Demographics	X									
Medical Status	X	X	X	X	X	X	X	X	X	X

The frequency of follow-up assessments may be modified depending on patient availability, or subject willingness to undergo more or less assessment.

Primary Dependent Measures:

The primary analyses for this study will involve multilevel modeling of longitudinal data over the course of treatment (e.g. baseline, mid-assessment, post-assessment). We hypothesize that the iCBT + TMS will demonstrate more rapid improvement in these five symptom scales compared with TMS alone.

In addition, secondary analyses will involve multilevel modeling of symptom score relapse (e.g. baseline, end of treatment, 6 months post-treatment, 9 months post-treatment). We hypothesize that iCBT + TMS will demonstrate more lasting change in these five symptom scales compared with TMS alone, such that the combined treatment reduces the likelihood of symptom relapse.

Finally, analyses will assess changes in cognitive functioning during the course of treatment, using a electroencephalography (baseline, mid-assessment) and a well-validated Stroop Task (baseline and post-treatment). Changes in cognitive functioning will be assessed with multilevel modeling in parallel to the primary analyses above as a means of exploring whether changes in cognitive functioning coincide with changes in treatment.

Symptom Scales:
HAM-D (baseline, mid, post, 6 months)
IDS (Inventory for Depression Symptomatology) (weekly from baseline to end of TMS, and at 6 month and 9 month follow-up)
DARS (Dimensional Anhedonia Rating Scale) (baseline, mid, post, 6 months, 9 months)
GAD-7 (baseline, mid, post, 6 months, 9 months)

Functioning Scale:
Sheehan Disability scale (baseline, mid, post, 6 months, 9 months)

Cognitive Functioning:
EEG (baseline, mid)
STROOP (baseline, post)

Additional Measures:
Patient Attitude and Expectancy Form
Demographics and medical status

Modified intent-to-treat analyses will be conducted using linear multilevel modeling in Stata 18.0 using the *mixed* function. All models include random effects of the intercept and fixed slopes for each participant. Group will be included as a categorical variable in all analyses. Time will be included as a continuous variable in primary analyses, with secondary analyses including Time as a categorical variable to evaluate pairwise Group comparisons. Age (continuous) and Gender (categorical) will be included in all analyses as covariates.