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# How does brain stimulation work? Neuroversion and other putative mechanisms of action

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# How does brain stimulation work? Neuroversion and other putative mechanisms of action

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# Editorial: How does brain stimulation work? Neuroversion and other putative mechanisms of action

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Editorial on the Research Topic
How does brain stimulation work? Neuroversion and other putative mechanisms of action

Brain stimulation is an evolving treatment modality with significant utility in the management of various psychiatric and neurological disorders. Historically, electroconvulsive therapy (ECT) is the oldest brain stimulation technique in psychiatry and served as the only available neuromodulation technique for several decades. Over the past 50 years, however, advances in the field have introduced several other brain stimulation techniques, including deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), and magnetic seizure therapy (MST). These techniques employ either electrical or electromagnetic stimuli to trigger neurochemical, electrophysiological, and neuroimmune changes in the brain that in turn lead to therapeutic effects (1–4). With the increasing use of these brain stimulation techniques and expanding research efforts to understand their mechanisms of action, our knowledge of how these treatments work continues to grow.

The Research Topic "How Does Brain Stimulation Work? Neuroversion and Other Putative Mechanisms of Action" brings together research on various approaches to brain stimulation that is expected to enrich the understanding of researchers and clinicians to stimulate further research and influence practice. This Research Topic includes 10 articles authored by 76 authors covering a broad range of brain stimulation techniques, including ECT, tDCS, rTMS, DBS, and theta burst stimulation (TBS) in various neuropsychiatric disorders. Of the 10 articles, four are case reports and the remaining six are original research, including two clinical trials.

In a case report, Katzell et al. discussed the use of ECT in a patient with refractory status epilepticus on VNS. This patient had a history of developmental delay, and traumatic brain injury with subsequent sequelae of hygroma, which resulted in the development of progressive aphasia, status epilepticus, and a deteriorating sensory level. The patient received right anterior, and left temporal (RALT) ECT followed by sessions of bitemporal ECT, with no improvement in status epilepticus. In another case report, Katzell et al. reported on the beneficial role of ECT in the treatment of Neuroleptic Malignant Syndrome (NMS). Another prospective study investigated a potential therapeutic mechanism of ECT (Erchinger et al.). The levels of brain N-acetyl aspartate were temporarily reduced following ECT in patients with moderate to severe depression and normalized within six months following ECT. Deep brain stimulation was used in the management of a patient with intractable obsessive-compulsive disorder (OCD) in a case study by Beydler et al. In this case study a 58-year-old woman with childhood-onset OCD who did not respond to trials of serotonergic medications, psychotherapy, or even ECT was treated with DBS targeting the anterior limb of the internal capsule and nucleus accumbens. The patient showed significant improvement following DBS.

Another case report by Beydler et al., discussed the role of high-frequency rTMS in the management of a mixed affective state. The patient was a 68 year-old woman, who did not respond to adequate trials of multiple mood stabilizers and antipsychotic medications. She received nine sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex at 120% of motor threshold (MT), with significant improvement in the affective symptoms. Senczyszyn et al., conducted a pilot randomized controlled trial by using rTMS in older adults with mild cognitive impairment. Patients with mild cognitive impairment receiving high-frequency rTMS alone or in combination with computer-based cognitive rehabilitation showed significant improvement in their overall cognitive function. Zhang et al. conducted a randomized crossover study involving 20 young healthy adults who received single sessions of intermittent theta burst stimulation (iTBS) at serially increasing MTs (50%, 70%, or 100%) on separate occasions with serial monitoring of brain physiology by using functional near-infrared spectroscopy (fNIRS). A U-shaped response (non-linear) was found between the change in MT and prefrontal hemodynamic changes following iTBS intervention. Quinn et al. also evaluated the role of iTBS delivered in an accelerated fashion over the right dorsolateral prefrontal cortex in late-life depression. A positive correlation was found between the electric field over the ventrolateral prefrontal cortex and the antidepressant effect, whereas a negative correlation was found between the posterior dorsolateral prefrontal cortex and the antidepressant effect.

Isik et al. explored the combination of tDCS with auditory stimulation to test the entrainment of frontal alpha activity during interventions under general anesthesia. Although the intervention was found to be safe and feasible, it was not found to increase alpha power. Lee et al. used tDCS in the treatment of bipolar depression as an adjuvant treatment modality in the home setting. This randomized controlled trial did not find any superiority of active tDCS over sham tDCS in the management of bipolar depression.

Overall, this Research Topic highlights the diverse applications of brain stimulation techniques and the emerging evidence supporting their benefits. As the research in this field advances, these findings will help refine clinical practice and stimulate further investigation into the mechanisms underlying brain stimulation therapies.

## Author contributions

SK: Writing – original draft. AS: Writing – review & editing. ML: Writing – review & editing. ZD: Writing – review & editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Efficacy and safety of daily home-based transcranial direct current stimulation as adjunct treatment for bipolar depressive episodes: Double-blind sham-controlled randomized clinical trial

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**Background:** Although transcranial direct current stimulation (tDCS) is known to be a promising therapeutic modality for unipolar depression, the efficacy and safety of tDCS for bipolar depressive episodes (BD) are still unknown and clinical trials of home-based tDCS treatment are scarce. As a result, we set out to investigate the efficacy and safety of home-based tDCS for the treatment BD.

**Methods:** Participants ($n$ = 64), diagnosed as bipolar disorder as per the diagnostic and statistical manual of mental disorders (DSM-5), were randomly assigned to receive tDCS. Hamilton Depression Rating Scale (HDRS-17) scores were measured at the baseline, week 2, 4, and 6, and home-based tDCS (for 30 min with 2 mA) was self-administered daily.

**Results:** Of the 64 patients (15.6% bipolar disorder I, 84.4% bipolar disorder II), 41 patients completed the entire assessment. In the intention-to-treat analysis, time-group interaction for the HDRS-17 [$F_{(3,\ 146.36)}$ = 2.060; $p$ = 0.108] and adverse effect differences between two groups were not statistically significant, except the pain score, which was higher in the active group than the sham group (week 0–2: $p < 0.01$, week 2–4: $p < 0.05$, and week 4–6: $p < 0.01$).

**Conclusion:** Even though we found no evidence for the efficacy of home-based tDCS for patients with BD, this tool was found to be a safe and tolerable treatment modality for BD.

**Clinical trial registration:** [https://clinicaltrials.gov/show/NCT03974815], identifier [NCT03974815].

KEYWORDS

**bipolar depressive episodes, transcranial direct current stimulation, clinical trial, double-blind, efficacy, safety**

## Introduction

Bipolar disorder is a chronic and severe mental illness (1), In bipolar disorder depressive episodes are more chronic and more common than (hypo) manic episodes (2). Pharmacological treatments are standard for bipolar depressive episodes (BD), but they have limitations such as inadequate efficacy and common adverse effects (AE) that include sedation, weight gain, and teratogenicity (3). Moreover, few pharmacological treatments have proven to be highly and consistently effective in BD (4). Due to these limitations there is increasing interest in non-pharmacological approaches that encompass cognitive-behavioral therapy, psychoeducation, family-focused interventions, and neuromodulation. Transcranial direct current stimulation (tDCS) is a non-invasive form of treatment that involves application of a very low amplitude (1–3 mA) direct electrical current to the scalp (3) and an alternative therapeutic option to other neuromodulation modalities such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS). Given the necessity of hospitalization and anesthesia associated with ECT, the high cost, and risk of seizures associated with rTMS (5) tDCS is more tolerable for patients (6). Furthermore, the frequency of AEs seems to be low for tDCS (7 ).

Recent meta-analyses (8, 9) have suggested that tDCS is effective for treating unipolar depression. Moreover, double-blind randomized clinical trials (RCTs) (10, 11) and a meta-analysis (12) have reported that tDCS is an effective and safe augmentation option for BD. These results show the benefits of tDCS in the context of BD. However, in real-world situations, the traditional tDCS setting has drawbacks such as requiring daily visits to the hospital, transportation costs, disruption of daily activities, and work schedules, which decrease patient compliance (13). Thus, home-based tDCS was designed to address these limitations (14) and no critical side effects have been revealed to date (15). However, research on the efficacy and safety of home-based tDCS in patients with BD is lacking.

Therefore, we aimed to examine the efficacy and safety of home-based tDCS for treating BD. We conducted a randomized sham-controlled double-blind clinical trial involving participants in a home-based setting for 6 weeks. As evaluated by changes in the 17-item Hamilton Depression Rating Scale (HDRS-17) scores after 6 weeks of treatment, we hypothesized that active tDCS would have larger antidepressant effects than sham tDCS. We also hypothesized that tDCS would significantly alleviate depression symptoms, as defined by other efficacy measures, and that AE rates would be comparable in both groups.

## Patients and methods

The study was conducted at the Seoul National University Bundang Hospital, from July 2019 to May 2021. The study used a parallel design in which 64 patients were randomly assigned, by a computer-generated list using random block sizes, to the sham or the active tDCS group. The research protocol was approved by the Seoul National University Bundang Hospital Institutional Review Board and registered with ClinicalTrials.gov (NCT03974815, https://clinicaltrials.gov/show/NCT03974815). Written informed consent was obtained from all the participants. The study followed the ethical principles of the Declaration of Helsinki.

### Participants

Participants were recruited by physician referrals and in-hospital poster advertisements. They were pre-screened via in-person interviews, and those who met the general criteria were subjected to additional screening. All participants were screened by trained, board-certified psychiatrists who used the modified Mini-International Neuropsychiatric Interview (16) to diagnose BP (type I or II) in a major depressive episode.

To be included in the study, patients had to be between 19 and 65 years of age and have active symptoms of a current depressive episode [4 or more on the Clinical Global Impression Severity of Bipolar Scale (CGI—BP)] (17). We included

patients taking mood stabilizers (lithium, divalproex, or lamotrigine) for at least 4 weeks before the day of screening. We considered the first-, second-, or third-line pharmacotherapies for adequate pharmacologic intervention in accordance with the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2018 bipolar guidelines (18). Quetiapine, lithium, lamotrigine, valproate sodium, aripiprazole adjuvant therapy, carbamazepine, and venlafaxine adjuvant therapy were considered valid for bipolar I and II depressive episodes. In addition to patients treated with the CANMAT first-, second-, or third-line pharmacotherapies, those treated with propranolol, gabapentin, olanzapine, quetiapine, risperidone, ziprasidone, amisulpride, aripiprazole, clozapine, or benzodiazepines were also included according to their AE profile or symptomatology.

The study excluded individuals with a history of neurological disease, intellectual disability, cognitive impairment (inability to understand instructions or operate equipment), or those with a high risk of suicide that required hospitalization. Those who had metal equipment, coils, and electronic devices (such as cochlear implants or heart pacemakers) were also excluded. We also excluded those who had dermatological problems, such as an allergic skin reaction on the location of the electrodes. Women of childbearing potential who did not agree to use the medically permitted methods of contraception (such as barrier contraceptives, oral contraceptives lasting for at least 3 months, injection or insertion contraceptives, intrauterine contraceptives) for up to 24 weeks after using the tDCS medical device were also excluded.

Patient losses occurred if (1) they did not visit the hospital at weeks 2, 4, or 6; (2) compliance was less than 60%; (3) during the trial, there were serious clinical or psychiatric problems, such as suicide attempt/ideation or full-blown manic or hypomanic episodes; (4) patients were excluded for safety reasons, such as a significant worsening of their psychiatric condition or serious AEs; or (5) they withdrew their participation voluntarily.

## Intervention

Patients used a tDCS stimulation device at home and were trained to use it sufficiently by the research personnel. The tDCS procedure was performed using MINDD STIM (Ybrain Inc., Seoul, South Korea). This equipment can provide information about and when the patient applies the device and for how long. Patients were instructed to use the device within 2 h of setting it up. The anode and cathode were used for delivering electrical stimulation. Patients attached 28.26 $cm^2$ round electrodes, a montage known as the "bifrontal" setup (F3-Anode, F4-Cathode) that had been previously used in a major depression trial (19). The anode and cathode electrodes were placed over the left and right DLPFC, respectively. All patients read the instructions with the researcher and watched videos related to how to use the tDCS so that they could learn how to use the tDCS. In addition, when the first stimulation was performed at the hospital, the researcher confirmed with the patient whether they could use the device correctly on their own. When patients had any questions about how to use the device, they were able to contact the researcher, and they resolved their difficulties in using the device through voice or video calls. All patients were retrained on how to use it at each visit, and they were able to ask any questions they had about how to use the tDCS.

For up to 42 sessions, tDCS was applied for 30 min daily. For the verum tDCS condition, a constant current of 2 mA was delivered for 29 min with additional ramp-up and ramp-down phases of 30 s each at the beginning and the end of the session, respectively. For the sham tDCS condition after 30 s of ramp-up and 30 s of ramp-down, the device was turned off. Patients were asked to report any discomfort, including adverse events, on the list provided at enrollment. In addition, every time the patient visited the hospital, we inquired about any tDCS-related discomfort and pain during the tDCS usage by using Numeric Rating Scale. Neither the researcher nor the patient knew which stimulus-set tDCS they received until the end of the study to prevent researcher expectancy response bias. The appearance of the tDCS was the same, but the stimuli for each group were different, and neither the researcher nor the patient knew the difference.

Using the information recorded in the smartphone application connected to the tDCS, the researchers were able to confirm whether the participants completed the 30-min sessions. When participants were in an environment with no smartphone internet connection, a diary was created and confirmed.

## Outcomes

All the evaluations were carried out by the blinded researchers. Participants were evaluated at baseline, week 2, week 4, and week 6 of the study. At baseline, and weeks 2, 4, and 6, adverse events were documented. The primary outcome was the change in the HDRS-17 (20) score between groups over time. The secondary outcomes included (1) changes in the Hamilton Anxiety Rating Scale (HAM-A) (21), Young Mania Rating Scale (YMRS) (22), CGI-BP (17), and Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (QLESQ-SF); (2, 23) the AE rates. The summary of intervention and measurement periods are presented in **Supplementary Table 1**.

