Introduction

What is TMS?

TMS is a revolutionary way to treat depression using technology rather than medications. TMS Therapy use magnetic fields to strengthen a precise brain region that is weakened during depression. Restrengthening this weakened brain region restores the brain to electrochemical balance and alleviates depression. TMS has been cleared by the FDA for over 13 years to treat depression. A remarkable 2 out of 3 patients respond to TMS treatment, while 1 out of 2 achieve remission (symptom-free). Best of all, some people see results in days as opposed to many weeks with medications.
Note that this is a different technology from electroconvulsive therapy; no electric current flows into the brain with TMS.

What happens during TMS therapy?

During each TMS session, you'll sit in a comfortable chair while a paddle is placed on your forehead. During treatment, you will hear a tapping or clicking sound that usually lasts for a few seconds, followed by a pause. You'll also feel a tapping sensation on your forehead. Each of these sessions will last 5-10 minutes. An entire course of accelerated TMS is 40 sessions, which we spread across 5 days. Each day's treatment lasts about 8 hours because although each session is only up to 10 minutes, we need to wait 1 hour until we can begin the next session. In the intervening 50 minutes, you may do as you like.

What might the side effects be?

While TMS generally has a much more favorable side effect profile than antidepressants, it's important that you are aware of them. The most common side effects are headaches or scalp discomfort in the treatment area on the days of treatment. We recommend having an over-the-counter pain relieve available (e.g. aspirin, ibuprofen, naproxen). You also may experience tiredness after treatment, and patients often report sleeping longer and deeper than their normal sleep pattern.

Where do I receive treatment?

The procedure is either performed as concierge medicine at your residence, or in a local facility.

When can I expect results?

The majority of patients who respond to TMS start seeing positive results after a few weeks of receiving the treatment. However, some patients report positive results sooner than this and other patients can have a delayed response that at times happens towards the end of the 4th week of TMS treatment.

Additional Information

Videos

- Tianqiao & Chrissy Chen Institute, A Minds Wide Open Short: Nolan Williams new TMS therapy for depression
- TEDx, Neurohacking: rewiring your brain
- CBS, SAINT: Hope for new treatment of depression
- PsychSceneHub, Typical Response & Remission Rates of rTMS in Treatment-Resistant Cases
- MagVenture, How I overcame chronic depression with MagVenture TMS

Articles

- Clinical TMS Society, "It's All About Remission" Lecture Recap
- Stanford Daily, Stanford depression treatment nearly 80% effective
- UC San Diego Health, Transcranial Magnetic Stimulation (TMS) for Depression
- Clinical TMS Society, TMS Therapy
- Neuromodec, The Basics of Transcranial Magnetic Stimulation (TMS)

Frequently Asked Questions

Who does the treatment?

The physician indicates the details of TMS delivery in their prescription note. TMS delivery is facilitated by a trained & certified TMS technician. The prescribing provider may be virtually present, as needed.

How long does it last?

2 out of 3 patients retain their response 1 year after completing TMS.

How is TMS different from Antidrepressants?

Antidepressants work by modifying the actions of neurotransmitters (brain chemicals) or modifying neurotransmitter receptors. Treatment with antidepressants involves taking medications which are absorbed through the mouth, stomach and small intestine with possible side effects throughout the body. They can cause adverse effects such as gastrointestinal side effects weight gain and can have an effect on sexual function (reduced sex drive and delayed ejaculation). Patients can also be allergic to antidepressants or other chemicals contained in the medication. TMS does not involve the ingestion of chemicals, therefore, there are no systemic adverse effects. There is no impact on the digestive system, on sexual function, cognition and there are no allergic responses. The only side effect with TMS that occurs more than 5% of the time is transient site pain, a headache which abates typically within the first week as patients desensitize to the treatment. Antidepressants modify brain chemicals and receptors via an effect on protein synthesis. They can take between three to six weeks to work, while TMS has a faster onset of action. Studies show that in patients who have not responded to two or three antidepressants the response rate to the next antidepressant is 10-15%. If such patients are given TMS, the response rate is about 60%.

Frequently Asked Questions

What happens if I do not respond to treatment?

