# On the Concurrent Use of Self-System Therapy and Functional Magnetic Resonance Imaging–Guided Transcranial Magnetic Stimulation as Treatment for Depression

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**Objectives:** Despite the growing use of repetitive transcranial magnetic stimulation (rTMS) as a treatment for unipolar depression, its typical effect sizes have been modest, and methodological and conceptual challenges remain regarding how to optimize its efficacy. Linking rTMS to a model of the neurocircuitry underlying depression and applying such a model to personalize the site of stimulation may improve the efficacy of rTMS. Recent developments in the psychology and neurobiology of self-regulation offer a conceptual framework for identifying mechanisms of action in rTMS for depression, as well as for developing guidelines for individualized rTMS treatment. We applied this framework to develop a multimodal treatment for depression by pairing self-system therapy (SST) with simultaneously administered rTMS delivered to an individually targeted region of dorsolateral prefrontal cortex identified via functional magnetic resonance imaging (fMRI).

**Methods:** In this proof-of-concept study, we examined the acceptability, feasibility, and preliminary efficacy of combining individually fMRI-targeted rTMS with SST. Using the format of a cognitive paired associative stimulation paradigm, the treatment was administered to 5 adults with unipolar depression in an open-label trial.

**Results:** The rTMS/SST combination was well tolerated, feasible, and acceptable. Preliminary evidence of efficacy also was promising. We hypothesized that both treatment modalities were targeting the same neural circuitry through cognitive paired associative stimulation, and observed changes in task-based fMRI were consistent with our model. These neural changes were directly related to improvements in depression severity.

**Conclusions:** The new combination treatment represents a promising exemplar for theory-based, individually targeted, multimodal intervention in mood disorders.

**Key Words:** cognitive paired associative stimulation, depression, neurostimulation, psychotherapy, self-regulation, self-system therapy

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Repetitive transcranial magnetic stimulation (rTMS) produces brief pulses of magnetic fields that induce electrical currents in the cerebral cortex. These currents, in turn, evoke neural activity that modulates brain networks. Applied daily over a course of weeks, this process leads to cumulative changes in the brain that can be therapeutic. A course of rTMS sessions applied to left dorsolateral prefrontal cortex (DLPFC) has been shown to improve depression in treatment-resistant adults, and this use of rTMS has been cleared by the US Food and Drug Administration (FDA) for treatment of unipolar depression in individuals who have failed to achieve satisfactory response to at least 1 antidepressant medication. However, despite its increasing use, typical effect sizes of rTMS treatment have been modest.[1] For example, the response and remission rates in the trial that led to FDA clearance were 25% and 16%, respectively.[2] In addition, a recent meta-analysis of 29 studies (1371 patients) reported similar average rates (eg, 29% average response rate) across studies.[3] These rates are relatively disappointing when compared with typical remission rates of 65% to 75% using electroconvulsive therapy,[4] although it should be acknowledged that rTMS has a more favorable adverse effect profile.

Recent advances in transcranial magnetic stimulation (TMS) targeting and network engagement have the potential to significantly enhance the efficacy of TMS treatment of depression. However, to date, only modest progress has been made to incorporate these advances into standard clinical practice. One reason for this delay is that there has been no consensus as to what specific brain circuitry should be engaged to treat depression. Furthermore, optimizing the clinical efficacy of TMS is likely to require a deeper understanding of the elements of the delivered dosage, not only in terms of spatial location and temporal dynamics, but also in terms of the context of the stimulation.[5] Context includes concomitant medications as well as cognitive-behavioral factors, such as simultaneous psychotherapy or cognitive task performance during the period of brain stimulation. Coupling brain stimulation with simultaneous targeted cognitive interventions represents a potentially fruitful and relatively unexplored avenue to boost brain plasticity and enhance the therapeutic effects of cognitive training.[6]

Enhancement of efficacy through control over the context of cortical stimulation is exemplified in the well-developed paradigm of paired-associate stimulation (PAS), in which afferent stimulation of the median nerve in the wrist is used to control the initial state of sensorimotor cortex. In the standard PAS paradigm, the afferent stimulation is precisely timed so that it arrives in cortex simultaneously with a TMS pulse applied to the same cortical site. Repeating this paired stimulation over a number of trials produces an enhanced response from that site (as measured using motor potentials evoked by test TMS stimuli) lasting well after the paired conditioning trials are completed,[7] presumably due to a Hebbian-like synaptic mechanism.[8,9] This simple but highly reliable paradigm can be generalized such that brain state is not controlled by afferent stimulation, but rather by engaging a target cortical network via a compatible cognitive task. Recently, we introduced the term "cognitive paired associative stimulation," or C-PAS, to refer to the method of controlling brain state by delivering a

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cognitive task time-locked with simultaneous targeted TMS. We demonstrated that C-PAS can produce cortical network changes and suggested the utility of extending the C-PAS paradigm to therapeutic interventions.[10]