## Statistical analyses

All statistical analyses were performed using R, version 4.0.5 (lme4 package; R Foundation, Vienna, Austria). The sample size was estimated at a power of 80% and a two-tailed α level of 5%. Based on a previous study evaluating the efficacy of

tDCS in BD (10) we obtained a sample size of 56 participants. Assuming an attrition rate of 15%, we obtained a total sample size of 64 participants. We performed an intention-to-treat analysis. Differences in the baseline clinical and demographic variables of the groups were analyzed using *t*-tests or $\chi^2$-tests for continuous and categorical variables, respectively. The Wilcoxon rank sum test was also used for non-parametric data. The primary outcome was analyzed with a linear mixed-effect model incorporating group (two levels: active and sham) and time (four levels: baseline, weeks 2, 4, and 6), as well as their interaction, as independent variables, and the participant as a random-effects variable. The HDRS-17 score served as the dependent variable in the model. We also performed subgroup analyses based on bipolar type (I or II), sex, age ($<40$ or $\geq 40$), HDRS-17 score ($\leq$median or $>$ median), HAM-A score ($\leq$median or $>$ median), and medication usage (lithium, valproic acid). The potential confounding variables, including age, sex, diagnosis (bipolar I or II), current episode duration, and baseline HDRS-17 score were adjusted. Considering the regularity of the test intervals (2 weeks), an autoregressive covariance structure was assumed as the working correlation matrix. The main hypothesis was that there would be a significant interaction between time and group, with active tDCS outperforming the sham over time. The frequencies of AEs at weeks 2, 4, and 6 were compared between the groups using Fisher's exact test.

# Results

## Participants

The clinical and demographic characteristics of the patients are presented in **Table 1**. Of the 64 patients, 47 (73.4%) were women. The mean [standard deviation (SD)] age was 33.4 years (12.6 years). The proportion of patients with bipolar I disorder was 15.6%. The study flow chart is shown in **Figure 1**. Of the 64 patients included, 41 (19 in the active group and 22 in the sham group) received full 30-min tDCS sessions ranging from 18 to 42 days (mean = 38.00, SD = 4.69) and completed the final assessment. Thirteen patients were lost in the active group (8 under 60% compliance, 3 withdrawals, 1 due to participant's request, and 2 due to AE) and 10 patients were lost in the sham group (7 under 60% compliance, 1 non-compliance with the treatment procedure, 1 withdrawal due to participant's request, and 1 adverse effect).

## Integrity of blinding

There was no significant difference between the active and sham groups in relation to the likelihood of correctly guessing to which group they were assigned to ($\chi^2 = 0.065$, $p = 1.000$, 54.8 and 51.6% in the active and sham groups, respectively). Therefore, we assumed that the participants were unable to infer their actual groupings.

## Primary and secondary outcomes

The primary outcome was changes in the HDRS-17 scores. The linear mixed model analysis showed that there was no significant time-group interaction for the HDRS-17 score [$F_{(3,\ 146{\cdot}36)} = 2.060$; $p = 0.108$] (**Figure 2**). We also did not find a significant time-group interaction for the HDRS-17 score in the subgroup analysis (**Supplementary Table 2**). There were no significant time-group interactions between the other secondary outcomes (**Supplementary Table 3**).

## The frequencies of adverse effects in the groups were compared

The frequencies of all AEs were not significantly different. There were no treatment-emergent affective switch (TEAS) episodes during the trial (**Table 2**). We also examined suicidal ideation, aggressive behavior, and elated mood as side effects. Four participants reported suicidal ideation during weeks 2–4 and 4–6, and one participant reported an episode of aggressive behavior during weeks 4–6. The frequency of these events did not differ for the active and sham groups ($p > 0.99$ for suicidal ideation at weeks 2–4 and 4–6; $p = 0.47$ for aggressive behavior at weeks 4–6). The pain score was significantly higher in the active group than in the sham group during weeks 0–2 ($p < 0.01$), 2–4 ($p < 0.05$), and 4–6 weeks ($p < 0.01$).

# Discussion

In this study, we found that the active tDCS group did not show symptomatic improvement superior to that of the sham tDCS group. The frequency of AE did not differ in the active tDCS and sham groups. Tolerability was consistent with previous studies (10, 24, 25). Those who received tDCS reported significantly higher pain scores than the sham group during weeks 0–2, 2–4, and 4–6. However, the average pain score of the active tDCS group was 2.10 on a 10-point Likert scale, which indicated tolerability.

Our findings for efficacy were in contrast with those of previous double-blind RCT studies (10).

A previous study reported that active tDCS had superior symptomatic improvement than sham tDCS, based on the HDRS-17 scores. Two other studies that used small-sized open-label designs and involved patients with unipolar and BD reported that tDCS is efficacious for depressive symptoms (26, 27). One possible explanation for the lack of efficacy in our

TABLE 1 Clinical and demographic characteristics of the study sample at baseline.

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Sham (*n* = 32) | Active (*n* = 32) | Total (*n* = 64) |
| **Demographics** | | | |
| Women | 24 (75.0) | 23 (71.9) | 47 (73.4) |
| Age, mean (*SD*), years | 31.16 (11.9) | 35.66 (13.1) | 33.41 (12.6) |
| Years at school, mean (*SD*) | 13.72 (2.3) | 14.16 (2.5) | 13.94 (2.4) |
| Employed | 11 (34.4) | 16 (50.0) | 27 (42.2) |
| Married | 6 (18.8) | 9 (28.1) | 15 (23.4) |
| BMI, mean (*SD*) | 23.83 (3.2) | 24.00 (3.6) | 23.91 (3.4) |
| **Clinical characteristics** | | | |
| Onset age, mean (*SD*), y | 19.69 (8.8) | 22.00 (7.6) | 20.84 (8.2) |
| **Bipolar disorder** | | | |
| Type I | 5 (15.6) | 5 (15.6) | 10 (15.6) |
| Type II | 27 (84.4) | 27 (84.4) | 54 (84.4) |
| Previous episodes, mean (*SD*), No. | 12.50 (11.7) | 12.69 (14.3) | 12.59 (12.9) |
| Current episode duration > 12 months | 9 (28.1) | 13 (40.6) | 22 (34.4) |
| Severe depression | 27 (84.4) | 29 (90.6) | 56 (87.5) |
| Generalized anxiety disorder | 21 (65.6) | 16 (50.0) | 37 (57.8) |
| Panic disorder | 17 (53.1) | 16 (50.0) | 33 (51.6) |
| Social anxiety disorder | 7 (21.9) | 7 (21.9) | 14 (21.9) |
| Any anxiety disorder | 4 (12.5) | 2 (6.3) | 6 (9.4) |
| **Pharmacotherapies in the present episode** | | | |
| First-line treatments being used, mean (SD), no.[†] | 2.03 (0.7) | 1.84 (0.8) | 1.94 (0.7) |
| **Antidepressant drugs** | | | |
| SSRIs | 4 (12.5) | 3 (9.4) | 7 (10.9) |
| Venlafaxine | 1 (3.1) | 1 (3.1) | 2 (3.1) |
| Bupropion | 2 (6.3) | 0 | 2 (3.1) |
| **Mood stabilizers**[‡] | | | |
| Lithium | 29 (90.6) | 26 (81.3) | 55 (85.9) |
| Valproate | 12 (37.5) | 12 (37.5) | 24 (37.5) |
| Lamotrigine | 17 (53.1) | 14 (43.8) | 31 (48.4) |
| Carbamazepine[§] | 0 | 1 (3.1) | 1 (1.6) |
| **Antipsychotics** | | | |
| Quetiapine | 19 (59.4) | 19 (59.4) | 38 (59.4) |
| Olanzapine | 4 (12.5) | 3 (9.4) | 7 (10.9) |
| Clozapine | 5 (15.6) | 3 (9.4) | 8 (12.5) |
| Aripiprazole | 11 (34.4) | 10 (31.3) | 21 (32.8) |
| Risperidone | 6 (18.8) | 2 (6.3) | 8 (12.5) |
| Other SGAs[‡‡] | 2 (6.3) | 10 (31.3) | 12 (18.8) |
| **Other treatments** | | | |
| Benzodiazepines[¶] | 8 (25.0) | 3 (9.4) | 11 (17.2) |
| Other anticonvulsants[††] | 6 (18.8) | 4 (12.5) | 10 (15.6) |

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); No., number; SD, standard deviation; SGAs, second-generation antipsychotics; SSRIs, selective serotonin reuptake inhibitors. [†]First-line treatment for bipolar depressive episode per 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines. [‡]Recommended for bipolar depression treatment. [§] Third-line treatment for bipolar depressive episode per 2018 CANMAT guidelines. [¶] Clonazepam, lorazepam, alprazolam, and etizolam. [††]Gabapentin and topiramate. [‡‡]Ziprasidone and amisulpride.

study could be the different inclusion criteria that allowed for the concurrent use of medication. In our study, all patients were on at least one mood stabilizer during the study period. Mood stabilizers such as lithium, valproic acid, and lamotrigine can modulate cortical excitability, the mechanism associated with voltage-gated sodium channels (28, 29). Lithium selectively inhibits the function of voltage-gated sodium channels (30), and anticonvulsant-based mood stabilizers also target voltage-gated sodium channels (31, 32). This blockade of voltage-gated sodium leads to reduced neuronal excitability (33). Reduced cortical excitability may be associated with a poorer antidepressant response for tDCS (34–36). Another possible explanation for the discrepancy could be the significantly lower usage of antidepressant medications than in previous studies (10, 26, 27). No participants in our study were receiving antidepressant monotherapy. In addition,

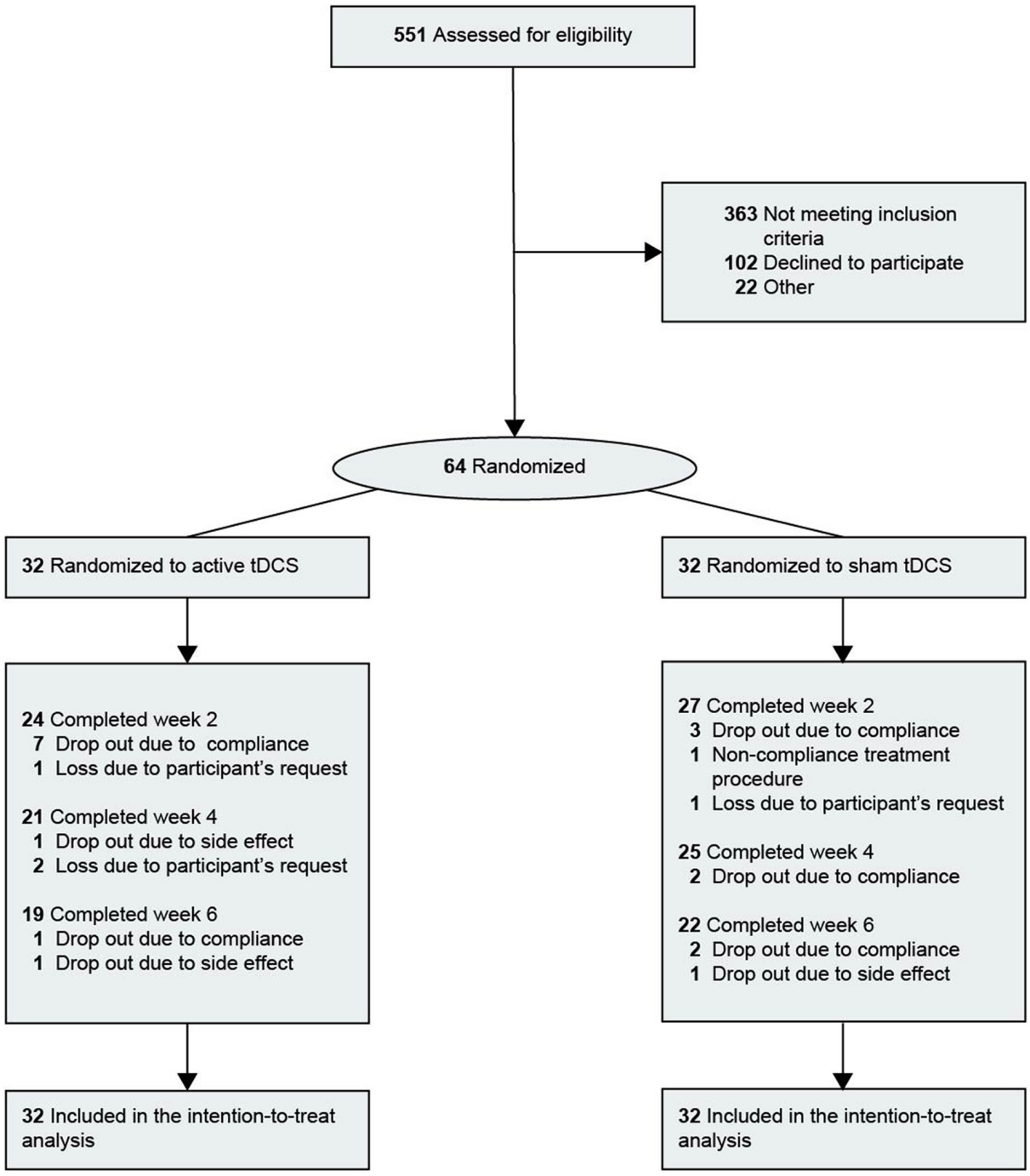


FIGURE 1
Flow diagram of participant selection. Ten participants were lost in the sham group and 12 participants were lost in the active group. tDCS, transcranial direct current stimulation.

only a few patients were prescribed antidepressants along with mood stabilizers (17.2%). Nitsche et al. (37) reported that enhancing serotonergic activity increases and prolongs facilitatory plasticity and converts the inhibitory plasticity into facilitation. Thus, enhancing the serotonergic activity of antidepressants may enhance the plasticity effect of tDCS (37), which may affect the efficacy of tDCS. In clinical practice, most guidelines (18, 38, 39) recommend combination therapy with mood stabilizers or antipsychotics rather than antidepressant monotherapy for BD. Therefore, our study design reflects the

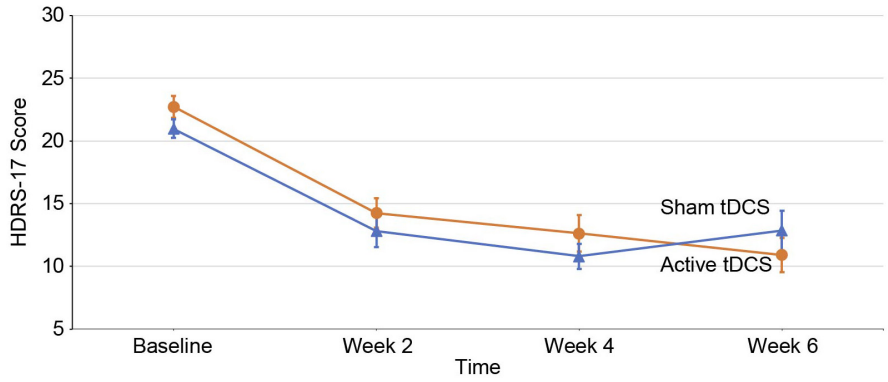


FIGURE 2
Changes in depression scores over time. Mean changes in 17-item Hamilton Depression Rating Scale (HDRS-17) scores (intention-to-treat analysis) from baseline to endpoint. Error bars indicate 1 standard error. The X-axis represents the hospital visit date and the Y-axis represents the HDRS-17 score evaluated for that week. tDCS, transcranial direct current stimulation.