Our providers are deeply committed to helping you. There is always hope and a way forward with your care. If you don't respond to your first TMS treatment course, your doctor may recommend another type of TMS. We have several advanced TMS treatment options to help you feel better.

Is there a recovery period after my treatment?

The physician indicates the details of TMS delivery in their prescription note. TMS delivery is facilitated by a trained & certified TMS technician. The prescribing provider may be virtually present, as needed.

Do some clinics only do one TMS treatment per day?

Yes, although we believe the research is now clear that doing multiple TMS treatments each day is more effective and works faster than simply doing one treatment per day. It's also significantly more convenient for patients to complete the entire course in one week.

Does it require anesthesia?

No.

Am I able to drive home after TMS treatment?

Yes, this is normal.

Significant Scientific Results

George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Basser, P., Hallett, M., & Post, R. M. (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport, 6(14), 1853–1856. https://doi.org/10.1097/00001756-199510020-00008

Converging evidence points to hypofunction of the left prefrontal cortex in depression. Repetitive transcranial magnetic stimulation (rTMS) activates neurons near the surface of the brain. We questioned whether daily left prefrontal rTMS might improve mood in depressed subjects and report a pilot study of such treatment in six highly medication-resistant depressed inpatients. Depression scores significantly improved for the group as a whole (Hamilton Depression Scores decreased from 23.8 +/- 4.2 (s.d.) at baseline to 17.5 +/- 8.4 after treatment; t = 3.03, 5DF, p = 0.02, two-tailed paired t-test). Two subjects showed robust mood improvement which occurred progressively over the course of several weeks. In one subject, depression symptoms completely remitted for the first time in 3 years. Daily left prefrontal rTMS appears to be safe, well tolerated and may alleviate depression.

Pascual-Leone, A., Rubio, B., Pallardó, F., & Catalá, M. D. (1996). Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. The Lancet, 348(9022), 233–237. https://doi.org/10.1016/s0140-6736(96)01219-6

Background: Lesion and neuroimaging studies suggest that left prefrontal lobe dysfunction is pathophysiologically linked to depression. Rapid-rate transcranial magnetic stimulation (rTMS) to prefrontal structures has a lateralised effect on mood in normal volunteers, and several preliminary studies suggest a beneficial effect of rTMS on depression. However, adequately controlled studies have not been conducted.
Methods: We have studied the effects of focal rTMS on the depressive symptoms in 17 patients with medication-resistant depression of psychotic subtype. The study was designed as a multiple cross-over, randomised placebo-controlled trial. Sham rTMS and stimulation of different cortical areas were used as controls.
Findings: Left dorsolateral prefrontal cortex rTMS resulted in a significant decrease in scores on the Hamilton depression rating scale HDRS (from 25.2 to 13.8) and the self-rated Beck questionnaire BQ (from 47.9 to 25.7). 11 of the 17 patients showed pronounced improvement that lasted for about 2 weeks after 5 days of daily rTMS sessions. No patient experienced any significant undesirable side-effects.
Interpretation: Our findings emphasize the role of the left dorsolateral prefrontal cortex in depression, and suggest that rTMS of the left dorsolateral prefrontal cortex might become a safe, non-convulsive alternative to electroconvulsive treatment in depression.

Significant Scientific Results

George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P. E., 3rd, Schwartz, T., & Sackeim, H. A. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Archives of General Psychiatry, 67(5), 507–516. https://doi.org/10.1001/archgenpsychiatry.2010.46

Context: Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment for depression, but previous work had mixed outcomes and did not adequately mask sham conditions.
Objective: To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder.
Design: Prospective, multisite, randomized, active sham-controlled (1:1 randomization), duration-adaptive design with 3 weeks of daily weekday treatment (fixed-dose phase) followed by continued blinded treatment for up to another 3 weeks in improvers.
Setting: Four US university hospital clinics.
Patients: Approximately 860 outpatients were screened, yielding 199 antidepressant drug-free patients with unipolar nonpsychotic major depressive disorder.
Intervention: We delivered rTMS to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil. Sham rTMS used a similar coil with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.
Main outcome measure: In the intention-to-treat sample (n = 190), remission rates were compared for the 2 treatment arms using logistic regression and controlling for site, treatment resistance, age, and duration of the current depressive episode.
Results: Patients, treaters, and raters were effectively masked. Minimal adverse effects did not differ by treatment arm, with an 88% retention rate (90% sham and 86% active). Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1% active rTMS and 5.1% sham) (P = .02). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32-13.24). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. Almost 30% of patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham).
Conclusion: Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham.