Another critical element for the successful implementation of a context-specific brain stimulation paradigm for depression is targeting, engaging, and modifying a specific functional brain network associated with depression. One candidate network (with a node in DLPFC, the FDA-cleared target for TMS treatment) is a recently described functional network associated with self-regulation of personal goal pursuit.[11] Research in the social cognition literature has shown that when individuals fail to meet their aspirations (*ideal* self-guides) they experience dejection/dysphoria, whereas when individuals fail to meet their duties and obligations (*ought* self-guidelines), they experience agitation/ anxiety, and that chronic perceived failure to attain positive outcomes is associated with vulnerability to depression.[12] This neural circuit model draws on regulatory focus theory (RFT), which distinguishes between 2 brain-behavior motivational systems for goal pursuit: a *promotion system* that is concerned with nurturance, advancement, and fulfilling hopes (ideals) and a *prevention system* that is concerned with security, safety, and fulfilling duties (oughts).[13] Strauman and colleagues[14] elucidated the neural correlates of the promotion and prevention systems by utilizing a rapid masked exposure technique in which participants were exposed subliminally to their own promotion and prevention goals and observed distinct patterns of neural activation associated with promotion versus prevention. Promotion priming led to activation in left prefrontal and occipital regions as well as caudate and thalamus, whereas prevention priming was associated with activation in precuneus and posterior cingulate cortex as well as right prefrontal cortex (PFC). More recent findings suggest 2 regions in the left PFC that reliably discriminate between depressed and nondepressed participants following exposure to promotion goal priming (middle frontal gyrus in DLPFC and orbital PFC, respectively).[15] Similarly, there was a region in the right DLPFC that discriminated between depressed and nondepressed participants following exposure to idiographic prevention goal priming and also discriminated between depressed participants with versus without generalized anxiety.

These functional magnetic resonance imaging (fMRI) studies provide evidence that the promotion and prevention systems are reliably distinguishable at the neural level in addition to their distinct behavioral, cognitive, and motivational characteristics and that promotion- and prevention-driven goal pursuits are both likely to be compromised in depression. Further, these findings regarding the neural correlates of self-regulation dysfunction in depression support the conceptual basis for the use of self-system therapy (SST), which was designed to target self-regulatory dysfunction.[16] Evidence that SST is an effective treatment for depression because of its self-regulation mechanisms of action has been found in a number of clinical trials, in which clients with significant promotion dysfunction showed significantly greater improvement from SST than from standard cognitive-behavioral therapy and other active comparison conditions.[17–19] Table 1 summarizes the key concepts for the model of concurrent treatment for depression on which this study was based.

We conducted a proof-of-concept trial testing whether (*a*) targeting TMS using a specific model of neurocircuitry (specifically the promotion/prevention model for self-regulation) and (*b*) controlling for state dependency by activating that cortical system using SST simultaneously with TMS would enhance the efficacy of TMS. The study included 5 adults diagnosed with major depressive disorder (MDD). In an initial magnetic resonance imaging (MRI) session, fMRI was recorded while subjects were engaged in an idiographic goal priming task derived from RFT. Using neuronavigation techniques, the fMRI image was overlaid on the subject's structural MRI, and the location in the left middle frontal gyrus that was most activated in response to idiographic promotion priming in each individual was chosen as the target for TMS. Transcranial magnetic stimulation was applied using FDA-cleared standard parameters over a 4-week course of treatment. In addition, following the C-PAS paradigm, each patient received SST simultaneously with the TMS, with the goal of inducing a Hebbian-like synergistic interaction between the plasticity induced by the TMS and the neural circuitry activated in response to the SST. The self-regulation–based procedures of SST were designed to activate the same self-regulation neural circuitry as that targeted using the fMRI guidance.

## MATERIALS AND METHODS

### Participants

Participants were 3 men and 2 women (mean age, 53.8 [SD, 4.32] years) who met diagnostic criteria for MDD using the clinician-administered M.I.N.I. International Neuropsychiatric Interview 6.0, a brief structured diagnostic interview developed to assess the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* psychiatric disorders[20] and scored greater than 16 on the Hamilton Rating Scale for Depression (HRSD).[21] In addition, participants met the diagnostic criteria for dysthymia (80%), generalized anxiety disorder (60%), panic disorder (40%), and social anxiety disorder (20%). On average, participants met the criteria for 3 *Diagnostic and Statistical Manual of Mental Disorders* disorders (range, 1–5). Average depression severity at intake was 42.20 (SD, 6.34) on the Inventory of Depressive Symptoms (IDS)[22] and 19.80 (SD, 5.81) on the HRSD, indicating that participants were moderately to severely depressed at the beginning of

**TABLE 1.** Concepts Included in the Model of Concurrent Treatment for Depression

*Cognitive paired associative stimulation (C-PAS)*: A paradigm for using neurostimulation to produce functional changes in cortical networks by delivering a cognitive task (in this study, a series of SST worksheets focusing on evaluation of the patient's personal goals) time-locked with simultaneous TMS.

*Self-regulation*: The capacity for individuals to guide themselves, intentionally as well as automatically, toward important goals. According to regulatory focus theory, human self-regulation is organized for pursuit of 2 kinds of goals: promotion goals, which represent ideals, achievements, and accomplishments, and prevention goals, which represent responsibilities, obligations, and moral imperatives.