TABLE 2 Frequency of adverse events and mean score of pain and discomfort[†].

| Adverse event | Weeks 0–2 | | | Weeks 2–4 | | | Weeks 4–6 | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. (%) | | *P*-value[‡] | No. (%) | | *P*-value[‡] | No. (%) | | *P*-value[‡] |
| | Sham (*n* = 27) | Active (*n* = 24) | | Sham (*n* = 25) | Active (*n* = 24) | | Sham (*n* = 23) | Active (*n* = 20) | |
| Headache | 1 (3.7) | 0 (0.0) | >0.99 | – | – | – | – | – | – |
| Neck pain | – | – | – | – | – | – | – | – | – |
| Tingling | 2 (7.4) | 2 (8.3) | >0.99 | 1 (4.0) | 4 (16.7) | 0.19 | 2 (8.7) | 4 (20.0) | 0.39 |
| Itching | – | – | – | – | – | – | – | – | – |
| Burning | – | – | – | 0 (0.0) | 1 (4.2) | 0.49 | – | – | – |
| Skin redness | 0 (0.0) | 2 (8.3) | 0.22 | – | – | – | – | – | – |
| Sleepiness | – | – | – | – | – | – | – | – | – |
| Trouble concentrating | – | – | – | – | – | – | – | – | – |
| Fatigue | – | – | – | – | – | – | – | – | – |
| Nausea | – | – | – | – | – | – | – | – | – |
| Dizziness | – | – | – | – | – | – | 0 (0.0) | 1 (5.0) | 0.47 |
| Suicidal ideation | – | – | – | 1 (4.0) | 1 (4.2) | >0.99 | 1 (4.3) | 1 (5.0) | >0.99 |
| Aggressive behavior | – | – | – | – | – | – | 0 (0.0) | 1 (5.0) | 0.47 |
| Skin color | – | – | – | – | – | – | 0 (0.0) | 1 (5.0) | 0.47 |
| Elated mood | – | – | – | – | – | – | – | – | – |
| TEAS episode | – | – | – | – | – | – | – | – | – |
| Pain (10-point Likert scale) and discomfort score (4-point Likert scale) | | | | | | | | | |
| | Sham (*n* = 27) | Active (*n* = 24) | *P*-value[‡] | Sham (*n* = 25) | Active (*n* = 23) | *P*-value[‡] | Sham (*n* = 22) | Active (*n* = 20) | *P*-value[‡] |
| Pain score, mean (*SD*) | 1.39 (1.1) | 2.38 (1.2) | 0.004 | 1.17 (1.0) | 1.97 (1.5) | 0.03 | 0.96 (0.7) | 1.96 (1.4) | 0.006 |
| Discomfort score, mean (*SD*) | 0.85 (0.5) | 0.92 (0.3) | 0.58 | 0.79 (0.4) | 0.83 (0.4) | 0.76 | 0.72 (0.5) | 0.79 (0.4) | 0.64 |

NA, not applicable; TEAS, treatment-emergent affective switch. [†]Adverse events were assessed using an adverse effects questionnaire. During transcranial direct current stimulation (tDCS) application, all participants were asked to complete this questionnaire daily, describing the presence of an adverse event. [‡]*P*-values were determined using $\chi^2$ or Fisher's exact test and independent *t*-test or Wilcoxon rank-sum test. One sham-allocated participant did self-harm and concluded not related to tDCS application. Two active-allocated participants who reported suicidal ideation discontinued the further study.

clinical guidelines for BD. However, our study did not directly compare the antidepressant use and non-use groups; therefore, further research is needed. A third possible explanation for the lack of efficacy in our study could be the variable response to the sham condition. A single-blind parallel tDCS study (40) for healthy participations suggested that sham conditions previously assumed to be inactive may alter neuronal function. A systematic review (41) of tDCS for depression showed that the sham response in tDCS depression trials was large. The possibility that the sham conditions of 30 s of ramp-up and 30 s of ramp-down may have had a stimulation effect cannot be excluded.

The tolerability results of tDCS in our study were consistent with those of other studies (10, 24, 25), that reported no significant difference in AEs between the active and sham groups. Another systematic review (42) of tDCS did not have conclusions for tolerability, not because of AEs, but most involved studies did not report adequate AEs. Four patients reported suicidal ideation. The number of occurrences was equal in active and sham groups. There was no occurrence of TEAS, including manic switching or suicidal attempt, which is a concern when treating BD (43–45). This finding is similar to the outcome of previous studies (10, 26, 27) even though our study participants received more frequent stimulation [up to 42 times compared to 30 of previous studies (10, 26, 27)]. These AE findings postulate the tolerability of tDCS for BD.

Similar to the primary outcome results, the active tDCS group did not show a significant difference from the sham group for the secondary outcomes. Although previous double-blind RCTs (10) reported no significant difference in CGI-BP scores between the active and sham groups, few studies have reported on YMRS, Q-LES, and HAM-A for BD. A randomized controlled study (46) reported no improvement in the HAM-A scores in patients with generalized anxiety disorder using tDCS. No significant difference in the YMRS scores between the active and sham groups seems to support the safety of tDCS for BD related to manic switch (47). We performed subgroup analysis and found no significant results within each group. However, these results should be interpreted with caution due to the limited sample size.

There have been three home-based tDCS studies, one for major depressive disorder (48), chronic stroke (49), and Alzheimer's dementia (50), but none have examined tDCS for BD. In our study, 8 participants in the active group (25.0%) and 7 participants in the sham group (21.9%) dropped out due to low compliance. The dropout rate in our study was higher than previous studies on chronic stroke (49) and Alzheimer dementia (50). One major difference is that caregivers applied tDCS in these previous studies, whereas in our study, patients applied tDCS on themselves. Moreover, the requirement to apply the device over the weekend might have also decreased the compliance in our study. Comparing previous RCT studies for tDCS in patients with mood disorder (10, 26, 27), the dropout rate in our study was comparable. These results suggests that home-based tDCS is feasible and applicable in outpatient and home-based settings.

This is the first study of home-based tDCS for BD patients, and it suggests the safety and tolerability of tDCS for BD, even with a relatively high number of stimulations. Furthermore, we monitored compliance not only by self-report but also with smartphone data, which improved the reliability of the compliance rate. In addition, this study was a double-blind RCT, and the integrity of blinding was adequate.

This study had several limitations. First, the fact that each participant was on different medications could have affected the efficacy of tDCS. Allowing various medications such as mood stabilizers, benzodiazepines, antipsychotics, and antidepressants may have made it difficult to examine the efficacy of tDCS. Future clinical trials that restrict medication variance and medication subgroup analyses are required. Second, this study was conducted in single-center with a limited sample size. There is a need for large samples and multicenter home-based clinical trials to investigate the efficacy of home-based tDCS. The study also unexpectedly revealed a dropout rate of 25% in the active group due to restrictions on distance movement restrictions implemented during the COVID-19 pandemic. Although there were high drop out rates and no positive association between tDCS and efficacy in our sample size, our study results suggested the directions of future studies as an exploratory study. Third, the sham condition designed to maintain the integrity of blinding had minimal electrical stimulation, so this may have affected the efficacy analysis. It may be necessary to develop a sham condition without electrical stimulation while maintaining the integrity of blinding. In addition, we verified the patients' compliance but could not confirm whether the patient used the device correctly at home, which is a major weakness of home-based device designed study. In order to compensate for this limitation, this study allowed enough time for device education in order for patients to use the tDCS by themselves through researcher's demonstration and watching videos of handling the device. This device education was focused on how the patients could correctly position the electrodes, and this training sessions were held multiple times on the patients' visit whenever it was necessary. Further studies will still need to check patients' compliance, but will need sophisticated systems to check whether patients use the tDCS as the suggested directions.

## Conclusion

tDCS was not proven effective but was found to be both tolerable and safe in this home-based trial conducted for patients

with bipolar I or II disorders. The negative results of our study should be re-examined in further studies with larger samples.

## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board, Seoul National University Bundang Hospital (E-1902-523-002). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

WM and TH had full access to all the data in the study and took responsibility for the integrity of the data, the accuracy of the data analysis, contributed to concept and design, critical revision of the manuscript for important intellectual content, and supervision. CL, YJ, YP, and HY were involved in data acquisition. JL, CL, YJ, and JSY drafted the manuscript. CL and EJ contributed to statistical analysis. WM obtained the funding. All authors who met authorship criteria were listed as authors, and certify that they participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript and contributed to interpretation of data and writing of the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.969199/full#supplementary-material

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# Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study

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**Introduction:** Intermittent theta-burst stimulation (iTBS) is a non-invasive brain stimulation paradigm that has demonstrated promising therapeutic benefits for a variety of neuropsychiatric disorders. It has recently garnered widespread favor among researchers and clinicians, owing to its comparable potentiation effects as conventional high-frequency repetitive transcranial magnetic stimulation (rTMS), but administered in a much shorter time frame. However, there is still a lack of agreement over the optimal stimulation intensity, particularly when targeting the prefrontal regions. The objective of this study was to systematically investigate the influence of different stimulation intensities of iTBS, applied over the left dorsolateral prefrontal cortex (DLPFC), on brain activity and executive function in healthy adults.

**Methods:** Twenty young healthy adults were enrolled in this randomized cross-over experiment. All participants received a single session iTBS over the left DLPFC at intensities of 50, 70, or 100% of their individual resting motor threshold (RMT), each on separate visits. Functional near-infrared spectroscopy (fNIRS) was used to measure changes of hemoglobin concentrations in prefrontal areas during the verbal fluency task (VFT) before and after stimulation.

**Results:** After stimulation, iTBS to the left DLPFC with 70% RMT maintained the concentration change of oxyhemoglobin (HbO) in the target area during the VFT. In contrast, 50% [$t_{(17)}$ = 2.203, $P$ = 0.042, $d$ = 0.523] and 100% iTBS [$t_{(17)}$ = 2.947, $P$ = 0.009, $d$ = 0.547] significantly decreased change of HbO concentration, indicating an inverse U-shape relationship between stimulation intensity and prefrontal hemodynamic response in healthy young adults. Notably, improved VFT performance was only observed after 70% RMT stimulation [$t_{(17)}$ = 2.511, $P$ = 0.022, $d$ = 0.592]. Moreover, a significant positive correlation was observed between task performance and the difference in HbO concentration change in the targeted area after 70% RMT stimulation ($r$ = 0.496, $P$ = 0.036) but not after 50 or 100% RMT stimulation.

**Conclusion:** The linear relationship between stimulation intensity and behavioral outcomes reported in previous conventional rTMS studies may not be translated to iTBS. Instead, iTBS at 70% RMT may be more efficacious than 100% RMT.

KEYWORDS

intermittent theta burst stimulation, stimulation intensity, functional near infrared spectroscopy, dorsolateral prefrontal cortex, executive function

## Introduction

Transcranial magnetic stimulation (TMS) is a well-established non-invasive brain stimulation technique that elicits action potentials through application of a magnetic field on the scalp (1). Repetitive transcranial magnetic stimulation (rTMS) has been shown to modify cortical excitability beyond the stimulation session. The underlying mechanism of these effects may be related to modulated long-term potentiation (LTP) and long-term depression (LTD), as observed in animal studies (2). Recently, theta-burst stimulation (TBS), a potent form of rTMS, has gained increased attention, due to its comparable potentiation effects as conventional rTMS, but administered in a much shorter time frame (3). TBS consists of a series of 3-pulse bursts at 50 Hz (theta rhythm), designed to mimic the firing patterns of hippocampal neurons in rats (4) and has been demonstrated to optimally induce LTP in animal studies (5). In humans, TBS protocols were first tested on the primary motor cortex at an intensity of 80% active motor threshold (AMT) by Huang et al. (3) who showed that the intermittent form of TBS (iTBS) induces excitatory effects while the continuous form of TBS (cTBS) induces inhibitory effects on brain activity. Since its first description, TBS has been applied to other non-motor areas. The past decade has seen the rapid development of application of TBS on the dorsolateral prefrontal cortex (DLPFC) for the treatment of various neurological and psychiatric disorders (6–9). However, questions have been raised about the optimal parameters for maximizing the response to TBS. For instance, one of the current discussions pertains to the TBS intensity used for the DLPFC neuromodulation. Huang and Rothwell (10) reported an increased MEP with increasing intensity (50, 70, and 80% AMT) of 50 Hz burst stimulations of the motor cortex (10). In more recent treatment studies, TBS is used at wide ranging intensities, from 80% AMT to 120% resting motor threshold (RMT) (11, 12). In conventional rTMS studies, an almost linear relationship between stimulation intensity and neuromodulation is assumed in conventional rTMS studies (13, 14). However, caution should be taken when directly transferring this relationship from conventional rTMS to TBS, as the mechanism by which they alter brain excitability appears to differ (2, 15, 16). Furthermore, it is still unknown whether the linear relationship reported by Huang and Pothwell using low (50–80% AMT) TBS intensity in motor cortex also exists in high (≧80% AMT) intensity prefrontal stimulation.

Functional near infrared spectroscopy (fNIRS) allows to assess the concentration change of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in biological tissue (17). This is achieved by transmitting near infrared light (∼700–1,000 nm) into the brain and taking advantage of the transparency difference of tissue within this near infrared optical window (18). fNIRS has been demonstrated to be a very promising tool to monitor functional brain activity in a wide range of applications and populations, especially for the frontal lobe (17, 19). Previous studies reported a robust correlation between the NIRS signal, and the blood oxygenation level dependent (BOLD) signal as measured by functional magnetic resonance imaging (fMRI) (20–22). In the past three decades, fNIRS has become increasingly popular due to its low cost, safety, portability, and tolerability (19, 23, 24). The verbal fluency task (VFT) is a widely used neuropsychological test to evaluate executive functions in which subjects are instructed to generate as many unique words as possible from a category (phonemic or semantic) within a given time limit (25, 26). Previous and recent research demonstrate VFT-induced activation in frontal cortices, including the left DLPFC (27, 28).