Significant Scientific Results

O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., McDonald, W. M., Avery, D., Fitzgerald, P. B., Loo, C., Demitrack, M. A., George, M. S., & Sackeim, H. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial.BiologicalPsychiatry,62(11),1208–1216. https://doi.org/10.1016/j.biopsych.2007.01.018

Background: We tested whether transcranial magnetic stimulation (TMS) over the left dorsolateral prefrontal cortex (DLPFC) is effective and safe in the acute treatment of major depression.
Methods: In a double-blind, multisite study, 301 medication-free patients with major depression who had not benefited from prior treatment were randomized to active (n = 155) or sham TMS (n = 146) conditions. Sessions were conducted five times per week with TMS at 10 pulses/sec, 120% of motor threshold, 3000 pulses/session, for 4-6 weeks. Primary outcome was the symptom score change as assessed at week 4 with the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes included changes on the 17- and 24-item Hamilton Depression Rating Scale (HAMD) and response and remission rates with the MADRS and HAMD.
Results: Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a post hoc correction for inequality in symptom severity between groups at baseline), as well as on the HAMD17 and HAMD24 scales at weeks 4 and 6. Response rates were significantly higher with active TMS on all three scales at weeks 4 and 6. Remission rates were approximately twofold higher with active TMS at week 6 and significant on the MADRS and HAMD24 scales (but not the HAMD17 scale). Active TMS was well tolerated with a low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain.
Conclusions: Transcranial magnetic stimulation was effective in treating major depression with minimal side effects reported. It offers clinicians a novel alternative for the treatment of this disorder.

Significant Scientific Results

Berlim, M. T., van den Eynde, F., Tovar-Perdomo, S., & Daskalakis, Z. J. (2014). Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychological Medicine, 44(2), 225–239. https://doi.org/10.1017/S0033291713000512

Background: Meta-analyses have shown that high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) has antidepressant properties when compared with sham rTMS. However, its overall response and remission rates in major depression (MD) remain unclear. Thus, we have systematically and quantitatively assessed the efficacy of HF-rTMS for MD based on randomized, double-blind and sham-controlled trials (RCTs).
Method: We searched the literature from 1995 through to July 2012 using MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, SCOPUS, and ProQuest Dissertations & Theses. We used a random-effects model, odds ratios (ORs) and the number needed to treat (NNT).
Results: Data from 29 RCTs were included, totaling 1371 subjects with MD. Following approximately 13 sessions, 29.3% and 18.6% of subjects receiving HF-rTMS were classified as responders and remitters, respectively (compared with 10.4% and 5% of those receiving sham rTMS). The pooled OR was 3.3 ($p < 0.0001$) for both response and remission rates (with associated NNTs of 6 and 8, respectively). Furthermore, we found HF-rTMS to be equally effective as an augmentation strategy or as a monotherapy for MD, and when used in samples with primary unipolar MD or in mixed samples with unipolar and bipolar MD. Also, alternative stimulation parameters were not associated with differential efficacy estimates. Moreover, baseline depression severity and drop-out rates at study end were comparable between the HF-rTMS and sham rTMS groups. Finally, heterogeneity between the included RCTs was not statistically significant.
Conclusions: HF-rTMS seems to be associated with clinically relevant antidepressant effects and with a benign tolerability profile.

Significant Scientific Results

Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S. H., Bystritsky, A., Xia, G., Tendler, A., Daskalakis, Z. J., Winston, J. L., Dannon, P., Hafez, H. M., Reti, I. M., Morales, O. G., Schlaepfer, T. E., Hollander, E., Berman, J. A., Husain, M. M., Sofer, U., Stein, A., ... Zangen, A. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry: Official Journal of the World Psychiatric Association , 14(1), 64–73. https://doi.org/10.1002/wps.20199