*Promotion system*: A brain-behavior system that is engaged when the individual is pursuing a promotion goal. This system has a strategic preference for approach and is associated with the presence or absence of positive affect (eg, happiness vs dysphoria) depending on progress toward the goal.

*Prevention system*: A brain-behavior system that is engaged when the individual is pursuing a prevention goal. This system has a strategic preference for avoidance and is associated with the presence or absence of negative affect (eg, calmness vs anxiety) depending on progress toward the goal.

*Goal priming*: A form of cognitive priming (a technique used in experimental psychology) in which the individual is exposed (in or out of conscious awareness) to a cue that signifies an important personal goal. Goal priming reliably activates cognitive processes associated with goal pursuit.

the study. All participants were medically cleared by a psychiatrist to receive treatment with rTMS. Four participants were not currently taking any psychotropic medications. One participant was on a stable dose of levomilnacipran for depression and was taking clonazepam as needed for anxiety. All participants had a history of being treated with at least 2 different courses of antidepressants and being treatment resistant to antidepressant medication. In order to be included in this study, participants had to have manifested clinical depression for the past 8 weeks (minimum). Participants were otherwise healthy and were screened for contraindications to TMS and MRI, as well as substance abuse/dependence and pregnancy. Potential participants were recruited from Duke University Hospital outpatient clinics and referrals from other studies of depression and received a total of $300 compensation over the course of their involvement; participants did not incur costs for treatment or for any study procedure. All participants provided written informed consent for the study, which was approved by the institutional review board of the Duke University Medical Center and adhered to all relevant ethical standards as stipulated by the institutional review board.

## Procedures

Referred participants were phone screened and then assessed in person using the M.I.N.I. International Neuropsychiatric Interview 6.0. Participants also completed a battery of self-reports, including the IDS and the Selves Questionnaire.[23] Following the screening session, eligible participants underwent an MRI scan. This was followed by 4 weeks of daily combined TMS/SST treatment. Safety and tolerability of the combined treatment were assessed in every session via a brief rTMS adverse effect rating scale administered before and after each rTMS session. Changes in depression were examined weekly using the HRSD and the IDS. After completion of treatment, participants underwent a second MRI scan, an end-of-treatment assessment including an exit interview that examined feasibility and acceptability, and a follow-up assessment at 3 months. Depression ratings are missing from 2 participants at the 3-month follow-up.

## Measures

### Inventory of Depressive Symptoms

The self-report version of the IDS includes 30 items, of which 28 are rated on a 0- to 3-point scale, and its total score ranges from 0 to 84. Examinations of item-total correlations, internal consistency, and concurrent validity have established that the IDS has acceptable psychometric properties.[24]

### Selves Questionnaire

This semistructured self-report instrument is a free-response measure that asks participants to list distinct attributes of the actual, ideal, and ought self via 6 open-ended questions examining personal versus parental expectations about identity (eg, "What are the attributes of the type of person you believe you actually are?"). Each of these characteristics is rated on a scale from 1 (not at all) to 4 (extremely) with regard to how close it is to the person's perceived sense of self. Of these attributes, the ones rated highest and lowest for the ideal self were selected as individualized cues for promotion goal pursuit success or failure using a previously validated algorithm.[14] The attributes rated highest and lowest for the ought self are selected as targets for prevention success and failure. Participants were asked to generate a total of 5 ideal and 5 ought goals, and the same attribute could not be listed more than once. These personal goals were then used as individualized priming stimuli in the rapid masked goal priming fMRI paradigm.

### Tolerability Questionnaire

At each TMS session, we asked all participants to rate on a scale from 0 to 3 (absent, mild, moderate, severe) the intensity of their headache, neck pain, scalp pain, seizure (as observed by technician), hearing impairment, and any other adverse effect that they might have experienced from the TMS treatment. Participants provided ratings for each of these questions before and after each session.

### Exit Interview

We developed an interview to examine feasibility and acceptability as directly relevant to the study and to collect participant feedback. The interview was administered at the 3-month follow-up, and it included open-ended questions about the overall experience, positives, and issues with the current treatment, as well as Likert-type questions about feasibility of the intervention (eg, difficulty with limiting movement, level of comfort, ability to concentrate given the TMS noise, distress about the procedures, ease to hear and understand clinician, connection with clinician, and session engagement), acceptability (of session frequency, treatment length, concurrent intervention, assignments, TMS procedures), and overall satisfaction (ie, likelihood to recommend to someone else). Feasibility and acceptability questions were rated on a scale from 0 (not at all) to 9 (extremely), and scores were reversed as needed and averaged in order to compute an overall feasibility and acceptability score, where 0 represented not feasible/acceptable at all and 9 represented very feasible/acceptable. Satisfaction was rated on a 0- (low) to 100-point (high) continuous scale.