Our study set out to systematically investigate the influence of different stimulation intensities of iTBS, applied at the left DLPFC, on brain activity and executive function in healthy adults. We probed (1) a hypothesized linear relationship between iTBS intensity and activation of the DLPFC; and (2) a linear relationship between task performance and stimulation intensity.

## Materials and methods

### Participants

Convenience sampling was used for recruitment at the Hong Kong Polytechnic University from May 2021 to July 2021. We included 20 right-handed, healthy adults in this study (age: 22.3 ± 3.54 years, 10 female). Participants had

to be native Chinese speakers between the age of 18 and 35 years and completed at least 6 years of formal education. They had to have normal or corrected to normal eyesight and be able to understand the verbal instructions. Subjects with any of the following conditions were excluded from this study: (1) a history of seizure; (2) current or past psychiatric disorders; (3) current or past severe internal or neurological illness; (4) any TMS contraindications; (5) history of substance dependence or abuse within the last 3 months; (6) intake of any medication (i.e., benzodiazepines, anticonvulsants) known to affect the excitation threshold. The study was conducted according to the Declaration of Helsinki and received the ethical approval from the Human Subjects Ethics Subcommittee (HSESC20181212008) of the Hong Kong Polytechnic University. Written informed consent was obtained from all participants before enrollment.

## Study design and setting

This study was a prospective, randomized cross-over clinical trial with repeated measures. Subjects were instructed to visit our lab three times with 7–9 days between each visit. After enrollment, they were randomly assigned to receive iTBS at an intensity of 50, 70, or 100% RMT in each session. The sequence of stimulation intensities was determined by a simple, computer-generated, random number list, and counterbalanced among subjects. fNIRS measurements were performed immediately before and around 15 min (i.e., the time required to place the fNIRS probe on a subject's head) after stimulation. During both fNIRS measurements, before and after stimulation, subjects performed the VFT. The summary of the procedure is illustrated in the flowchart shown in **Figure 1**. This study is a part of a research program which has been registered at clinicaltrials.gov (NCT04031105).

## Intermittent theta burst stimulation

iTBS was delivered using a figure-of-eight shaped cooling coil (Cool-B65), connected to a MagPro magnetic stimulator (MagVenture, Denmark). We adhered to the initial 3-min iTBS protocol (3 pulses × 10 bursts × 20 trains = 600 pulses) developed by Huang et al. (3), which consists of 20 trains of 3-pulse bursts with 50 Hz intra-burst frequency. Each train contains 10 bursts delivered at 5 Hz and separated by 8 s of rest. The RMT for each subject was determined using a single pulse at the left primary motor cortex, defined as the minimum intensity capable of eliciting motor evoked potentials (MEPs) with at least 50 μV peak-to-peak amplitude in at least five out of 10 consecutive measurements of the relaxed right first dorsal interosseous muscle (FDI). iTBS was delivered at intensities of 50, 70, or 100% RMT for each subject on a given session. 70% RMT was chosen because it corresponds to 80% AMT used in study that first reported the application of TBS in human (3). We utilized 100% RMT due to the higher neural activity response to increased stimulation intensity observed in conventional rTMS studies (13, 29). In addition, stimulation at 50% RMT was regarded as an active control condition as a previous study reported that TBS at a low intensity did not affect brain excitability (30). We targeted the left DLPFC at the MNI coordinate of (x-38, y + 44, z + 26), as done previously (31, 32). The stimulation target was identified and monitored by a navigation system (LOCALITE® TMS Navigator Germany) during iTBS. Self-reported side effects were documented after each stimulation, using the self-rate Numeric Pain Rating Scale [from 0 (No Pain) to 10 (Worst Imaginable Pain)] (33). All subjects were naïve to TMS.

## fNIRS measurement

Hemodynamic activity was measured using a continuous wave near-infrared (695 and 830 nm) spectroscopy device (ETG-4000, Hitachi Medical Co., Tokyo, Japan) with a sampling rate of 10 Hz. We used a 3 × 11 probe design with 52 channels for data collection (**Figure 2**). The probe was placed on the forehead with the lower edge aligned with the T4-Fpz-T3 line of International 10–20 system and the sixth column aligned with the brain's middle line. The area between two nearby sources and detectors is defined as a channel (Ch). The distance between a pair of emitter and detector was 3 cm, which allowed to measure the concentration change of HbO and HbR at 2–3 cm below the skin and scalp surface. The probe was registered to the surface of the standard brain embed in the AtlasViewer toolbox (34) and projected to the cortex to estimate the MNI coordinate of each channel (the midpoint between each pairs of source and detector). The estimation of probabilistic anatomical locations of channels based on the Brodmann area (BA) atlas shows that our probe arrangement enabled to detect the hemoglobin changes in bilateral DLPFC (BA 9, 46), frontopolar area (BA 10), anterior superior temporal gyrus (BA 22), and middle temporal gyrus (BA 21). MNI coordinates of each channel's midpoint and the estimated corresponding BA area for each channel are shown in **Supplementary material**. Participants were told to sit still and avoid head movements during the measurement. Measurements started once the fNIRS signal was stable.

## Verbal fluency task

The design of the VFT was adapted from previous fNIRS studies, which utilized a counterbalanced block design (26, 35, 36). The task consisted of two experimental blocks and two control blocks. Animals and means of transportation were used as semantic categories for the VFT before stimulation (VFT

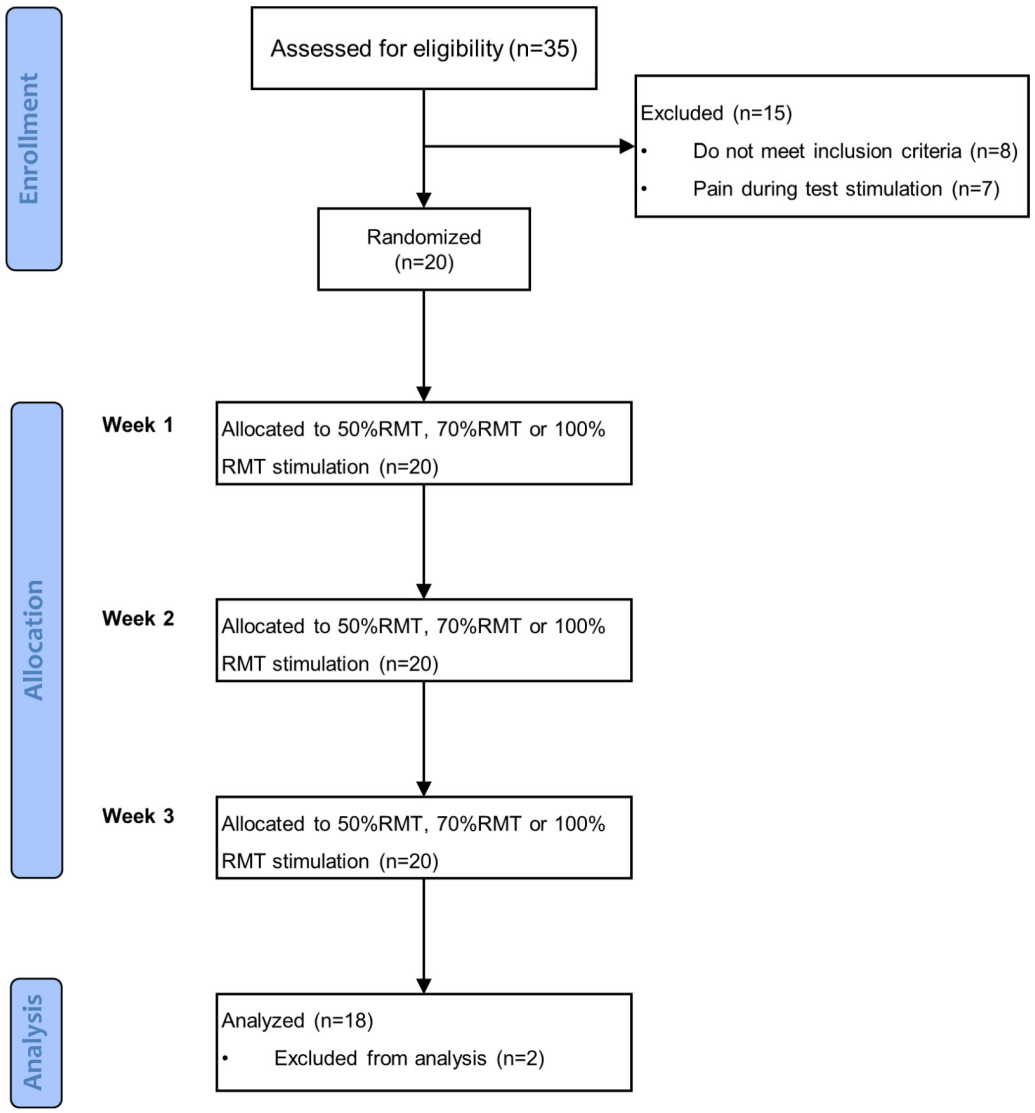


FIGURE 1
Flowchart of the experiment procedure.

version 1) while clothes and fruits/vegetables were used as categories for the VFT after stimulation (VFT version 2). Both versions started with a 60-s block of the control condition, followed by a 60-s block of the experimental condition. During the experiment, subjects sat comfortably and 50 cm in front of a computer screen. During the experimental condition, participants were told to generate as many words as possible that belonged to the semantic category shown on the center of the screen without repetition. During the control block, they needed to repeat the numbers "1, 2, 3, 4, 1, 2, 3, 4. . ." at a steady pace, as done previously (26). The purpose of these control blocks was to account for changes in hemodynamic response caused by talking. Prior to the start of the task, subjects were given a practice trial (i.e., semantic category of flowers) to ensure that they understood how to complete the task correctly. The overall duration of the VFT task was 240 s. All stimuli were presented using E-Prime 2 (Psychology Software Tool, Pittsburgh, PA, USA).

## Data analysis

### fNIRS data analysis

fNIRS data analysis was performed using the HOMER 2 toolbox and custom scripts developed in MATLAB 2013b (The MathWorks, Inc., Natick, MA) (37). For preprocessing, channels with an optical density higher than 140 dB were excluded for further analysis to omit saturated channels (38). The raw fNIRS

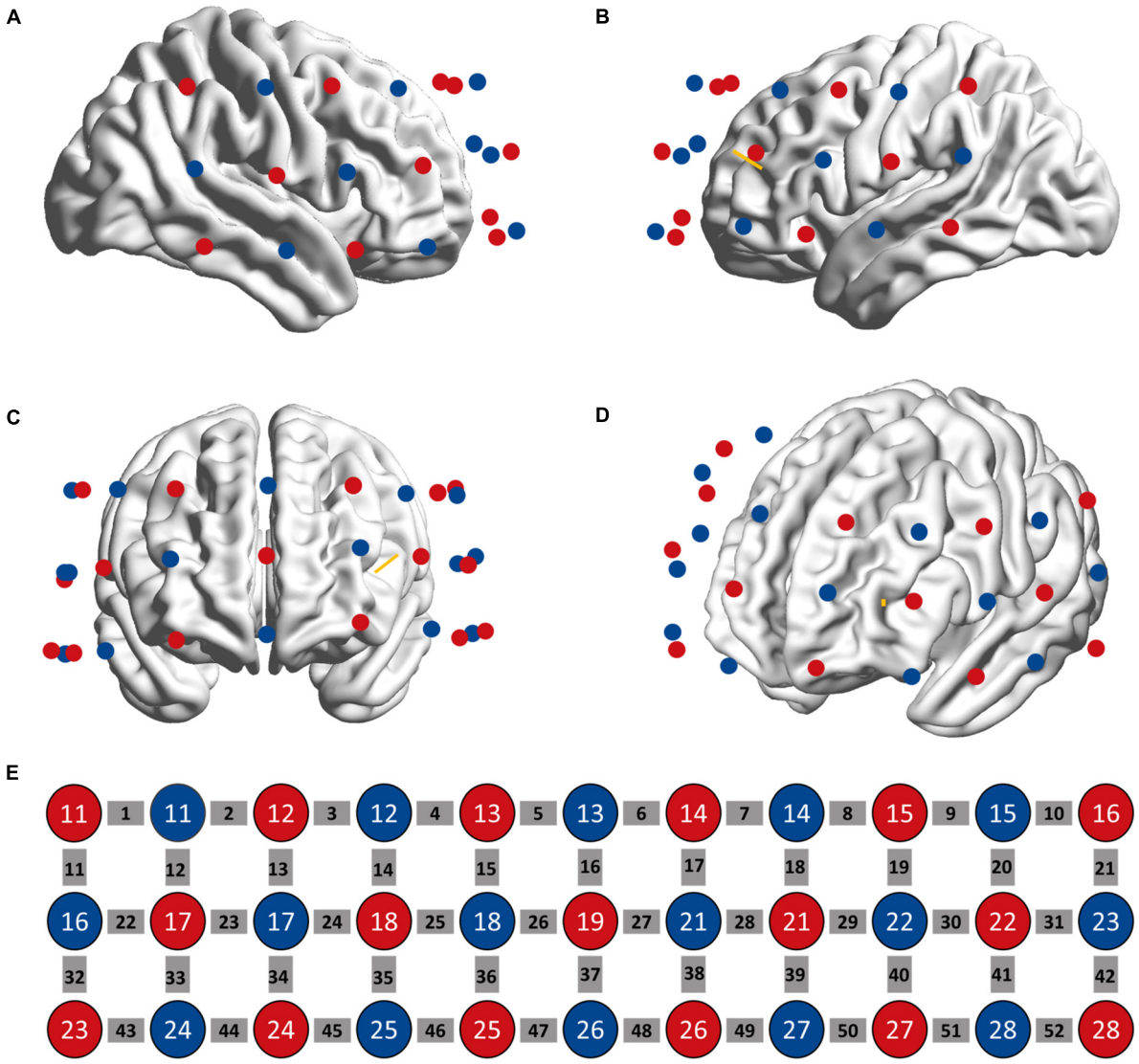


FIGURE 2
Location of fNIRS sources (red circle) and detectors (blue circle) on the head as seen from the right **(A)**, left **(B)**, anterior **(C)**, and left frontal **(D)** perspectives. **(E)** The sources and detectors were laid out in a 3*11 configuration. The gray squares represent measuring channels. The yellow bar denotes the projection of stimulation target.

data was then converted to optical density (OD) (39). Motion artifacts were detected and corrected by a mixed approach based on the spline interpolation method and Slvitzky-Golay filtering of each channel (40). A bandpass filter (0.002–0.08 Hz) was then employed to remove physiological noise caused by heartbeat, respiration, and drifts (41). These preprocessed signals were converted to the concentration change of HbO (ΔHbO) based on the modified Beer-Lambert Law with a differential pathlength factor of six (42, 43). The time course HbO concentration change (0–60 s) for the experimental conditions was calculated using the *hmrR_BlockAvg* function (37). Lastly, the data of experimental blocks were averaged. Baseline correction was performed per experimental block using the mean of the last 5 s signal of control block (44). We also investigated the hemodynamic response during the early VFT task period (0–30 s) because a previous study reported that the early semantic VFT phase (0–30 s) was supported by executive functions while the late phase (31–60 s) was mainly dependent on the semantic network activation (45). The region of interest was defined as the stimulated area that corresponds most closely to the location of Ch28. In this study, we used HbO signals as an indicator of hemodynamic response since HbO is more sensitive to regional cerebral blood flow than Hb (46). The mean of HbO concentration change for different groups were used for further analysis. To visualize the difference of the left DLPFC activation during VFT task before and after stimulation, we contrasted

the mean of ΔHbO (0–60 s) before and after stimulation for each intensity using paired *t*-test results. This analysis yielded three t-maps which show the *t*-value for ch28 at each intensity. The *t*-values and MNI coordinates were first converted to *.img files using nirs2im function[1] in the xjview toolbox.[2] Next, the transformed image files were visualized on a 3D brain model (ICBM512 template) using a BrainNet Viewer toolbox (47).