Major depressive disorder (MDD) is a prevalent and disabling condition, and many patients do not respond to available treatments. Deep transcranial magnetic stimulation (dTMS) is a new technology allowing non-surgical stimulation of relatively deep brain areas. This is the first double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS in MDD. We recruited 212 MDD outpatients, aged 22-68 years, who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments during the current episode. They were randomly assigned to monotherapy with active or sham dTMS. Twenty sessions of dTMS (18 Hz over the prefrontal cortex) were applied during 4 weeks acutely, and then biweekly for 12 weeks. Primary and secondary efficacy endpoints were the change in the Hamilton Depression Rating Scale (HDRS-21) score and response/remission rates at week 5, respectively. dTMS induced a 6.39 point improvement in HDRS-21 scores, while a 3.28 point improvement was observed in the sham group (p=0.008), resulting in a 0.76 effect size. Response and remission rates were higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, p=0.013; remission: 32.6 vs. 14.6%, p=0.005). These differences between active and sham treatment were stable during the 12-week maintenance phase. dTMS was associated with few and minor side effects apart from one seizure in a patient where a protocol violation occurred. These results suggest that dTMS constitutes a novel intervention in MDD, which is efficacious and safe in patients not responding to antidepressant medications, and whose effect remains stable over 3 months of maintenance treatment.

Significant Scientific Results

Brunoni, A. R., Chaimani, A., Moffa, A. H., Razza, L. B., Gattaz, W. F., Daskalakis, Z. J., & Carvalho, A. F. (2017). Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis.JAMAPsychiatry,74(2),143–152. https://doi.org/10.1001/jamapsychiatry.2016.3644

Importance: Although several strategies of repetitive transcranial magnetic stimulation (rTMS) have been investigated as treatment of major depressive disorder (MDD), their comparative efficacy and acceptability is unknown.
Objective: To establish the relative efficacy and acceptability of the different modalities of rTMS used for MDD by performing a network meta-analysis, obtaining a clinically meaningful treatment hierarchy.
Data sources: PubMed/MEDLINE, EMBASE, PsycInfo, and Web of Science were searched up until October 1, 2016.
Study selection: Randomized clinical trials that compared any rTMS intervention with sham or another rTMS intervention. Trials performing less than 10 sessions were excluded.
Data extraction and synthesis: Two independent reviewers used standard forms for data extraction and quality assessment. Random-effects, standard pairwise, and network meta-analyses were performed to synthesize data.
Main outcomes and measures: Response rates and acceptability (dropout rate). Remission was the secondary outcome. Effect sizes were reported as odds ratios (ORs) with 95% CIs.
Results: Eighty-one studies (4233 patients, 59.1% women, mean age of 46 years) were included. The interventions more effective than sham were priming low-frequency (OR, 4.66; 95% CI, 1.70-12.77), bilateral (OR, 3.96; 95% CI, 2.37-6.60), high-frequency (OR, 3.07; 95% CI, 2.24-4.21), θ-burst stimulation (OR, 2.54; 95% CI, 1.07-6.05), and low-frequency (OR, 2.37; 95% CI, 1.52-3.68) rTMS. Novel rTMS interventions (accelerated, synchronized, and deep rTMS) were not more effective than sham. Except for θ-burst stimulation vs sham, similar results were obtained for remission. All interventions were at least as acceptable as sham. The estimated relative ranking of treatments suggested that priming low-frequency and bilateral rTMS might be the most efficacious and acceptable interventions among all rTMS strategies. However, results were imprecise and relatively few trials were available for interventions other than low-frequency, high-frequency, and bilateral rTMS.
Conclusions and relevance: Few differences were found in clinical efficacy and acceptability between the different rTMS modalities, favoring to some extent bilateral rTMS and priming low-frequency rTMS. These findings warrant the design of larger RCTs investigating the potential of these approaches in the short-term treatment of MDD. Current evidence cannot support novel rTMS interventions as a treatment for MDD.