## MRI Procedures

Structural MRI and fMRI were collected on a 3.0-T GE Signa EXCITE HD system (GE Healthcare, Chicago, IL) at the Duke Brain Imaging and Analysis Center. After obtaining a T1-weighted structural MRI (echo-planar sequence), fMRI data were recorded from subjects while they participated in a previously validated goal priming task individualized using the Selves Questionnaire. Stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Subjects viewed the screen via a mirror system located in the head coil. Task onset was electronically synchronized with the MRI acquisition computer. Task administration and collection of reaction times and accuracy data were computer controlled. Functional images sensitive to blood oxygenation level–dependent (BOLD) contrast were acquired using an inverse spiral pulse sequence (repetition time, 1.5 s; time to echo, 35 milliseconds; field of view, 24 cm; image matrix, 642; 34 contiguous axial slices; voxel size $3.75 \times 3.75 \times 3.8$ mm). Each of the 5 runs consisted of the acquisition of a time series of 242 brain volumes. Four initial RF excitations were performed (and discarded) to achieve steady-state equilibrium. High-resolution structural images were acquired using a 3-dimensional fast spoiled gradient echo pulse sequence (repetition time, 12.2 milliseconds; time to echo, 5.3 milliseconds; field of view, 24 cm; image matrix, 2562; voxel size $0.9375 \times 0.9375 \times 1.9$ mm). A semiautomated high-order shimming program was used to ensure global field homogeneity.

### Goal Priming fMRI Task

The goal priming task[14] was used to visually observe the promotion/prevention neural network activation in each individual participant such that sites of peak activation could be used for subsequent rTMS intervention. Briefly, the event-related fMRI paradigm adapted from Diaz and McCarthy[25] uses multiple rapid, masked exposures to an individual participant's ideal (promotion)

and ought (prevention) goals that the individual believes he/she has successfully achieved or that he/she has not achieved as obtained in the screening session from the Selves Questionnaire. A continuous visual display of 12 characters was presented. Most of the displays were sets of 12 "#" characters alternating with sets of 12 "%" characters, each shown for 155 milliseconds. Every 1500 milliseconds, a letter set was inserted into the sequence, lasting for 33 milliseconds, with the next "#" or "%" stimulus acting as a pattern mask for it. Most of the letter sets were strings of nonword letters, but every 12 to 15 seconds, the stimulus was an actual word. The words were from 3 categories: they could be either from 1 of 2 sets of words representing personal promotion and prevention goals derived from the subject's responses in the previous Selves Questionnaire, or from a set of control words. The control words were goals generated by a different participant from their Selves Questionnaire, and these were chosen to be semantically unrelated to the goals generated by the target participant. The word stimuli were also 12 characters in length, with the target word or nonword in the center surrounded by pound or percent sign. Subjects were instructed to make a button press response when they detected a pound sign string presented in either blue or red font (to keep subjects engaged during the scanning). These target events occurred infrequently (mean interval, 25 seconds) and were not in close temporal proximity to the masked goal trials. There were 4 runs of these rapid serial visual presentations, each lasting 400 seconds, with a total of 40 presentations of each of the 3 word classes (promotion goals, prevention goals, and controls), 10 for each fMRI run, over the 4 runs.

## TMS Procedures

All treatment procedures were conducted in the Noninvasive Neuromodulation Neuroscience Laboratory in the Duke Department of Psychiatry and Behavioral Sciences. Subjects were seated comfortably in a chair and wore earplugs to protect hearing. Transcranial magnetic stimulation was delivered with a 70-mm Double Air Film Coil using a Rapid2 stimulator (Magstim Co, Whitland, South West Wales, United Kingdom). The first treatment session consisted of establishing the motor threshold (MT) for the patient and introducing the TMS/SST protocol. Motor threshold was defined as the minimum magnetic intensity needed to evoke motor potentials of at least 50 μV recorded via electromyogram from the first dorsal interosseus muscle of the participant's right hand in at least 5 of 10 stimulations. Motor threshold was determined for each hemisphere with the muscle at rest (verified by baseline electromyogram). Individual MT was used to determine the intensity of stimulation for each participant, as recommended by safety guidelines. Motor threshold assessments were repeated weekly throughout treatment. Repetitive transcranial magnetic stimulation targeting was accomplished via optically tracked frameless stereotaxic neuronavigation (Brainsight: Rogue Research, Montreal, Quebec, Canada). Brainsight software was used to superimpose fMRI activations on a subject's structural MRI in order to identify the rTMS target on an individualized basis. This system uses an infrared camera to monitor the relative positions of the coil and the target site on the subject's head, which could be tracked in real time and allowed the coil to be placed and maintained to within 1 mm of the cortical target throughout the session. Patients received the following dose of rTMS delivered over the left PFC: 10 Hz, 120% MT, 4-second pulse train, 26-second intertrain interval, 3000 pulses per session, one 37.5-minute session per day, 5 days a week (Monday–Friday), over a 4-week course of concurrent TMS/SST treatments. These parameters were within published safety guidelines and followed consensus guidelines for the use of TMS in depression treatment.[26]