### Statistical analysis

One-way repeated measures analysis of variance (ANOVA) was used to compare the baseline difference of VFT performance and brain activity. In order to investigate the stimulation effects, behavioral as well as imaging data were analyzed by two-way repeated measures ANOVA using time (pre, post) and intensity (50, 70, and 100%) as within-subjects factors. In case of significant main effects, *post* hoc pairwise comparisons were corrected using Fisher least significant difference (LSD) procedure in accordance with the closed test principle: *post* hoc comparisons were declared non-significant if the global *p*-value of the main effect (testing equality of both time points or of all 3 intensities simultaneously) was non-significant but carried out without further correction in case of a significant global main effect. Statistical significance was set at $P < 0.05$. Pearson correlation was used to analyze the relationship between VFT performance and difference of ΔHbO. SPSS version 24 for Windows (SPSS Inc., Chicago, IL)[3] was used for statistical analyses.

## Results

Two subjects were excluded from the data analysis due to poor quality of fNIRS signals and interruption of the program during measurement. Finally, 18 subjects (9 female, mean age: 22.30 ± 3.54 years) were included for the data analysis. One-way repeated measures ANOVA did not reveal a significant difference in the time interval between the second fNIRS measurement and iTBS between groups [50%RMT group: 20.780 ± 2.533 min; 70%RMT group: 19.889 ± 2.720 min; 100%RMT group: 20.778 ± 2.942 min; $F_{(2,\ 34)} = 0.727$, $P = 0.491$]. Prior to stimulation, the subjects generated 41.39 ± 10.05, 40.11 ± 7.75, 42.33 ± 9.00 accurate words for 50, 70, and 100% RMT stimulation condition, respectively. After stimulation these values increased to 43.67 ± 9.42 [$t_{(17)} = 1.06$, $P = 0.305$, $d = 0.249$], 44.61 ± 8.24 [$t_{(17)} = 2.511$, $P = 0.022$, $d = 0.592$], and 44.28 ± 9.04 [$t_{(17)} = 1.421$, $P = 0.173$, $d = 0.335$], respectively. The averaged fNIRS signal during the VFT task in the left DLPFC (Ch28) among different conditions is shown in **Figure 3A**. There were no baseline differences regarding VFT behavioral performance [$F_{(2,\ 34)} = 0.500$, $P = 0.611$, $\eta_p^2 = 0.029$] and brain activity [$F_{(2,\ 34)} = 0.267$, $P = 0.767$, $\eta_p^2 = 0.015$] between groups. Two-way repeated measures ANOVA on VFT accuracy showed a significant main effect of time [$F_{(1,\ 17)} = 4.455$, $P = 0.05$, $\eta_p^2 = 0.208$] but not of intensity [$F_{(2,\ 34)} = 0.165$, $P = 0.849$, $\eta_p^2 = 0.010$] nor an interaction of time × intensity [$F_{(2,\ 34)} = 0.958$, $P = 0.394$, $\eta_p^2 = 0.053$]. Exploratory *post* hoc comparisons indicated a significant performance increase after stimulation compared to baseline at the intensity of 70%RMT [$t_{(17)} = 2.511$, $P = 0.022$, $d = 0.592$] but not at the other two intensities ($P > 0.05$) (**Figure 3B**). Brain activation analysis for the early task period showed a significant main effect of time [$F_{(1,\ 17)} = 4.873$, $P = 0.041$, $\eta_p^2 = 0.223$], and an interaction effect of time and intensity [$F_{(2,\ 34)} = 4.442$, $P = 0.019$, $\eta_p^2 = 0.207$] but no main effect of intensity [$F_{(2,\ 34)} = 2.130$, $P = 0.134$, $\eta_p^2 = 0.111$]. *Post* hoc analyses using change scores to resolve the interaction effect indicated significantly higher HbO values post stimulation at 70% RMT, compared to 50% [$t_{(17)} = 2.203$, $P = 0.042$, $d = 0.523$] and 100% RMT [$t_{(17)} = 2.947$, $P = 0.009$, $d = 0.547$] (**Figure 3C**). Analysis for early phase behavioral performance also showed the same inverse U-shape curve despite not reaching significance [time: $F_{(1,\ 17)} = 0.349$, $P = 0.563$, $\eta_p^2 = 0.020$; intensity: $F_{(2,\ 34)} = 0.015$, $P = 0.985$, $\eta_p^2 = 0.001$; time × intensity: $F_{(2,\ 34)} = 1.528$, $P = 0.232$, $\eta_p^2 = 0.082$] (**Figure 3D**). No significant results were observed when looking at the HbO change averaged across the whole task period (**Figure 4**). However, correlation analysis revealed a significant positive correlation between behavioral accuracy and the difference in HbO concentration change in left DLPFC after 70% RMT stimulation (Pearson's $r = 0.496$, $P = 0.036$) but not after the other two intensities (**Figure 5**).

## Discussion

In this study, we investigated the effects of varying stimulation intensities of iTBS of the left DLPFC on executive function and underlying cortical activity using fNIRS. While several previous studies have investigated iTBS effects on the brain using EEG (9, 48, 49), we investigated such effects using fNIRS, as it is more tolerant to lip and jaw movements during VFT task performance (19). In all stimulation intensity, descriptively, the number of words generated by subjects after stimulation was increased than before stimulation. However, the improvement of executive performance was only significant after 70% RMT stimulation. Besides, iTBS to the left DLPFC with 70% RMT maintained the concentration change of HbO in the target area, whereas 50% iTBS and 100% iTBS decreased change of HbO concentration, indicating an inverse U-shape relationship between stimulation intensity and prefrontal hemodynamic response. Moreover, a significant positive correlation was observed between behavioral accuracy

1 https://www.alivelearn.net/?p=2230

2 https://www.alivelearn.net/xjview/

3 www.spss.com

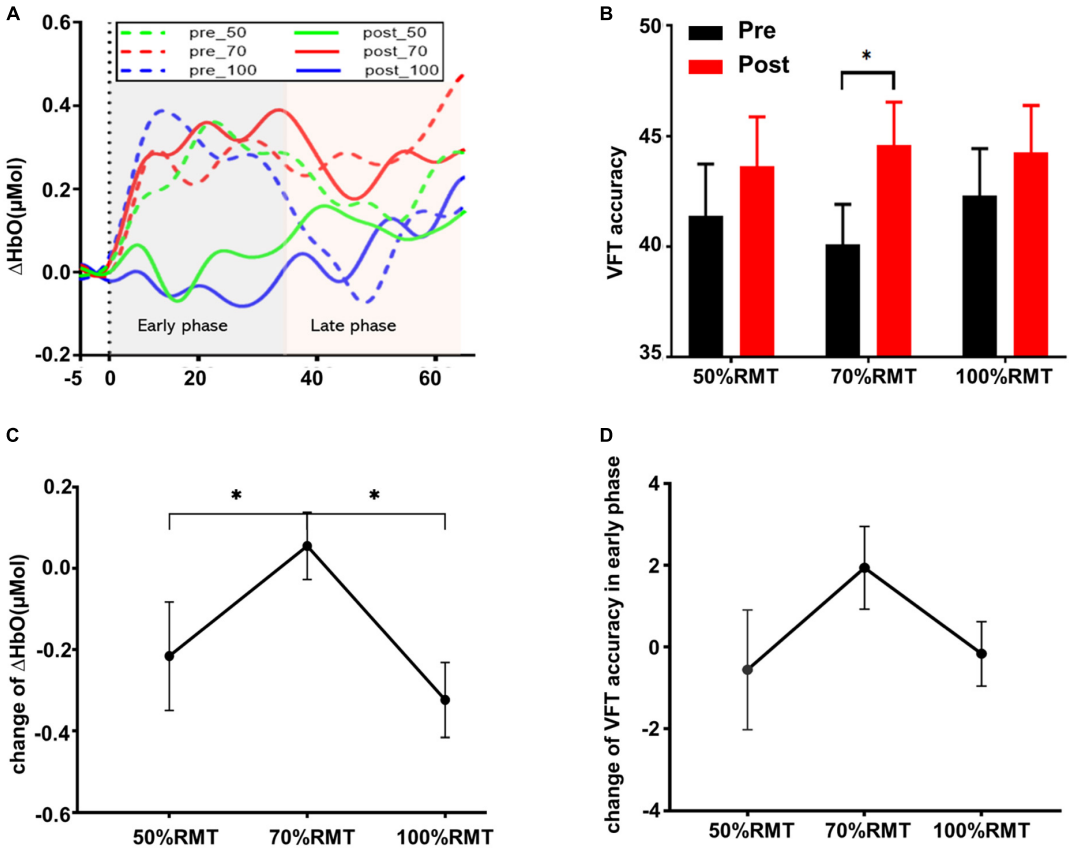


FIGURE 3
**(A)** Group averaged time course HbO concentration change during the experimental condition in the left DLPFC (Ch28) before and after stimulation at each intensity. The *Y*-axis represents the mean of ΔHbO. **(B)** VFT behavior performance (mean ± SEM) for the whole task period (0–60 s). **(C)** Change of ΔHbO in the early task phase (0–30 s) for each stimulation intensity. Data were calculated by subtracting the mean of ΔHbO before stimulation from the mean of ΔHbO after stimulation. **(D)** VFT behavior performance change (mean ± SEM) in early task phase for each stimulation intensity. *$p < 0.05$.

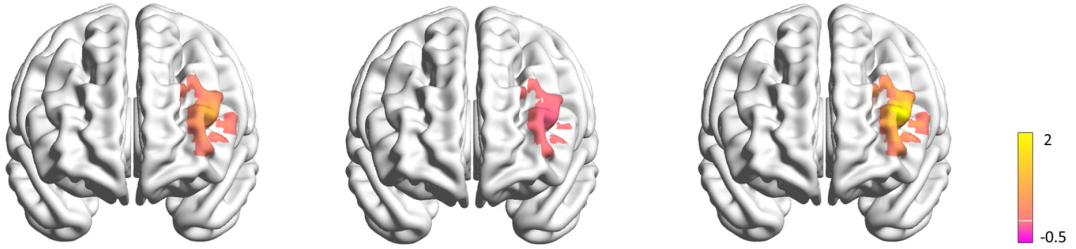


FIGURE 4
Maps of the left DLPFC activation difference before and after stimulation during VFT task in 50% RMT condition **(left)**, 70% RMT condition **(middle)**, 100% RMT condition **(right)**. The color bar indicates the *t*-values render over on a 3D head model. The yellow color represents less ΔHbO after stimulation, while the purple color represents more ΔHbO after stimulation.

and the difference in HbO concentration change in the targeted area after 70% RMT stimulation.

The modest enhancements of VFT performance in all intensity conditions supports the beneficial effects of excitatory stimulation of iTBS stimulation on executive functioning (50, 51). However, contrary to our hypothesis, our results did not demonstrate a linear relationship between stimulation intensity and brain activity, as observed in conventional rTMS studies (13, 52) and a study examining low TBS intensity (10). Specifically, we found significant improvement of executive function only after 70% RMT iTBS; the corresponding hemodynamic response revealed that iTBS to the left DLPFC with 70% RMT maintained