Significant Scientific Results

Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S. H., Lam, R. W., Daskalakis, Z. J., & Downar, J. (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet, 391(10131), 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2

Background: Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) by use of high-frequency (10 Hz) left-side dorsolateral prefrontal cortex stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37·5 min for a standard 10 Hz treatment session. We aimed to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

Methods: In this randomised, multicentre, non-inferiority clinical trial, we recruited patients who were referred to specialty neurostimulation centres based at three Canadian university hospitals (Centre for Addiction and Mental Health and Toronto Western Hospital, Toronto, ON, and University of British Columbia Hospital, Vancouver, BC). Participants were aged 18-65 years, were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode, were receiving stable antidepressant medication doses for at least 4 weeks before baseline, and had an HRSD-17 score of at least 18. Participants were randomly allocated (1:1) to treatment groups (10 Hz rTMS or iTBS) by use of a random permuted block method, with stratification by site and number of adequate trials in which the antidepressants were unsuccessful. Treatment was delivered open-label but investigators and outcome assessors were masked to treatment groups. Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered on 5 days a week for 4-6 weeks. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, with a non-inferiority margin of 2·25 points. For the primary outcome measure, we did a per-protocol analysis of all participants who were randomly allocated to groups and who attained the primary completion point of 4 weeks. This trial is registered with ClinicalTrials.gov, number NCT01887782.

Findings: Between Sept 3, 2013, and Oct 3, 2016, we randomly allocated 205 participants to receive 10 Hz rTMS and 209 participants to receive iTBS. 192 (94%) participants in the 10 Hz rTMS group and 193 (92%) in the iTBS group were assessed for the primary outcome after 4-6 weeks of treatment. HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·103 [corrected], lower 95% CI -1·16; p=0·0011), which indicated non-inferiority of iTBS. Self-rated intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group (mean score on verbal analogue scale 3·8 [SD 2·0] vs 3·4 [2·0] out of 10; p=0·011). Dropout rates did not differ between groups (10 Hz rTMS: 13 [6%] of 205 participants; iTBS: 16 [8%] of 209 participants); p=0·6004). The most common treatment-related adverse event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208).

Interpretation: In patients with treatment-resistant depression, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. By use of iTBS, the number of patients treated per day with current rTMS devices can be increased several times without compromising clinical effectiveness.

Significant Scientific Results

Carmi, L., Tendler, A., Bystritsky, A., Hollander, E., Blumberger, D. M., Daskalakis, J., Ward, H., Lapidus, K., Goodman, W., Casuto, L., Feifel, D., Barnea-Ygael, N., Roth, Y., Zangen, A., & Zohar, J. (2019). Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. The American Journal of Psychiatry, 176(11), 931–938. https://doi.org/10.1176/appi.ajp.2019.18101180

Objective: Obsessive-compulsive disorder (OCD) is a chronic and disabling condition that often responds unsatisfactorily to pharmacological and psychological treatments. Converging evidence suggests a dysfunction of the cortical-striatal-thalamic-cortical circuit in OCD, and a previous feasibility study indicated beneficial effects of deep transcranial magnetic stimulation (dTMS) targeting the medial prefrontal cortex and the anterior cingulate cortex. The authors examined the therapeutic effect of dTMS in a multicenter double-blind sham-controlled study.

Methods: At 11 centers, 99 OCD patients were randomly allocated to treatment with either high-frequency (20 Hz) or sham dTMS and received daily treatments following individualized symptom provocation, for 6 weeks. Clinical response to treatment was determined using the Yale-Brown Obsessive Compulsive Scale (YBOCS), and the primary efficacy endpoint was the change in score from baseline to posttreatment assessment. Additional measures were response rates (defined as a reduction of ≥30% in YBOCS score) at the posttreatment assessment and after another month of follow-up.

Results: Eighty-nine percent of the active treatment group and 96% of the sham treatment group completed the study. The reduction in YBOCS score among patients who received active dTMS treatment was significantly greater than among patients who received sham treatment (reductions of 6.0 points and 3.3 points, respectively), with response rates of 38.1% and 11.1%, respectively. At the 1-month follow-up, the response rates were 45.2% in the active treatment group and 17.8% in the sham treatment group. Significant differences between the groups were maintained at follow-up.

Conclusions: High-frequency dTMS over the medial prefrontal cortex and anterior cingulate cortex significantly improved OCD symptoms and may be considered as a potential intervention for patients who do not respond adequately to pharmacological and psychological interventions.