## Concurrent SST Therapy

Self-system therapy is an evidence-based, brief, structured, skill-based therapy for depression that is similar in structure and organization to cognitive therapy (CT) but focuses primarily on self-regulation as opposed to CT's primary focus on cognitive distortions. Self-system therapy was specifically designed for adults whose socialization history did not lead to the establishment of an effective promotion system or whose socialization led to chronic prevention system hyperactivation. Self-system therapy is hypothesized to work by altering maladaptive self-regulation, using techniques that include changing the availability and accessibility of personal goals, changing the importance and affective significance of such goals, and changing regulatory system engagement strength.[27] The treatment was adapted for the current study in order to be more easily combined with rTMS. Adaptations included (*a*) breaking down the SST content into smaller delivery units aimed to be delivered using an interactive computerized presentation, (*b*) standardizing the length to 20 sessions, (*c*) modifying homework assignments to be feasible to implement on a daily basis, and (*d*) training the therapist in how to enhance alliance while being outside the visual field of the patient. Given the exploratory nature of the study, patients were permitted flexibility in the self-directed pace at which the successive modules of the treatment were presented and processed.

During concurrent sessions (all sessions except the first), an approximately 40-minute SST therapy session was begun simultaneously with the 37.5-minute TMS application. The participants sat in a chair facing a computer on which PowerPoint slides with the therapy content were presented. The therapist sat on one side and was able to see both patient and computer. The patient was instructed to not move his/her head and to look straight at the computer (and not at the therapist). The treatment was divided into 3 phases: orientation, exploration, and adaptation. The orientation phase introduced SST and described what the therapy would entail (eg, "We will look at the important experiences and relationships in your life, both past and present"; "We will talk about how depression affected your relationships, goals, and daily responsibilities."). The exploration phase looked at situations that have been difficult or painful recently, and about personal goals, standards, and beliefs that may have been related to those difficulties. The adaptation phase offered specific training in how to develop adaptive goals and standards and strategies to help reach goals. These different phases were spread across 20 sessions. Enough slides were created so that there would be novel material for each session. In each session, slides began with explanations and instructions and then proceeded to specific questions. The subject was to answer the questions aloud (while trying not to move relative to the TMS coil and while continuing to look at the computer screen). The duration of each slide was dependent on the participant, although they were advanced by the therapist when the activities on the slide were deemed to be finished. Both the therapist and the client at times took breaks in speaking during 4-second rTMS trains when the TMS noise may have made conversation more difficult. The therapist also monitored the TMS coil positioning and adjusted it as needed.

The treatment was administered by a TMS technician who was naive to psychotherapeutic work but who received 1 month of training in SST and suicide risk management and who was supervised by an experienced clinician (A.N.) throughout the treatment. One therapist, a BA level TMS technician, saw the first 2 patients; the second therapist, a cognitive psychologist without previous clinical training (S.D.) saw the other 3 patients. We chose to have individuals without expertise in psychotherapy serve as therapists because we wanted to determine whether the combined

treatment might be delivered effectively by a nonexpert (which could be desirable from a treatment dissemination perspective).

## Data Analysis

### Interview and Self-report

Exploratory data analyses were initially conducted to assess whether the self-report and interview data satisfy the assumptions required for later analyses at each of the time points of collection. Statistical analyses were planned based on the distribution that best fit the outcome variable examined. Longitudinal outcomes (ie, depression severity) were examined using hierarchical linear modeling (HLM).[28] Appropriate covariance structures were analytically determined based on a comparison of model fit criteria. Missing data imputations were not specified. Instead, a restricted estimated maximum likelihood model was used to account for missing data in HLM analyses. Hierarchical linear modeling is the best analysis for testing the proposed hypotheses (ie, improvement over time in depression severity) because it allows for individual variability and because it provides the best approach to handling missing data. In this approach, time is treated as a continuous variable, and a regression line is modeled for each participant based on the number of available time points.[29]

### Acceptability, Tolerability, and Feasibility

Because of the pilot nature of this study, we recorded adverse effects (headaches, neck pains, scalp pains, and any subjective cognitive difficulties) in each TMS session and conducted an exit interview examining acceptability and feasibility. Qualitative feedback provided by participants during the exit interview was also obtained and is described in the Results section.

### fMRI Data

Analysis of the BOLD fMRI data was performed using the general linear model within FSL. Images for each subject were realigned to the middle volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute [MNI] template) using a 12-parameter affine model followed by nonlinear matching to a customized template image, and smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter, set at 8-mm full width/half maximum. Voxelwise signal intensities were ratio normalized to the whole-brain global mean. Following preprocessing, linear contrasts using canonical hemodynamic response functions were used to estimate condition-specific BOLD activation across the runs (each of which represented a different priming condition) for each subject. These individual contrast images (ie, weighted sum of the β images) were then used in a second-level random-effects model, which accounted for both run-to-run and subject-to-subject variability, to identify regions significantly activated by the different tasks within each run (goal, nonword, and color detection under each of the priming conditions). Note that the variance of interest for testing hypotheses was the variance within each run associated with goal priming trials, and we therefore focus on the presentation of single words representing promotion and prevention goals (collapsing across success) for both pretreatment and posttreatment scanning sessions.