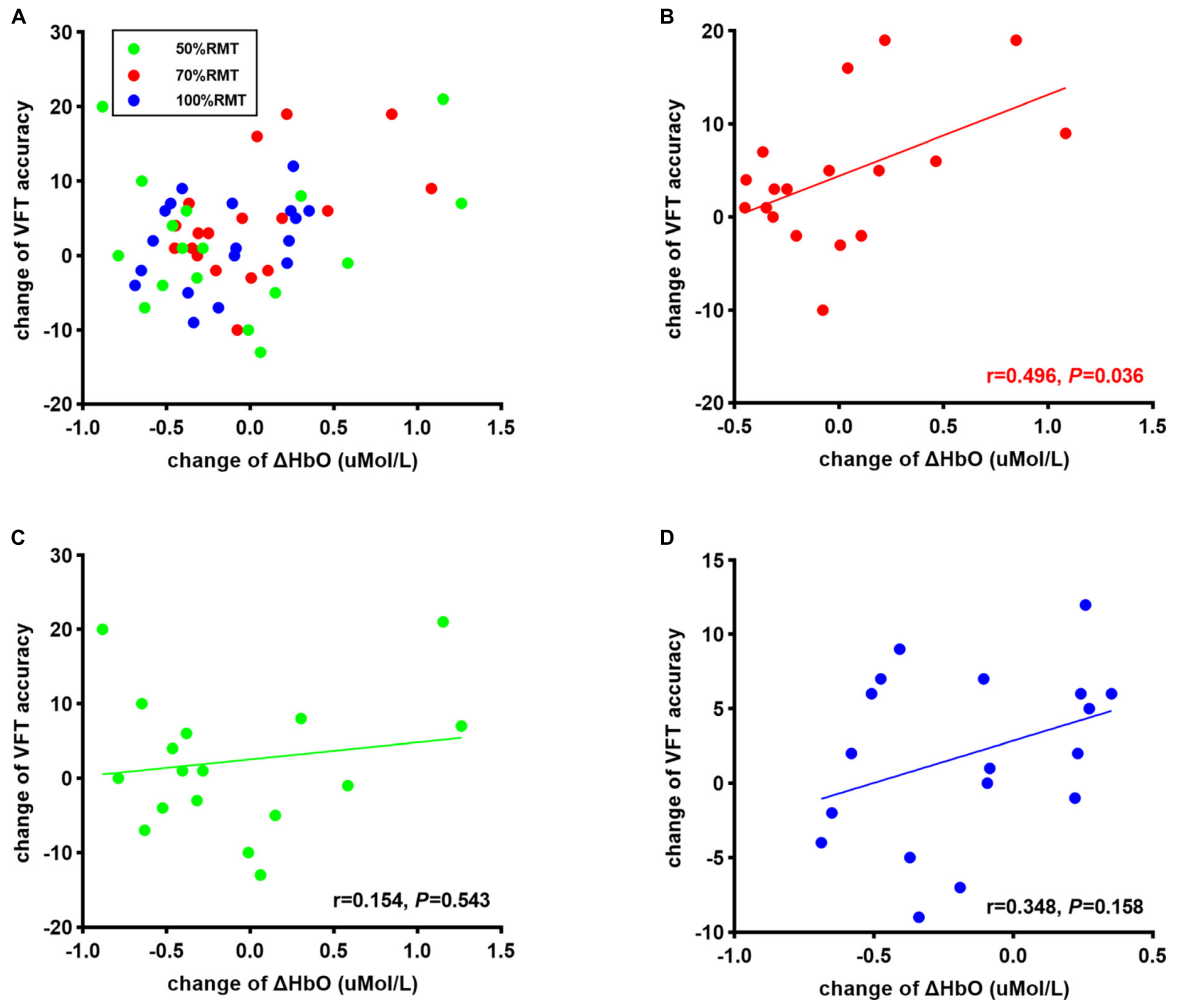


FIGURE 5
**(A)** Correlation between change of corrected words generated during VFT task and change of ΔHbO at all stimulation intensities Correlation between change of corrected words generated during VFT task and change of ΔHbO in 70% RMT stimulation **(B)**, 50% RMT stimulation condition **(C)**, and 100% RMT stimulation **(D)**.

the concentration change of HbO in the target area, whereas 50% iTBS and 100% iTBS decreased ΔHbO. A possible explanation for these observations is related to mechanisms of theta-frequency-dependent LTP induction (53, 54). Normally, a single burst activates a glutamatergic (excitatory) synapse and also a gamma-aminobutyric acid (GABA)-ergic (inhibitory) synapse on a pyramidal neuron, producing both an excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) on this neuron. This IPSP undercuts the EPSP triggered by this burst and the next burst for a short period of time, preventing the hyperexcitability of the downstream pyramidal neuron. However, this IPSP can be suppressed for a short period of time if a second burst is delivered at theta frequency (53). The underlying mechanism is further GABA release from the GABAergic presynaptic terminal that follows this second burst, inhibits future GABA release through activation of $GABA_B$ autoreceptors (55). Consequently, this GABA-mediated disinhibition induces LTP effects via activation of N-methyl-D-aspartate (NMDA) receptors (56). A previous study reported that a second burst delivered at 200 ms after the initial burst produces maximal excitatory effects by using this mechanism of disinhibition, i.e., by inducing more GABA release to activate $GABA_B$ autoreceptors (54, 55). Bursts given outside of this window (above or below 200 ms) may not result in such optimal effects in human brains, possibly because burst effects encounter an already-present IPSP from previous activations or recovered IPSP (53, 57). An important caveat it that the onset of this disinhibition may be modulated by stimulus intensity (57). Therefore, TBS at high intensities (such as 100% RMT) may off-set this temporal window and fail to elicit the maximal excitatory effects of theta frequency on brain activity. Consistent with this view, Chung et al. found that iTBS

at 75% RMT intensity showed maximal neuromodulatory effects on brain activity in humans (58).

We observed a relative lower ΔHbO following 50 and 100% RMT stimulation compared to before stimulation despite increased VFT performance. This appears to be contradictory to the general understanding of the neurovascular coupling phenomenon. According to this principle, a cognitively demanding task such as the VFT should lead to a rise in HbO needs, indicating an increase in cortical activation, as a result of increased neuronal mobilization (28, 59, 60). It is theorized that higher cortical activation should be accompanied with a better behavioral performance, since higher cortical activation suggests more cognitive resources are being mobilized to complete a task (61). However, previous studies also reported that increased DLPFC activation may be a compensatory strategy for reduced available neural resources, or alternatively, an inefficient employment of neural resources (62, 63). Recent evidence suggests that excitatory rTMS to the left DLPFC increases neural efficiency, observed as reduced concentration change of total hemoglobin after stimulation during Speed of Processing task (64). This finding corroborates cognitive efficiency theories which propose that people with a more efficient cortical processing require less cognitive resources to achieve better performance (62, 65, 66). Therefore, TBS benefits to behavioral performance may be due to improved efficiency of neurons, such that the same levels of cortical activation (captured by fNIRS) provides increased processing power, improving performance.

Imaging results revealed a significantly higher HbO concentration change following 70% RMT stimulation than 50% RMT and 100% RMT only in the early task phase but not the whole task period. This can be explained by the dynamic model of retrieval process involved in the semantic fluency tasks. A previous study indicated that early phases of the semantic VFT task is mediated more by executive processes while the late phase is mainly dependent on semantic network activation (45). It has been well established that the DLPFC plays an important role in supporting executive control (67–70). Therefore, it is not surprising that the potentially optimal iTBS intensity enhanced the excitability of the left DLPFC and further boosted the behavioral performance.

Certainly, our study is not free of limitations. First, we did not have a real sham condition in this experiment. Nonetheless, our study included a low intensity (50% RMT) condition, comparable to a number of TMS studies that have adopted the strategy of lowering stimulation intensity as a sham condition (49, 71, 72). Second, due to the inherent limitation of the fNIRS equipment used, such as the height profile of our fNIRS probes we were unable to measure the hemodynamic response to iTBS during and immediately after the stimulation. To demonstrate this, further studies using a concurrent TMS-fNIRS set up are needed. Thirdly, Fisher LSD method does not offer full control of the type I error. However, it is known to preserve the experiment-wise type I error at the nominal significance level if there are three groups (73). Fourth, the choice of intensities used in our study is not representative of all often-used stimulation intensities in clinical settings (e.g., 90, 110, and 120% RMT). We adopted relatively lower TBS intensities, as an endorsed advantage of TBS protocols in clinical applications is the lower necessary intensity for treatment, allowing for more comfortable sessions (74, 75). Additionally, on methodological grounds, our results are comparable to Huang et al. (3), who used low intensities (80% AMT) to study the patterned effects of TBS on MEPs. Even so, our findings have limited generalizability to suprathreshold TBS intensities. Further studies comparing these effects are needed.

## Conclusion

The linear association between stimulation intensity and behavioral improvement observed in healthy people receiving conventional rTMS may not extend to iTBS. Our investigation revealed an inverted U-shaped association between iTBS intensity and the excitatory effects on brain activity, suggesting that iTBS at 70% RMT may be more efficacious than 100% RMT.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Human Subjects Ethics Subcommittee of the Hong Kong Polytechnic University. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

BZ: conceptualization, methodology, software, investigation, data curation, formal analysis, writing—original draft, writing—review and editing, and visualization. RK: methodology, software, formal analysis, writing—review and editing. CG: methodology, formal analysis, and writing—review and editing. TL: software, formal analysis, visualization, and writing—review and editing. S-YY: writing—review and

editing and supervision. GK: resources, conceptualization, methodology, writing—original draft, writing—review and editing, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1049130/full#supplementary-material

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# Electroconvulsive therapy use for refractory status epilepticus in an implantable vagus nerve stimulation patient: A case report

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**Introduction:** Status epilepticus (SE) has a mortality rate of 20 to 50%, with acute symptomatic SE having a higher risk compared to chronic SE. Electroconvulsive therapy (ECT) has been utilized for the treatment of refractory SE with a success rate estimate of 57.9%. There are no known reported cases of concomitant use of vagus nerve stimulation (VNS) and ECT for the treatment of super refractory SE (SRSE) available in the literature.

**Case description:** We present a 44-year-old female with a history of developmental delay, epilepsy, an implantable VNS for 6 years, and traumatic brain injury with subsequent hygroma who presented with progressive aphasia, declining mental status, and daily generalized seizures lasting up to 20 min. Seizures had increased from her baseline of one seizure per day controlled with topiramate 200 mg three times daily and lamotrigine 400 mg twice daily. She was diagnosed with SRSE after being intubated and placed on eight anti-epileptic drugs (AEDs) that failed to abort SE. ECT was attempted to terminate SE. Due to a prior right craniotomy with subsequent right hygroma, eight treatments of ECT were performed over three sessions using a right anterior, left temporal (RALT) and subsequently a bitemporal electrode placement. The VNS remained active throughout treatment. Various ECT dosing parameters were attempted, varying pulse width and frequency. Although ECT induced mild transient encephalographic (EEG) changes following ECT stimulations, it was unable to terminate SE.

**Discussion:** This case describes various treatment strategies, constraints, and device limitations when using ECT for the treatment of SE. With wide variability in efficacy rates of ECT in the treatment of SE in the literature, successful and unsuccessful cases offer information on optimizing ECT total charge dose and parameters that yielded success. This case demonstrates an instance of ECT inefficacy in the treatment of SRSE. Here, we discuss the rationale behind the various ECT settings that were selected, and constraints arising from the antiepileptic burden, VNS, and intrinsic limitations of the ECT device itself.

KEYWORDS

**electroconvulsive therapy, status epilepticus, vagus nerve stimulation, refractory epilepsy, case reports**

## Introduction

Status epilepticus (SE) has a mortality rate purported to be 20 to 50%, with acute symptomatic SE having a higher risk compared to chronic SE (1). Electroconvulsive therapy (ECT) has been utilized for the treatment of SE when traditional therapies fail, however, success rates of ECT in cases of super refractory SE (SRSE) have not been well-documented. In 2012, the success rate of ECT in the treatment of SE was reportedly 80%, however, an analysis in 2016 demonstrated the rate as 57.9% (2, 3). While the mechanism behind the efficacy of ECT in SE remains unclear, proposed mechanisms include the release of inhibitory transmitters, such as GABA; prolongation of the refractory period; elevation of the seizure threshold, which has been demonstrated in patients receiving ECT for treatment of mood disorders; and induction of endogenous seizure termination mechanisms (1, 3). Vagus nerve stimulation (VNS) has been approved for use in drug-resistant epilepsy in the United States since 1997 and has been shown to reduce SE occurrence and its recurrence (4). VNS interrupted refractory SE in 74% of patients, with a median duration of 8 days post-implantation for cessation (4). Most reported cases of concomitant use of VNS with ECT detail circumstances in which the VNS was turned off prior to ECT treatment. There are no known reported cases of concomitant use of VNS and ECT in treatment of SRSE available in the literature. Here we present a case of the use of ECT to treat SRSE in a patient with an active VNS.

## Case description

Here we present a 44-year-old female with a history of developmental delay, localization-related epilepsy diagnosed at age 16, VNS placement at age 38, and status post-head injury with intracranial bleed that required craniotomy 1 year prior who presents with daily prolonged periods of generalized seizures lasting up to 20 min that had increased from her baseline of one seizure per day previously controlled by her home regimen of topiramate 200 mg TID and lamotrigine 400 mg BID (**Figure 1**). Upon admission, she was experiencing progressive aphasia and declining mental status. Lumbar puncture revealed HHV-6 encephalitis for which she was started on foscarnet. She was subsequently intubated and due to medication refractory SE, started on an increasingly large antiepileptic regimen including lamotrigine, levetiracetam, topiramate, Perampanel, clobazam, pregabalin, cannabidiol, phenobarbital, propofol drip, and ketamine drip.

She was determined to not be a candidate for a ketogenic diet. Ultimately, the multidisciplinary team decided to attempt ECT to terminate the SRSE. The VNS remained on throughout the three-session ECT treatment course, with parameters set at 1.75 mA, 250 μs pulse width, 30 s on, and 1.1 min off time. The risk of concurrent treatment in patients with a VNS implant arises from the use of strong electromagnetic fields such as seen with diathermy (i.e., short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy), where such treatment anywhere in the body could potentially lead to injury *via* heating or damage the implanted VNS stimulator, even when the VNS is turned off (5). This includes electromagnetic fields seen with transcranial magnetic stimulation. Even so, the VNS Therapy System is safe for use in 1.5 and 3 T MRI scanners (6). However, ECT creates an electrical field within the brain, and heating *via* diathermy would not be expected. The VNS uses an implanted pulse generator in the chest connected to an electrode in the neck outside the ECT electrical field. Similarly, numerous case reports have shown the safe use of ECT in those with deep brain stimulation implants that are within the electrical field produced with ECT (7). Given that the VNS impulses that reach the tractus solitarius arise from the implanted pulse generator in the periphery, the creation of thermal injury was not expected (5, 6). Although turning the VNS device current to zero during ECT is the most customary practice (8), we were constrained to proceed with VNS on given intensive care unit (ICU) concerns of worsening the seizure burden in a SRSE patient should the device be turned off.

