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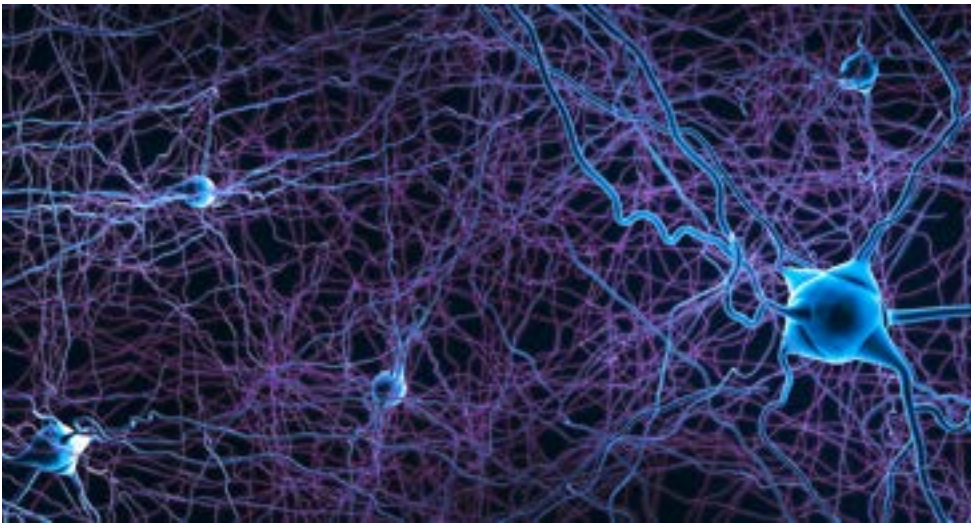
PULSE

A Monthly Update on Advances in Neuromodulation



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IN THIS ISSUE:

rTMS as a Superior Next-Step Treatment for Antidepressant Nonresponders

Collin Price, MD reviewing Dalhuisen, I et al., Am J Psychiatry 2024 Sep

In a multicenter, open-label RCT, rTMS demonstrated superior efficacy over a medication switch for moderate TRD after two failed antidepressant trials. The findings highlight rTMS as a viable next-step therapy in depression management algorithms.

TRD affects approximately one-third of patients diagnosed with MDD. While rTMS has demonstrated efficacy as a noninvasive treatment, its efficacy relative to pharmacological options has not been directly compared. This study sought to address this gap by comparing rTMS to an additional medication switch in patients unresponsive to at least two prior antidepressant trials.

This pragmatic, multicenter RCT enrolled 89 patients diagnosed with moderate-severe TRD (HAM-D >16), with failure to respond to at least two adequate antidepressant treatments, and a current depressive

episode lasting less than two years. Participants were randomized to either rTMS combined with psychotherapy and continued antidepressant use (if stable for at least six weeks) or a pharmacological switch following Dutch treatment guidelines, also combined with psychotherapy. The rTMS protocol consisted of 25 sessions of 3000 pulses at 10 Hz and 120% motor threshold targeting the left DLPFC, administered over five weeks. In the medication switch group, the most common new medications included venlafaxine (up to 300 mg/day) and mirtazapine (up to 45 mg/day). Both groups underwent manualized psychotherapy, emphasizing cognitive-behavioral techniques, delivered weekly for the study duration (8 weeks). Secondary outcomes included measures of anhedonia, anxiety, rumination, cognitive reactivity, and sleep disorders.

Patients receiving rTMS experienced significantly greater HAM-D reductions compared to those in the medication arm (mean reduction: 10.02 vs. 4.19; effect size = 0.77). A longitudinal linear mixed model revealed that while treatment, age, and gender did not independently predict changes in HAM-D scores, both time ($F=52.746$, $p<0.001$) and the interaction between time and treatment ($F=9.994$, $p=0.002$) were significant predictors of depression severity improvement. ITT response rates were higher in the rTMS group compared to the medication group (37.5% vs. 14.6%), as were remission rates (27.1% vs. 4.9%), with odds ratios favoring rTMS for both response (OR = 3.5) and remission (OR = 7.2). Kaplan-Meier analysis revealed faster median times to response (4.29 vs. 4.71 weeks; $\chi2=5.85$, $p=0.016$) and remission (4.47 vs. 4.93 weeks; $\chi2=7.88$, $p=0.005$) in the rTMS group. Secondary outcomes also favored rTMS, with significant reductions in anhedonia ($p=0.009$) and anxiety ($p=0.023$), while no significant differences were observed for rumination, cognitive reactivity, or sleep disorders. Baseline treatment expectancy was higher in the rTMS group ($p<0.001$), but not associated with baseline HAM-D; baseline expectancy was moderately correlated with HAM-D improvement ($r=-0.24$, $p=0.038$).