The first stage of the fMRI analysis was performed on the first-level contrast images recorded in the baseline (pre-TMS course) MRI session in order to locate, on an individualized basis, targets for rTMS treatment. The general linear model was used to detect voxels in left middle frontal gyrus showing a significant response to promotion > prevention goal words and constituted the individual localizer. The center of mass of the resulting cluster of active voxels was used as the target site for TMS. The second stage of the fMRI analysis examined changes pre- and post-TMS treatment course. To test for main effects as well as 2-way interactions, the first-level images were contrasted in a 2-factor analysis of variance model, with goal type (promotion, prevention words) and time point (T1, T2) as factors. Based on the sample size as well as the availability of data from previous studies of both healthy and depressed participants using the goal priming task, all analyses were thresholded at a voxel level of $P < 0.005$ and an extent threshold of at least 20 contiguous voxels.

# RESULTS

## Tolerability, Acceptability, and Feasibility

All 5 patients completed the protocol, and none expressed concerns about the combination of rTMS with computerized, therapist-assisted presentation of the structured psychological interventions. Reported adverse effects were minimal. Over the 100 TMS sessions, there was 1 report of a headache worsening during the session, 1 report of neck pain, and 1 report of scalp pain in post-session questionnaires.

At the exit interview, participants reported that they found the intervention very feasible ($mean_{feasibility}$, 6.5 [SD, 0.49]; range, 6.13–7.25) and highly acceptable ($mean_{acceptability}$, 8.53 [SD, 0.38]; range, 8.00–9.00). Participants also reported that they would be very likely to recommend this treatment to a friend or family member with depression ($mean_{satisfaction}$, 99.00 [SD, 2.24]; range, 95.00–100.00).

When asked the open-ended question, "What was it like being in our study?" all participants reported that they had a positive experience. Overall, themes that emerged were appreciating the structure of the psychotherapy (eg, several subjects made the comment "structure was good"), being able to think differently about situations that posed difficulty before, finding the treatment intense but liking the intensity, and seeing improvements posttreatment. For example, a participant commented, "I was in crisis before, but I see things differently now." Another also said, "I was out of control before the study, but I can see concrete results now." A theme that emerged related to the TMS was that it was initially a bit startling, and 2 of the 5 participants found the noise to be a "minor inconvenience."

When asked about what changes or improvements they might suggest, a suggestion was a more comfortable setting that looked less like a research laboratory. One patient also suggested a longer course of therapy because "it went by really quickly." In addition, a participant reported he/she would have benefited from learning how to relax while under TMS earlier in treatment in order to be able to focus on the SST content sooner. Per this subject's report, once he/she learned how to relax the jaw, it "all got better."

## Depression Severity

Depression severity as measured by the HRSD and IDS decreased over the course of treatment, as shown in Figure 1. Hamilton Rating Scale for Depression was normally distributed at each time point (Shapiro-Wilk $W > 0.9$) except posttreatment (Shapiro-Wilk $W = 0.85$). Skewness (−0.17) and kurtosis (−2.41) of the HRSD total score at posttreatment were within acceptable parameters for a normal distribution, and no transformations of the score across time points improved normality. The IDS was also normally distributed at each time point (Shapiro-Wilk $W > 0.9$, or if $W < 0.9$, skewness and kurtosis within acceptable range for a normal distribution). Therefore, no transformations were performed, and an HLM analysis was conducted using the raw data.

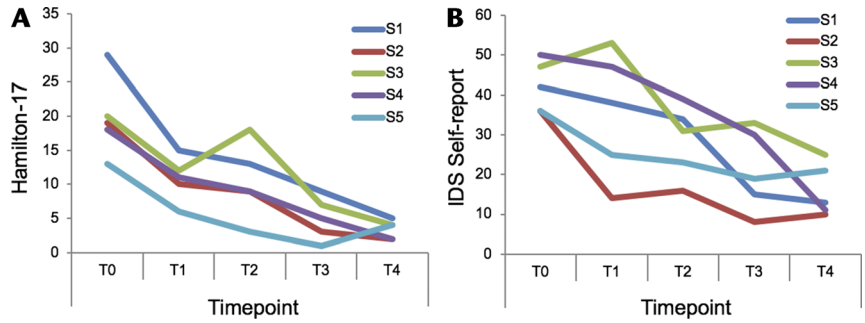


**FIGURE 1.** Hamilton Depression Rating Scale 17 total scores (A) and IDS total scores (B) for 5 patients suffering from major depressive episode, from the initial visit (T0), at weekly follow-up assessments (T1–T4) and at a 3-month follow-up assessment; all tests were administered before treatment. (Data are missing for the 3-month follow-up for S001 and S002.)

The participants showed a significant decrease in clinician-rated depression severity over time in the study, $F_{HRSD}$ (1, 10.70) = 16.69, $P < 0.01$. All participants scored within the remitted HRSD range (mean, 3.40 [SD, 1.34]) at the end of the treatment phase of the study. There was a trend for self-reported depression severity to improve significantly over time as well, $F_{IDS}(1, 1.86) = 11.00$, $P = 0.09$.