Significant Scientific Results

Fitzgerald, P. B., Hoy, K. E., Reynolds, J., Singh, A., Gunewardene, R., Slack, C., Ibrahim, S., & Daskalakis, Z. J. (2020). A pragmatic randomized controlled trial exploring the relationship between pulse number and response to repetitive transcranial magnetic stimulation treatment in depression. Brain Stimulation, 13(1), 145–152. https://doi.org/10.1016/j.brs.2019.09.001

Background: Repetitive transcranial magnetic stimulation treatment (rTMS) is an effective treatment for depression but the optimal methods of administration have yet to be determined. In particular, it is unclear whether there is a relationship between elements of the dose of stimulation (i.e., number of pulses) and clinical response. To address one aspect of dose, we conducted a trial comparing standard and high dose versions of high frequency left sided and low frequency right sided rTMS protocols (left standard = 50 trains, left high = 125 trains, right standard = 20 min, right high = 60 min, all per day in a single session).

Method: 300 patients with treatment resistant depression were enrolled in a four arm randomized controlled trial across a four week time period. The primary outcome assessment was a comparison of response and remission rates on data from the 17-item Hamilton Rating Scale for Depression Rating Scale (HRSD-17).

Results: The rate of response exceeded 45% in all groups. There was no significant difference between groups on initial analysis of the primary or secondary outcome measures (response rates: standard left = 52.5%, high left = 47.3%, standard right = 49.1%, high right = 48.4%). There was a greater remission rate with high compared to moderate dose left sided treatment when controlling for illness duration. We also found significant improvements in quality of life across all treatment groups. Illness duration was weakly associated with response.

Conclusions: There was no consistent association between the antidepressant effect of rTMS and the number of TMS pulses provided across the ranges investigated in this study. Increasing TMS pulse number in individual sessions seems unlikely to be a method to substantially improve clinical outcomes, and future research should explore alternative means of improving clinical response.

Significant Scientific Results

Cole, E. J., Stimpson, K. H., Bentzley, B. S., Gulser, M., Cherian, K., Tischler, C., Nejad, R., Pankow, H., Choi, E., Aaron, H., Espil, F. M., Pannu, J., Xiao, X., Duvio, D., Solvason, H. B., Hawkins, J., Guerra, A., Jo, B., Raj, K. S., ... Williams, N. R. (2020). Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. American Journal of Psychiatry, 177(8), 716–726. https://doi.org/10.1176/appi.ajp.2019.19070720

Objective: New antidepressant treatments are needed that are effective, rapid acting, safe, and tolerable. Intermittent theta-burst stimulation (iTBS) is a noninvasive brain stimulation treatment that has been approved by the U.S. Food and Drug Administration for treatment-resistant depression. Recent methodological advances suggest that the current iTBS protocol might be improved through 1) treating patients with multiple sessions per day at optimally spaced intervals, 2) applying a higher overall pulse dose of stimulation, and 3) precision targeting of the left dorsolateral prefrontal cortex (DLPFC) to subgenual anterior cingulate cortex (sgACC) circuit. The authors examined the feasibility, tolerability, and preliminary efficacy of Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), an accelerated, high-dose resting-state functional connectivity MRI (fcMRI)-guided iTBS protocol for treatment-resistant depression.

Methods: Twenty-two participants with treatment-resistant depression received open-label SAINT. fcMRI was used to individually target the region of the left DLPFC most anticorrelated with sgACC in each participant. Fifty iTBS sessions (1,800 pulses per session, 50-minute intersession interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold (adjusted for cortical depth). Neuropsychological testing was conducted before and after SAINT.

Results: One participant withdrew, leaving a sample size of 21. Nineteen of 21 participants (90.5%) met remission criteria (defined as a score <11 on the Montgomery-Åsberg Depression Rating Scale). In the intent-to-treat analysis, 19 of 22 participants (86.4%) met remission criteria. Neuropsychological testing demonstrated no negative cognitive side effects.

Conclusions: SAINT, an accelerated, high-dose, iTBS protocol with fcMRI-guided targeting, was well tolerated and safe. Double-blinded sham-controlled trials are needed to confirm the remission rate observed in this initial study.