Impact: This pragmatic open-label RCT demonstrated that rTMS is a more effective next-step intervention than medication switching for TRD, supporting its role in treatment algorithms after two failed antidepressant trials. Secondary analyses suggest rTMS may specifically target anhedonia and anxiety, supporting symptom-focused treatment decisions. However, the open-label design and higher baseline treatment expectancy in the rTMS group, which correlated with improvement, introduce potential bias. The study's design also involved a shorter active treatment period for rTMS (5 weeks) than for the pharmacological switch (8 weeks), which reflects real-world practices but limits direct comparisons of sustained treatment effects. Despite limitations, these findings support earlier rTMS integration in TRD management. Further research should explore long-term efficacy, cost-effectiveness, and the feasibility of earlier incorporation into treatment algorithms.

Dalhuisen I, van Oostrom I, Spijker J, et al. rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches. Am J Psychiatry. 2024;181(9):806-814. doi:10.1176/appi.ajp.20230556

Accelerated iTBS Shows Rapid and Safe Efficacy for Bipolar Depression

Collin M Price, MD reviewing Sheline, YI et al. JAMA Psychiatry 2024 Sep

This sham-controlled RCT assessed the efficacy and safety of accelerated intermittent theta-burst stimulation (aiTBS) for treatment-resistant bipolar depression (BD). Active aiTBS significantly reduced depressive symptoms compared to sham stimulation, with no serious adverse events, including manic or hypomanic episodes. Findings highlight aiTBS as a promising neuromodulation therapy for BD, warranting further research to confirm long-term efficacy and explore its utility in broader populations.

Bipolar depression (BD) is an often-chronic condition marked by depressive episodes that are frequently resistant to standard treatments. rTMS, FDA-approved for treatment-resistant major depressive disorder (MDD), has shown mixed results in the treatment of BD. Accelerated protocols like Stanford Neuromodulation Therapy (SNT) aim to intensify stimulation schedules, achieving rapid symptom relief. This study examines neuronavigated of accelerated intermittent theta-burst stimulation (aiTBS) as a novel approach for BD.

In this double-blind, sham-controlled RCT, 24 participants diagnosed with Bipolar II (92%) or Bipolar I (8%) disorder were randomized to active (n=12) or sham (n=12) aiTBS. All participants had MADRS scores ≥20, were stabilized on mood stabilizers for at least four weeks, and had failed at least two antidepressant trials. Exclusion criteria included rapid cycling BD, other primary psychiatric diagnoses (e.g., personality disorders), or unstable medical conditions. The aiTBS protocol consisted of 10 sessions/day for five days (90,000 pulses total) at 90% RMT, targeting the left DLPFC at locations personalized based on resting-state fMRI connectivity with the subgenual ACC. The sham group received inactive aiTBS using the same double-sided Cool-B65 A/P coil, but only the sham side was activated, along with simultaneous cutaneous electric pulses to mimic active stimulation. Assessments occurred at baseline, during treatment, post-treatment (Day six), and at four-week follow-up. The primary outcome was MADRS score change.

MADRS scores fell from 30.4 (SD 4.8) to 10.5 (SD 6.7) in the active group, versus 28.0 (SD 5.4) to 25.3 (SD 6.7) in the sham group. The between-group difference was -14.75 (95% CI: -19.73 to -9.77, $p<0.001$, Cohen's $d = -2.19$). Half of the active group achieved remission (MADRS ≤10) compared to none in the sham group. Statistical models confirmed a significant group-time interaction ($F1,22 = 64.72$, $p<0.001$). No adverse events, including manic episodes, were reported. Blinding integrity was upheld, with treatment allocation guesses showing no significant differences between groups (data not shown).