## fMRI Changes in Response to the Goal Priming Task

The fMRI analyses focused on the outcomes of contrasts that identified the neural correlates of goal-directed behavior, specifically the promotion versus prevention contrast during a pretreatment and posttreatment scan session. In order to provide subject-specific TMS targets for therapeutic stimulation, we first described the critical promotion > prevention contrast at T1 (pretreatment) in each participant, using a liberal statistical threshold ($P < 0.01$) to best visualize that subjects' individual pattern of activation. The main findings for our analyses using fMRI guidance to locate TMS targets on an individualized basis are summarized in Figure 2. Specifically, Figure 2A describes the peak locations for all 5 participants displayed in MNI space.

Turning to the results of our critical contrast compared between T1 and T2 (posttreatment), we observed no main effects of goal type × time point, but we did observe a significant goal type × time point interaction in 2 key brain regions. Figure 2B describes regions associated with this interaction; although we had no pre-experimental predictions concerning the outcome of these contrasts, we observed a significant interaction of treatment in the right orbitofrontal cortex ($x/y/z$ = 24/32/−12, $t_4$ = 5.55, 40 voxels, $P < 0.005$) and right hippocampus ($x/y/z$ = 22/−6/24, $t_4$ = 4.35, 24 voxels, $P < 0.005$), both contralateral to the site of stimulation. Comparison of the effects for each condition in these regions suggests a regional specificity based on goal type, with treatment-related increases for promotion goals localized to orbitofrontal cortex, whereas treatment-related increases for prevention goals were focused on the hippocampus.

## DISCUSSION

We developed and pilot tested a novel multimodal treatment for MDD consisting of a theory-based protocol for individualized fMRI-guided rTMS site selection plus a concurrent cognitive intervention targeting the same dysfunctional neural circuitry used to identify the rTMS target. While intentionally limited both in scope and in sample size, this proof-of-concept study demonstrated the feasibility of combining fMRI-guided, individualized TMS targeting with a psychotherapeutic intervention designed to activate the same neural circuitry around which the targeting had been organized. The primary outcome from this pilot study is the feasibility of the protocol itself. The observation that all 5 patients reported substantial symptom reduction (and were rated by a clinician as having improved significantly) is a positive sign

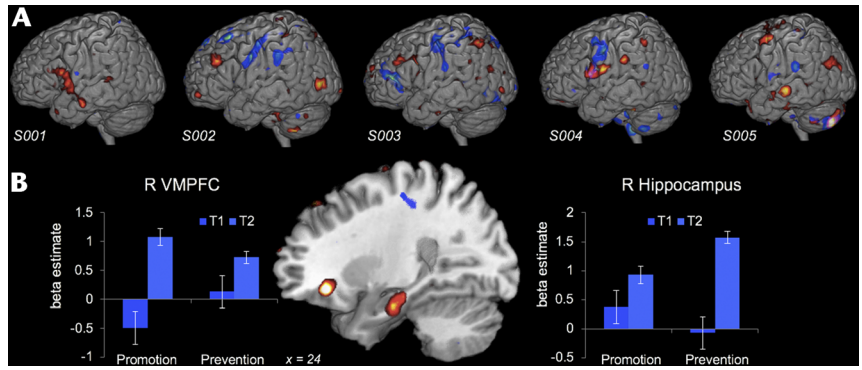


**FIGURE 2.** Neuroimaging results. We represent the critical contrast between words presented to participants representing promotion > prevention goals, displayed in MNI space. A, Individual contrast maps for this contrast suggest a moderate regional heterogeneity to the effect. Although all subjects demonstrated significant left prefrontal cortex activity ($P < 0.01$), generating a localizer for TMS therapy, the specific region differed among our study sample. B, A 2-factor analysis of variance with goal type and time point as factors demonstrated a significant interaction in orbitofrontal cortex and hippocampus, suggesting that promotion-related modulation in response to treatment in the former and prevention-related modulation in the latter.

and a basis for larger-scale randomized trials. These encouraging preliminary results suggest that the specific approach taken here, targeting the left middle frontal gyrus with TMS on an individual basis using fMRI while simultaneously manipulating context by activating networks involved with depression with SST, may enhance the antidepressant effects of TMS. The initial success of this specific implementation lends credence to our more general recommendations that TMS targeting be based on more precise, theory-driven, neuronavigational methods and that neurostimulation can be combined synergistically with cognitive interventions using the C-PAS approach to integrating treatment modalities. To our knowledge, this study represents the first to localize a depression treatment target using fMRI activation based on a neurobehavioral construct hypothesized to underlie cognitive/motivational dysfunction in depression.