Due to the patient's prior right craniotomy and subsequent right hygroma (**Figure 2**), initial ECT sessions were performed with a right anterior, left temporal (RALT) lead placement using a MECTA spECTrum 5000Q ECT Device (9). To maximize cortical recruitment and depolarization to break the SRSE, with or without induction of a seizure, ECT session 1 (total charge dose: 2.0 ms, 3 s, 120 Hz, 800 mA) was performed on day 17 with propofol and ketamine drips paused 30 min before treatment. SE continued so an attempt to induce a seizure with more contemporary parameter settings as seen in psychiatric ECT was utilized. Here the patient was restimulated twice at 60-s intervals using more efficient settings for seizure induction with an ultra-brief pulse width and longer stimulus train to induce a seizure (0.37 ms, 6 s, 120 Hz, 800 mA). ECT session 1 was unable to induce seizures nor halt her baseline seizure activity, and seizure burden continued to increase from 11 to 20% burden over the next 24 h. ECT session 2 was performed with the intensivist team finally agreeing on day 18 to pause ketamine and propofol infusions 2 h prior to the session, having previously been reluctant to do so for fear of worsening SE. Session 2 consisted of four stimulations each separated by 60 s, with the first two using 1 ms, 6 s, 60 Hz, 800 mA and the latter two stimulations using 2 ms, 3 s, 60 Hz, 800 mA. Shorter pulse widths were not used as these settings would have prevented 100% of the total device energy that was to be used. ECT session 2 induced transient epileptiform activity with burst suppression but was then followed by an almost immediate return to baseline SE. Seizure burden continued to increase to 30% despite a combination of treatments. ECT session 3 was performed on day 19, now with ketamine and propofol infusions paused 3 h before the session. It consisted of one stimulus at 0.5 ms, 3 s, 60 Hz, 800 mA with a 3-min hiatus followed by 1 ms, 3 s, 60 Hz, 800 mA. The final stimulus attempted to maximize interelectrode distance with bitemporal lead configurations (**Table 1**). ECT session 3 again induced mild epileptiform activity with subsequent return to baseline without meaningful change in seizure burden post-ECT stimulus. The VNS remained on during ECT as the primary team was reluctant to turn the device off; VNS interrogation following ECT treatments showed its proper functioning. In discussion with the epileptologist and neurologic critical care team, as the seizure burden had continued to steadily worsen over the course of the patient's illness, and with only mild transient encephalographic (EEG) changes from ECT treatment, the decision was made to discontinue ECT treatment. The patient's family opted for comfort care measures, and the patient died on day 24.

## Discussion

When ECT is used in mood disorders, techniques are employed to lower the seizure threshold such as inducing hypocarbia with hyperventilation or the use of proconvulsant administration prior to an ECT session. However, such strategies become problematic


FIGURE 1
Timeline of clinical events.

TABLE 1 Electroconvulsive therapy (ECT) series parameters.

| | Pulse width (ms) | Duration (s) | Frequency (Hz) | Amplitude (mA) | Configuration |
|---|---|---|---|---|---|
| Session 1 | 2.0 | 3 | 120 | 800 | Right anterior, left temporal (RALT) |
| | 0.37 | 6 | 120 | 800 | RALT |
| | 0.37 | 6 | 120 | 800 | RALT |
| Session 2 | 1 | 6 | 60 | 800 | RALT |
| | 1 | 6 | 60 | 800 | RALT |
| | 2 | 3 | 60 | 800 | RALT |
| | 2 | 3 | 60 | 800 | RALT |
| Session 3 | 0.5 | 6 | 60 | 800 | RALT |
| | 1 | 3 | 60 | 800 | Bitemporal |

when trying to balance the use of ECT in a patient that is in SE, where the lowering of seizure threshold could worsen the underlying condition. There is wide variability in efficacy rates of ECT in the treatment of SE, and, problematically, unsuccessful cases often go unreported. Moreover, eliciting a seizure in the context of SE is often difficult, primarily due to the typically large anticonvulsant pharmacological load used in treating these patients, such as coma induction *via* barbiturate, and for our patient the anti-epileptogenic implantable VNS, as well as her other antiepileptics, all of which hinder seizure induction through ECT. Should the goal have been to stimulate a large volume of brain to abolish a seizure, analogous to electrical cardioversion of electrical dysrhythmias? Or should the aim be to induce a seizure itself that endogenously and spontaneously resolves, thus terminating the underlying status; or is it through raising the seizure threshold itself by repeated ECT treatments that underlies its efficacy? Without clear answers to these questions, we attempted all strategies. Information on the positioning of the stimulating electrodes, total ECT charge, and parameter breakdown yielding termination of SE are often sparsely documented. The rise in seizure threshold that is seen in a classic Index Series of ECT with multiple sessions can be leveraged for the treatment of SE. However, it is unclear if the rates of rise in seizure threshold is similar for SE patients, but repeated ECT sessions have led to termination of SE (10, 11).

In the classic use of ECT for mood disorders, seizure quality parameters are often observed to deem seizure quality. Such data might include information such as post-ictal suppression index, time to peak coherence, and energy after an ECT treatment. Here we are unable to provide equivalent information on induced epileptiform activity as seen with the typical ECT treatments for two reasons. First, we were unable to induce seizures long enough that would have been interpretable by the ECT device. Second, our intensive care unit patient already had continuous long-term EEG monitoring. We employed MECTA's ECT stimulus electrodes for delivery of the stimulus but did not attach the MECTA ECT device's two, two lead EEG montage, rather observing the stimulus results with the 21 scalp electrodes using the International 10–20 System recommended by the International Federation of Clinical Neurophysiology (IFCN). The digital EEG operated continuously at the patient's bedside. Standard digital video EEG techniques were used throughout, including computerized spike and seizure detection with a technologist review *in situ*. The digital analysis methodology was interpreted by the ICU's epileptologist who used quantitative EEG analysis where long term trending was performed including compressed density spectral array and spectral measures of rhythmicity, symmetry, power, amplitude, and alpha/beta ratio.

For this case, initial settings were selected that were deemed the most likely to create a large volume depolarization event, endeavoring to break status, even should induction of a seizure not occur.

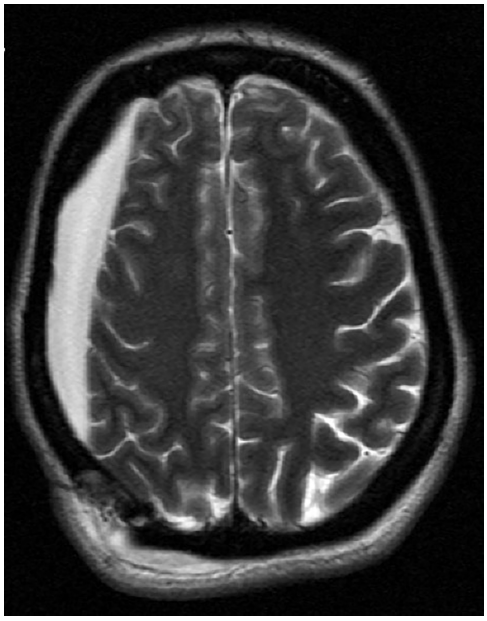

FIGURE 2
Magnetic resonance imaging showing patient's right hygroma prior to initiation of electroconvulsive therapy (ECT).

Although the decision to use the longer pulse width prior to an ultra-brief pulse in this trial was seemingly arbitrary; however, it was assumed it would be difficult to elicit a seizure given the intravenous antiepileptic burden and the active VNS. It was hoped that one stimulation with a large volume depolarization event, maximizing cortical recruitment, might fortuitously terminate the SE irrespective of whether a quality ECT seizure had been induced (as would desirable when treating refractory mood disorders). This would obviate the need for further ECT, including the multiple sessions that might be required to try to raise the seizure threshold to achieve termination of SE. However, it was also unclear if this strategy of using a longer 2 ms pulse width initially might transiently interfere with the threshold, making it more difficult to induce a seizure on immediately subsequent stimulation if needed should SE not terminate (as was the case). In consideration of this, on subsequent days the order of longer pulse width preceding the shorter was reversed (see **Table 1**).

The initial pulse width selected, 2 ms, theoretically would recruit axons that are both larger and smaller in diameter (12, 13). It should be noted that the 2 ms pulse width has been abandoned in contemporary ECT treatments for the initial treatment of mood disorders as this parameter selection is remarkably inefficient at seizure induction, given that it exceeds the chronaxie for neuronal depolarization throughout most of the cortex (14). Of note, this is contrary to some case reports that have shown that such settings with high cortical volume involvement were the only way seizure induction had been possible, including when more efficient parameter settings of brief pulse widths had previously failed (13, 14). For our case, the long pulse width failed to terminate the SE and did not induce a generalized seizure.

After the first stimulation, a 1-min repolarization hiatus was taken, and we transitioned to briefer pulse widths and longer stimulus trains. These theoretically were more efficient parameters for seizure induction. Here, the rationale was to induce a generalized seizure, thereby potentially terminating SE as the induced seizure subsided. An equally valid approach for improving the efficiency of seizure induction may have been to use a lower frequency on the device, allowing greater repolarization between paired pulses. However, the lower frequency would require longer stimulation trains, interfering with the ability to achieve maximum device output for our ECT device. Such low frequency and brief pulse widths are the standard approach in contemporary ECT and allow for more efficient seizure induction at a lower total device charge by avoiding stimulus crowding (15).

Initial electrode placement was RALT. This placement was used to avoid the region with underlying cortical pathology, i.e., the chronic hygroma. RALT allowed for reasonable interelectrode distance. This is opposed to an idealized placement of the stimulating electrodes immediately over a solitary seizure focus, which is impractical given the extreme shunting of electricity through the scalp that would arise through reducing the interelectrode distance. Such shunting and current spreading *via* the scalp, and the skull's high resistance, during electrical stimulation is a known problem that can interfere with ECT. Novel approaches for seizure induction such as Magnetic Seizure Therapy attempt to resolve this issue (16). When multiple attempts at this placement failed, we proceeded with bitemporal ECT despite its positioning the electrical field bilaterally across the cortex, and over the hygroma. This placement was selected to maximize interelectrode distance in an attempt to minimize interelectrode shunting through the scalp. Unfortunately, bitemporal ECT also failed to terminate status in this patient.

It should be noted that, during ECT for depression, the implantable VNS device is typically turned off to avoid interference with ECT from its antiepileptic effects. Moreover, to diminish interference with seizure threshold during ECT, anesthesia induction agents have been optimized to have the least impact. Moreover, there is conflicting information regarding the impact of anti-epileptic drugs (AEDs) on the efficacy of ECT in mood disorders. Such reports typically cite a reduced seizure duration in patients on AEDs which might suggest reduced seizure efficacy. However, this effect seems less pronounced after a first induced seizure is obtained, and newer guidelines recommend against discontinuation of AEDs prior to ECT initiation (17).

There were a few limitations that hindered our ability to elicit seizure. One was the understandable reluctance of the primary team to lower agents that might allow for easier seizure induction due to fear of worsening SE. Moreover, our patient was on multiple AEDs rather than a single drug, with doses designed to suppress seizure activity. This undoubtedly contributed to our difficulty in inducing a seizure. It is also unclear to what extent such AEDs would affect an ECT induced seizure's ability to increase seizure threshold in SE. However, reports show efficacy of ECT in patients on who are on multiple AEDs (18, 19). After the initial ECT session failed to produce a seizure, antiepileptic infusions were held prior to subsequent ECT sessions. In these sessions, ECT-induced brief epileptiform. Reducing propofol dosing further or turning off the implantable VNS would potentially have given ECT a greater chance of success than the more conservative strategy that presumably hampered any potential gains from ECT. Regarding the concurrent use of ECT with her active VNS, VNS interrogation revealed proper functioning throughout and after ECT.

Another serious limitation was the device constraint for the allowed total charge that may be delivered. For psychiatric ECT, it

is known that a successful response is correlated with the magnitude of the seizure EEG discharge and subsequent inhibitory processes. This response magnitude is correlated with some minimum degree to which the seizure threshold is superseded. It is plausible that merely inducing a seizure may be inadequate for driving the seizure threshold upward for SE. This need to supersede threshold is constrained for the ECT devices used in the United States and Canada where the maximal charge is limited at either 504 or 576 mC, depending on which device is used (20, 21). The same devices in much of the world have double this limit and would afford a marked theoretical advantage (22). Available stimulus output was noted to be insufficient for 5% of patients, which could represent the most severe cases, such as those with SRSE, such that there is a call for an increase in maximum stimulus output for ECT devices (20). In support of this need for larger device output is a university research group (who introduced the use of ECT in SE with good success) using research devices with three times the contemporary United States limit (21).

Unfortunately, ECT was ineffective in aborting this patient's SE. Plausible causes contributing to this failure are cited above. However, ECT has been shown to be successful in terminating SE. And, with well-documented reporting of both positive and negative outcomes, and the ECT techniques that are used, better outcomes can be achieved. This will aid in the establishment of treatment guidelines and suggestions for approaching ECT in SE. Such suggestions would include AED reduction strategies, determining optimal parameter selection and electrode placements, and exploration of mitigation strategies for the United States/Canadian devices with their less efficient total charge dosing.

## Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

LK and BC wrote first and final drafts of the manuscript. EB and RH assisted in draft revisions. LR-R performed manuscript review. All authors approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Case report: Rapid symptom resolution of a mixed affective state with high-frequency repetitive transcranial magnetic stimulation

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**Introduction:** Bipolar major depressive episodes with mixed features are diagnosed in patients who meet the full criteria for a major depressive episode exhibiting three additional concurrent symptoms of hypomania or mania. Up to half of patients with bipolar disorder experience mixed episodes, which are more likely to be treatment-refractory than pure depression or mania/hypomania alone.

**Case:** We present a 68-year-old female with Bipolar Type II Disorder with a four-month medication-refractory major depressive episode with mixed features referred for neuromodulation consultation. Previous failed medication trials over several years included lithium, valproate, lamotrigine, topiramate, and quetiapine. She had no history of treatment with neuromodulation. At the initial consultation, her baseline Montgomery-Asberg Depression Rating Scale (MADRS) was moderate in severity at 32. Her Young Mania Rating Scale (YMRS) was 22, with dysphoric hypomanic symptoms consisting of heightened irritability, verbosity and increased rate of speech, and decreased sleep. She declined electroconvulsive therapy but elected to receive repetitive transcranial magnetic stimulation (rTMS).

**Interventions:** The patient underwent repetitive transcranial magnetic stimulation (rTMS) with a Neuronetics NeuroStar system, receiving nine daily sessions over the left dorsolateral prefrontal cortex (DLPFC). Standard settings of 120% MT, 10 Hz (4 sec on, 26 sec off), and 3,000 pulses/session were used. Her acute symptoms showed a brisk response, and at the final treatment, her repeat MADRS was 2, and YMRS was 0. The patient reported feeling "great," which she defined as feeling stable with minimal depression and hypomania for the first time in years.

**Conclusion:** Mixed episodes present a treatment challenge given their limited treatment options and diminished responses. Previous research has shown decreased efficacy of lithium and antipsychotics in mixed episodes with dysphoric mood such as the episode our patient experienced. One open-label study of low-frequency right-sided rTMS showed promising results in patients with treatment-refractory depression with mixed features, but the role of rTMS in the management of these episodes is largely unexplored. Given the concern for potential manic

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mood switches, further investigation into the laterality, frequency, anatomical target, and efficacy of rTMS for bipolar major depressive episodes with mixed features is warranted.