Impact: This RCT highlights aiTBS as a safe and effective treatment for reducing depressive symptoms in treatment-resistant BD, particularly Bipolar II. The absence of manic or hypomanic episodes is encouraging, though notably only 8% of the study population were diagnosed with Bipolar I. While these findings are promising, the study's limited sample size and focus on Bipolar II patients necessitate further trials to assess long-term outcomes, safety in Bipolar I disorder, and comparisons with other neuromodulation and pharmacological treatments.

Sheline YI, Makhoul W, Batzdorf AS, et al. Accelerated Intermittent Theta-Burst Stimulation and Treatment-Refractory Bipolar Depression: A Randomized Clinical Trial [published correction appears in JAMA Psychiatry. 2024 Sep 1;81(9):948. doi: 10.1001/jamapsychiatry.2024.2327]. JAMA Psychiatry. 2024;81(9):936-941. doi:10.1001/jamapsychiatry.2024.1787

Scrambler Therapy Significantly Reduces Pain in Poststroke Patients

Mohamad Shamas, PhD reviewing Stowell-Campos R et al. Ann Clin Transl Neurol. 2024 Sep

This pilot RCT demonstrates that scrambler therapy (ST), a noninvasive transcutaneous electroanalgesia device, has the potential to reduce pain severity in poststroke pain syndromes. Patients receiving ST experienced substantial short-term improvements, with significantly greater reductions in pain scores compared to sham treatment, though long-term benefits were less pronounced.

Approximately 10% of strokes lead to chronic, severe pain, often referred to as poststroke, central, or thalamic pain syndromes, due to disruptions in sensory pathways. Traditional pain treatments for poststroke pain have variable efficacy, and finding an effective regimen is challenging due to side effects and poor adherence. Scrambler therapy (ST; also known as transcutaneous electrical modulation pain reprocessing) is a non-invasive, FDA-approved treatment that delivers electrical stimulation through the skin to "scramble" pain signals, aiming to alleviate chronic neuropathic pain. Could ST provide a novel and more effective solution for poststroke pain management?

This randomized, single-blind, sham-controlled study enrolled 20 adult participants with chronic contralesional pain following a stroke. Exclusion criteria included contraindications to ST (i.e., implanted electrical devices), recent myocardial infarction, uncontrolled epilepsy, and symptomatic brain metastases. Current medications were continued without adjustments, except for gabapentin, which was held prior to treatment to avoid interference with ST. Participants were randomized to receive either ST (n=10) or sham (n=10) stimulation for five consecutive 40-minute sessions, with pain scores assessed by blinded raters at baseline, before/after each session, and 4 weeks post-intervention. Electrode placement was based on the participant's pain area, with a maximum of 5 electrode pairs placed in the affected dermatomes and ongoing adjustments for irritation or reduced pain. Primary outcomes included changes in pain Numerical Rating Scale (0-10) from baseline to after visit 5, as well as the proportion of patients reporting ≥50% pain reduction. Participants in the ST group received full 40-minute treatments, while the sham group experienced a brief increase in intensity followed by no stimulation; treatment providers were not blinded to group allocation.

The average participant age was 60.0 years in the ST group and 56.9 years in the sham group, with an average time since stroke of 35.0 and 29.5 months, respectively. The ST group was 30% female and 30% Black, while the sham group was 70% female and 60% Black (p=0.074 for both group differences). At baseline, both groups had comparable pain scores (mean NRS - ST: 6.68, sham 5.73; p = 0.267). After five sessions, 70% of ST patients reported >50% pain reduction (mean decrease: 3.73 points, 56%), compared to 10% in the sham group (mean decrease: 0.94 points, 16%; p = 0.006). At the 4-week follow-up, the ST group maintained a significantly greater reduction in pain scores (mean decrease: 2.57 vs. 0.25; p = 0.004), with 80% of ST participants reporting ongoing improvement compared to 40% in the sham group (p = 0.068). However, clinical response rates (>50% pain reduction) were no longer significantly different between groups (ST: 30%, sham: 10%; p = 0.264).