The standard clinical technique by which rTMS is used for the treatment of depression has been associated with modest efficacy to date. Such limited efficacy may be due to reliance on scalp-based targeting rather than methods that incorporate fMRI-guided neuronavigation based on a specific model of neurocircuit dysfunction. We introduced such a model for specific network engagement drawn from regulatory focus theory, which postulates 2 brain/behavior systems, the promotion and prevention systems, underlying goal pursuit, and noted that priming promotion versus prevention goals induces discriminable patterns of brain activation that are sensitive to the effects of depression and anxiety. Our model suggests that these left and right PFC locations can be directly targeted in an individualized manner for TMS. We used the standard TMS frequency of 10 Hz to enhance cortical excitability in left DLPFC, in line with general imaging findings that this region is hypoactive in depression, as well as our own findings that depressed patients show hypoactivation in left middle frontal gyrus during tasks that engage promotion goal pursuit. Conversely, 1-Hz TMS, which down-regulates cortical excitability, to right DLPFC has been shown effective in remediating depression. This too is in line with our recent fMRI findings, with hyperactivity in right DLPFC during prevention tasks for depressed patients who also have increased anxiety levels. Here our model suggests 1-Hz TMS individually targeted to right DLPFC may specifically help patients with comorbid anxiety (as we have previously reported)[30,31] and that in the future the particular sites and parameters of TMS interventions may be tailored to patients on an individual basis, depending on comorbidities.

In regard to neuronavigation, we also recommend that, as was performed here, individualized rather than group rTMS targeting should be utilized to precisely engage the identified brain mechanism. There is a great deal of individual spatial variation in functional cortical areas,[32,33] which can make appropriate coil placement challenging and may lead to inconsistent results. For example, a study found that when subjects performed a verbal working memory task, group analyses showed fMRI activation of left DLPFC that varied by as much as 2 cm between individuals based on Talairach coordinates.[34]

The analysis of fMRI changes in activation over the course of SST/TMS treatment points to a more objective, neurophysiological approach to assessing the effects of depression treatment. No strong conclusions can be made here based on BOLD changes in only 5 subjects. Nonetheless, the observation that the regions that significantly became more active across the TMS course, right orbitofrontal cortex and hippocampus (all of which are elements of brain networks thought to be involved in depression and specifically areas related and affected by top-down emotional regulation regions including those targeted here), is encouraging.[35–37]

This study was conducted as an open-label trial with small number of participants as a means to establish feasibility: first, given our conception of C-PAS and functional TMS targeting, whether it was possible to conduct SST concurrently with high-frequency TMS application. It was also a test of the entire procedure; for example, whether the prepared material for SST fit the time course of TMS, both within daily sessions and over 4 weeks. Although the successful completion of the course of TMS in all 5 participants provides evidence that our approach is feasible, it would be premature to interpret the observed remittance rate and changes in activation of depression-related brain regions as direct evidence for the efficacy of our technique. Nonetheless, we do see these findings as providing evidence that individually targeted rTMS can be integrated with cognitive interventions designed to activate the neural circuitry associated with promotion versus prevention, potentially allowing the neuroplasticity induced by the rTMS to benefit the systems most likely involved in remediating depression. This assertion is supported, as a proof-of-concept, by our initial feasibility data from a clinical paradigm in which depressed patients received TMS to the left middle frontal gyrus targeted on an individual basis using fMRI, while simultaneously receiving a previously validated self-regulation-based psychotherapy. Larger, blinded, sham-based randomized clinical trials will be required to test the possibility that this approach of fully engaging brain networks and controlling their functional state (here via simultaneous psychotherapy) represents a sounder and more efficacious approach to treating depression than the present FDA-approved method of using TMS alone, using scalp-based targeting.

While there is growing interest in combining cognitive or neurocognitive interventions with brain stimulation, we wish to emphasize the importance of a priori targeting of brain networks associated with depression. This kind of a priori targeting likewise should be individualized using targeted task-based activations within those networks, as well as by using a therapeutic intervention that the network will be responsive to. Doing so may produce better results and may help to achieve the goal of precision medicine in the case of treating mood disorders. The success in this study of showing the feasibility of this approach lends hope to the idea that the efficacy of TMS in treatment-resistant MDD can be improved. In terms of efficacy in treatment of MDD, the criterion standard remains electroconvulsive therapy, which has remission rates on the order of 65% to 75%. This is still far superior to what is currently reported in randomized controlled trials for TMS, which generally are between 20% to 30%. However, given the underutilization of electroconvulsive therapy in many regions and the more favorable adverse effect profile for TMS, an improvement in outcome using TMS in treatment-resistant depression could be a welcome addition. Further, the cognitive tools that could be developed using SST during (and possibly reinforced by) TMS might be potent in prevention of relapse and recurrence.

In summary, we hope to have provided an example of the use of noninvasive brain stimulation to help translate a conceptually guided program of neuroimaging research into an innovative means of improving therapeutic efficacy. The C-PAS paradigm provided a clear rationale for the simultaneous and theoretically based delivery of SST and rTMS. Cognitive paired associative stimulation represents an example of a larger family of multimodal therapies in which devices, psychosocial interventions, medications, and/or biologics are combined to achieve therapeutic ends. As reported in recent National Academy of Medicine proceedings, multimodal therapies for brain disorders represent a promising and relatively unexplored avenue for improving outcomes for a range of neurological and psychiatric conditions. Most of the work to date combining TMS with behavioral therapy has focused on motor and speech function, and the application of this approach to depression remains to be fully explored.[38] These promising open-label feasibility results should be followed up with a controlled

trial to control for placebo response and to evaluate the individual contributions of the SST and TMS components of C-PAS.

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