Significant Scientific Results

Cole, E. J., Phillips, A. L., Bentzley, B. S., Stimpson, K. H., Nejad, R., Barmak, F., Veerapal, C., Khan, N., Cherian, K., Felber, E., Brown, R., Choi, E., King, S., Pankow, H., Bishop, J. H., Azeez, A., Coetzee, J., Rapier, R., Odenwald, N., … Williams, N. R. (2022). Stanford Neuromodulation Therapy(SNT):ADoubleBlindRandomizedControlledTrial.TheAmericanJournalofPsychiatry,179(2),132–141. https://doi.org/10.1176/appi.ajp.2021.20101429

Objective: Depression is the leading cause of disability worldwide, and half of patients with depression have treatment-resistant depression. Intermittent theta-burst stimulation (iTBS) is approved by the U.S. Food and Drug Administration for the treatment of treatment-resistant depression but is limited by suboptimal efficacy and a 6-week duration. The authors addressed these limitations by developing a neuroscience-informed accelerated iTBS protocol, Stanford neuromodulation therapy (SNT; previously referred to as Stanford accelerated intelligent neuromodulation therapy, or SAINT). This protocol was associated with a remission rate of ~90% after 5 days of open-label treatment. Here, the authors report the results of a sham-controlled double-blind trial of SNT for treatment-resistant depression.
Methods: Participants with treatment-resistant depression currently experiencing moderate to severe depressive episodes were randomly assigned to receive active or sham SNT. Resting-state functional MRI was used to individually target the region of the left dorsolateral prefrontal cortex most functionally anticorrelated with the subgenual anterior cingulate cortex. The primary outcome was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 4 weeks after treatment.
Results: At the planned interim analysis, 32 participants with treatment-resistant depression had been enrolled, and 29 participants who continued to meet inclusion criteria received either active (N=14) or sham (N=15) SNT. The mean percent reduction from baseline in MADRS score 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group.
Conclusions: SNT, a high-dose iTBS protocol with functional-connectivity-guided targeting, was more effective than sham stimulation for treatment-resistant depression. Further trials are needed to determine SNT's durability and to compare it with other treatments.

Significant Scientific Results

Aaronson, S. T., Carpenter, L. L., Hutton, T. M., Kraus, S., Mina, M., Pages, K., Shi, L., West, W. S., & Sackeim, H. A. (2022). Comparison of clinical outcomes with left unilateral and sequential bilateral Transcranial Magnetic Stimulation (TMS) treatment of major depressive disorder in a large patient registry. Brain Stimulation, 15(2), 326–336. https://doi.org/10.1016/j.brs.2022.01.006

Background: It has been suggested that sequential bilateral (SBL) TMS, combining high frequency, left dorsolateral prefrontal cortex (DLPFC) stimulation and low frequency, right DLPFC stimulation, is more effective than unilateral TMS.
Objective: To contrast treatment outcomes of left unilateral (LUL) and SBL protocols.
Methods: Registry data were collected at 111 practice sites. Of 10,099 patients, 3,871 comprised a modified intent-to-treat (mITT) sample, defined as a primary MDD diagnosis, age ≥18, and PHQ-9 completion before TMS and at least one PHQ-9 assessment after baseline. The mITT sample received high frequency (10 Hz) LUL TMS exclusively (N = 3,327) or SBL TMS in at least 90% of sessions (N = 544). Completers (N = 3,049) were responders or had received ≥20 sessions and had an end of acute treatment PHQ-9 assessment. To control for site effects, a Matched sample (N = 653) included Completers at sites that used both protocols. To control for selection bias, the SBL group was also compared to a Restricted LUL group, drawn from sites where no patient switched to SBL after substantial exposure to LUL TMS. Secondary analyses were conducted on CGI-S ratings.
Results: The LUL group had superior outcomes compared to the SBL group for multiple PHQ-9 and CGI-S continuous and categorical measures in the mITT, Completer and Matched samples, including in the specified primary analyses. However, outcome differences were not observed when comparing the Restricted LUL and SBL groups. Within SBL protocols, the LUL-RUL order had superior outcomes compared to the RUL-LUL order in all CGI-S, but not PHQ-9, measures.
Conclusions: While limited by the naturalistic design, there was no evidence that SBL TMS was superior to LUL TMS. The sequential order of RUL TMS followed by LUL TMS may have reduced efficacy compared to LUL TMS followed by RUL TMS.