Impact: The pilot RCT suggests that ST offers an effective acute and potentially long-term treatment for poststroke pain, providing a promising alternative to pharmacologic analgesia. This study highlights the promise of ST as an effective non-pharmacologic therapy for poststroke pain, with minimal side effects. However, the small sample size and limited follow-up necessitate larger trials to validate its short- and long-term efficacy.

Stowell-Campos R, Lawrence E, Marsh EB, Merbach D. Scrambler therapy for treatment of poststroke pain. Ann Clin Transl Neurol. 2024;11(11):2904-2911. doi:10.1002/acn3.52201

A Unified Metric to Enhance TMS Coil Placement Accuracy

Mohamad Shamas, PhD reviewing Numssen O, et al. Brain Stimul. 2024 August

This paper proposes the Pulsewise Coil Displacement (PCD) as a simple yet powerful metric that quantifies trial-to-trial and overall TMS coil placement accuracy. By integrating positional and rotational displacements into a single value, PCD facilitates precise tracking of stimulation quality without MRI data or complex simulations. This innovation could prove useful in both clinical and research domains.

TMS has seen significant methodological advancements to address variability within and between treatment sessions. However, a simple and practical metric to assess coil placement accuracy in real time has been lacking. Current methods rely on complex post-stimulation electric field simulations, which are computationally demanding and impractical for clinical use. The PCD measure is proposed as a practical solution to enable real-time, simple quantification of coil motion using standard neuronavigation data.

PCD quantifies TMS coil displacements at the level of individual pulses, bursts, or stimulation trains using neuronavigation tracking data available from all major systems. The PCD calculation works by comparing the coil's position at each pulse to a defined reference point, such as an optimized starting position or a functionally-defined placement. Positional shifts (in millimeters) are measured along three axes, while rotational changes (in degrees) account for yaw, pitch, and roll. These values are initially calculated separately, as their impact on coil-cortex distance depends on coil geometry and TMS parameters, and then combined into a single PCD score that reflects overall displacement. The overall goal is to reflect reductions in target stimulation relative to the optimal coil placement. To validate the PCD metric, researchers conducted virtual and in-human analyses.

Virtual validation involved simulation of 50,100 TMS coil placements using realistic random drifts to test how PCD correlates with changes in cortical stimulation strength. These simulations showed strong correlations between PCD and the strength of induced electric fields at the stimulation target (positional component r = -0.81; rotational component r: -0.21; p < 0.001). The combined PCD metric showed superior performance over standard Euclidean error methods, particularly in capturing off-target effects. Simulated motor evoked potentials (MEPs) were computed at motor threshold (MEPlow) and saturation levels (MEPhigh) to examine the relationship between PCD and simulated corticospinal responses. PCD exhibited strong correlations with displacement-dependent changes in MEPs (MEPlow: r = -0.62; MEPhigh: r = -0.77), although the effects of rotational displacements may be slightly underestimated due to model limitations. Human validation during a repetitive theta burst stimulation (cTBS) protocol showed that PCD successfully tracked coil stability across stimulation trains. By capturing displacements caused by subject motion or coil handling, PCD provided real-time feedback on stimulation accuracy, underscoring its practical utility for both research and clinical settings.

Impact: This study introduces a novel, easily computed metric (PCD) for quantifying TMS coil movement. By integrating positional and rotational displacements into a single metric, PCD offers a practical tool for monitoring coil stability, validated through simulations and preliminary real-world applications.

These findings suggest potential for improving reproducibility in TMS research and consistency in clinical applications. However, generalizability may be limited by a reliance on neuronavigation data (though no neuroimaging is required). Further research is needed to validate PCD across a broader range of protocols and populations, investigate its impact on clinical outcomes, and account for individual anatomical differences.

Numssen O, Martin S, Williams K, Knösche TR, Hartwigsen G. Quantification of subject motion during TMS via pulsewise coil displacement. Brain Stimul. 2024;17(5):1045-1047. doi:10.1016/j.brs.2024.08.009

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)