KEYWORDS

transcranial magnetic stimulation (TMS), bipolar disorder, mixed features specifier, bipolar (affective/mood) disorders, hypomania, major depression (MDD), treatment-refractory depression

## Introduction

Given the high prevalence, refractory nature, and mortality of mood episodes with mixed features in bipolar spectrum disorders, further research is needed to identify novel treatments. In particular, one promising modality is repetitive transcranial magnetic stimulation (rTMS), which has demonstrated efficacy for patients with treatment-refractory depression with mixed features. At the present, no randomized controlled trials have evaluated rTMS for bipolar mixed states, which merits careful study due to the risk of manic switches. This case of a patient who achieved full remission of an episode of bipolar depression with mixed features aims to explore possible therapeutic mechanisms, safety considerations, anatomical targeting, nosology, and future directions for mixed-state neuromodulation.

## Patient information

We present a 68-year-old female with Bipolar II Disorder suffering from a treatment-refractory episode of major depression (TRD) with mixed features referred for TMS consultation. She had been a high-functioning individual and was retired from a career in finance. She was originally diagnosed with Bipolar II Disorder at age 45 and has a history of multiple hypomanic episodes and a single psychiatric hospitalization for a major depressive episode. She has never had any suicide attempts. Despite the reduction of symptoms during her various acute episodes, her symptoms failed to ever achieve full remission for many years.

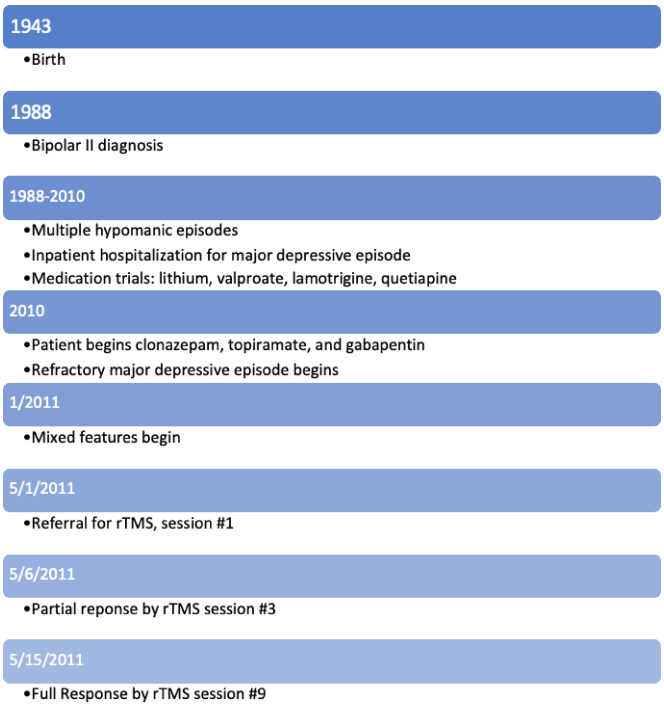
Previous treatment history included several years of medications that were either ineffective or merely transiently effective. Medication trials included lithium, valproate, lamotrigine, and quetiapine. Trials of adjunct antidepressants had occasional benefits. Unfortunately, her most beneficial treatment, lithium, was suspended following severe lithium-induced hypothyroidism that was treated with levothyroxine. She had no history of neuromodulation treatments of any modality. She declined the re-initiation of a mood stabilizer or antipsychotic given her frustration with previously unsuccessful trials. She also declined electroconvulsive therapy (ECT). Other medical history was significant for dyslipidemia, type II diabetes mellitus treated with combination sitagliptin-metformin, gastroesophageal reflux disease treated with omeprazole, and hypertension treated with furosemide and combination valsartan-hydrochlorothiazide.

The patient continued to decline ECT given concern for side effect profile, and as a result, the patient was ultimately referred for rTMS due to her unremitting, 4-month, mixed episode that was failing response despite a psychiatric medication regimen of clonazepam 1 mg TID, topiramate 50 mg BID, and gabapentin 200 mg TID.

## Clinical findings

Her depressive symptoms included depressed mood, anorexia, anhedonia, amotivation, poor concentration, and psychomotor agitation. She denied suicidal ideation. Hypomanic symptoms consisted of irritability, pressured speech, racing thoughts, distractibility, significant feelings of edginess and tension, and decreased need for sleep.

## Timeline




## Diagnostic assessment

At the time of presentation, her baseline Montgomery-Asberg Depression Rating Scale (MADRS) was 32 and Young Mania Rating Scale (YMRS) was 22. STMS was begun after obtaining informed consent, including a discussion of the possibility of inducing mania.

## Therapeutic intervention

Medications were held constant throughout her acute TMS treatment. She received nine daily sessions using the Neuronetics NeuroStar system. Treatment was administered over the left dorsolateral prefrontal cortex (DLPFC) with targeting fashioned after the standard Neurostar 5 cm rule (1). Similarly, the following standard settings were utilized: 120% MT, 10 Hz (4 sec ON, 26 sec OFF), and 3,000 pulses/session. She had a total of 9 treatment sessions on 9 separate days, with each TMS session consisting of 3,000 pulses, totaling 27,000 pulses over the course of treatment.

## Follow-up and outcomes

Our patient reported feeling better continuously throughout her TMS course, and irritability had subsided. A family member, who was around her most of the time, noted a significant benefit. The patient reported a noted response as early as TMS session #3; although encouraging, a placebo effect could not be ruled out. By TMS session #9 she reported feeling more stable than she had in years, with symptoms consistent with euthymia. Her reports of feeling stable were consistent with her MADRS of 2 and YMRS of 0. We offered a maintenance TMS taper, but the patient preferred to return home, to an area where there were no TMS psychiatrists. She followed up with her outpatient psychiatrist, and remained on the initial benzodiazepine dosage but discontinued all other pharmacotherapy. She experienced no symptoms of relapse in the year following her TMS course.

## Discussion

Bipolar disorder and its subtypes are chronic mood disorders affecting approximately 5% of the population (2, 3). Prominently classified in 1921 by Kraepelin (4) interest in bipolar disorder nosology traces back even further to the origins of psychiatric classification, with Hippocrates (460–337 BCE) identifying "melancholia, mania, and hypomania" (5). Kraepelin's "mixed forms" of affect in bipolar disorder occur in 40% of patients with bipolar depression (3), and are at present classified in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) as the specifier "with mixed features" (6). These episodes meet the full criteria for major depression, hypomania, or mania, with at least three symptoms of opposite polarity (6).

At baseline, patients with bipolar disorder have the highest rate of suicide of any psychiatric disorder, with rates 30 to 60 times higher than that of the general population at 20% (2). Mixed episodes further elevate suicide risk and are associated with higher rates of treatment resistance, comorbid medical and psychiatric illnesses, and decreased quality of life (2, 7, 8). There is no single pharmacologic agent indicated for mixed affective states of bipolar disorder based on randomized controlled trials (RCTs), with patients often trialing multiple medications with partial symptom improvement (3). The prevalence of polypharmacy in mixed states may result in decreased compliance and increased side effect profiles, such as lithium-induced hypothyroidism as in our patient. Management of lithium-induced hypothyroidism is consistent with that of primary hypothyroidism, with thyroxine initiation indicated for thyroid-stimulating hormone values > 10 mU/L (9). Given the straightforward treatment of lithium-induced hypothyroidism and the efficacy of lithium, its discontinuation is not recommended (9, 10). Patients like ours who decline lithium re-initiation should be presented with a thorough risk versus risk discussion, emphasizing the treatability of side effects and risks of uncontrolled mood episodes, before initiating an alternative mood stabilizer or another pharmacologic agent.

Despite their side effect profile, mood stabilizers including anticonvulsants remain first-line agents for mixed states, followed by atypical antipsychotics (3, 11). Thus, trialing a different mood stabilizer and then an atypical antipsychotic was recommended to our patient, but again she declined pharmacologic agents. Amongst mood stabilizers, lithium and lamotrigine may have decreased efficacy while valproate and carbamazepine have been shown to be effective in mixed states (3). While no RCTs have been performed using gabapentin and topiramate in mixed states, open-label studies have shown clinical benefit for patients, consistent with our patient's partial improvement on these agents (3).

Antidepressant monotherapy is contraindicated due to the concern for manic switches, and chronic benzodiazepine usage is discouraged due to concerns for rebound anxiety, dependence, and agitation (3, 11). Our patient's regimen of 3 mg of clonazepam daily at the time of presentation was not in line with these recommendations. Given her physiological dependence after a year on this medication, she declined dose adjustment at the time of the TMS consultation and we counseled her on tapering it with her outpatient psychiatrist. While benzodiazepines have been used to manage acute anxiety and agitation in refractory bipolar mania, recent work has shown that long-term use among bipolar benzodiazepine initiators is high, suggesting the need for caution in acute episodes given their concern for abuse potential and adverse side effects (12).

Electroconvulsive therapy, proven effective in both manic and depressive episodes of bipolar disorder, has also been reported to be highly effective in several refractory cases of mixed states (13). However, no standardized ECT protocol has been designed for mixed states, and no RCT has been conducted at this time (13, 14). Previous studies have shown equal response rates in bipolar and unipolar depression, low rates of manic switches, and up to 68% response to ECT in mixed states (13). Though ECT's antidepressant and antimanic mechanisms remain unknown, the anticonvulsant hypothesis has been proposed as an explanation for ECT's efficacy in bipolar disorder (15). Previous studies have shown decreased functional connectivity in the left DLPFC (Brodmann area 46) and adjacent Broca's area (Brodmann areas 44 and 45) after ECT (16). This is consistent with the hyperconnectivity model of limbic dysregulation (16, 17). ECT has been posited to exert inhibitory effects as an anticonvulsant in frontal areas as opposed to its neurogenic effects seen in temporal areas, which in turn may also play a role in its mood stabilization properties (15).

Given concern for ECT's side effect profile, wariness regarding the use of anesthesia, and the increasing availability of neuromodulation methods that do not elicit a seizure, patients like ours may elect to trial TMS off-label. However, it is prudent to have precautionary measures in place for off-label TMS, including the capability for inpatient hospitalization should symptoms worsen. Though side effects may be avoided with TMS, its response rates in unipolar depression remain inferior to those of ECT. TMS has been proven to be an effective treatment with minimal side effects for unipolar depression, for which it is FDA-approved (18, 19). Following Faraday's Law, the TMS coil works by generating an alternating electric current, which

discharges a magnetic field on the scalp resulting in an orthogonal electric field affecting cortical neurons to restore physiological rhythms that may be aberrant. High-frequency (10 Hz) TMS is thought to be excitatory, causing cortical neuron depolarization, and low-frequency (1 Hz) TMS is believed to be inhibitory, causing cortical neuron hyperpolarization (20). Given the durability of TMS after treatment, it is believed to exert effects through dopaminergic and glutamatergic neurotransmission, leading to lasting downstream long-term potentiation and depression (21).

Though robust literature exists on TMS for unipolar depression, at present, no RCTs have demonstrated efficacy of TMS for mania, hypomania, or mixed states (19, 22–24). However, various studies have shown promising related findings, utilizing TMS for treatment-resistant bipolar depression, maintenance treatment in bipolar disorder, and acute treatment in mixed states (25–28). One open-label study of 1 Hz right-DLPFC rTMS for mixed states showed promising preliminary findings (28). However, the risk of inducing mania with TMS remains equivocal and warrants further study (23, 29, 30). Choosing low-frequency stimulation to the right DLPFC target would have been reasonable for our patient. At the time this patient was treated, the literature on TMS in mixed states was even more scarce, so the decision was made to utilize the protocols in place for unipolar depression for technician consistency.

Though currently no clinical practice guidelines or validated protocols exist for TMS for bipolar depression, hypomania, mania, or mixed states, one meta-analysis showed that patients who underwent 10 Hz left-DLPFC rTMS had statistically significantly lower depression scores than 1 Hz right or bilateral DLPFC rTMS when compared to sham TMS (31). Another study found efficacy for bipolar depressive episodes using 10 Hz rTMS delivered to the left-DLPFC as well, with response and remission rates greater than those in unipolar depression (32). This is further corroborated by an observational study which found that 10 Hz rTMS delivered to the left-DLPFC in patients with bipolar depression had higher response rates versus patients with unipolar depression, especially for those on non-lithium mood stabilizers, such as our patient (33).

Previous work has shown that the predominant polarity across a patient's lifetime, e.g., depression versus hypomania or mania, often guides clinician treatment selection in patients with bipolar spectrum disorders (34). Additionally, quantifying the predominant polarity in a "polarity index" has been shown to predict response to pharmacologic and psychotherapeutic treatments (34–36). However, this approach has not taken mixed features into account, with the majority of patients falling into the "undetermined predominant polarity" group, which suffers from higher aggression and relapse rates (34, 37, 38). The primary affective disturbance within a mixed episode may be a useful predictor of response to treatment (38). In line with this hypothesis, our patient's dominant depression symptoms may have further contributed to her response to 10 Hz left-DLPFC rTMS, which is the approved protocol for unipolar major depression and has been demonstrated to be safe and effective for treatment-resistant unipolar depression (18).

Another possible factor in our patient's response is the stimulation target. While initial estimates of DLPFC location based on the 5-cm target lack the precision and fidelity of more sophisticated Beam F3 or functional MRI (fMRI)-guided methods which yield a more anterolateral target, greater efficacy in bipolar disorder has resulted from using the 5-cm target (39, 40). Additionally, the 5-cm target has shown peak negative connectivity to the mania network map in the left DLPFC and peak positive connectivity in the right DLPFC (39).

Another theory that supports the role of predominant polarity in guiding treatment in bipolar spectrum disorders using neuromodulation is the frontal asymmetry hypothesis. Previous fMRI studies have shown asymmetrical cerebral hemisphere activation, with positive emotional valence associated with left hemisphere hyperactivity (decreases in prefrontal inhibitory alpha oscillations) and negative valence with right hemisphere hyperactivity in healthy controls (39, 41, 42). Additionally, lesion studies have shown right-hemispheric hypoactivity in mania and left-hemispheric hypoactivity in depression (39, 43–45). It follows that an approach to treating a patient with dominant manic symptoms would be exciting the hypofunctional area (right DLPFC) or inhibiting the hyperfunctional area (the left DLPFC). Previous studies have shown efficacy for 10 Hz right-DLPFC rTMS in mania (45), and additional work has shown negative connectivity between this stimulation target and the mania network map (39). At this time, no studies to our knowledge have examined hemispheric activation in mixed states. Given the concomitant nature of mixed episodes, further study of hemispheric asymmetry is needed to determine the role predominant symptom polarity plays in selecting a TMS treatment protocol for medication-refractory patients.

## Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

BC and EB wrote the first draft of the manuscript and conceptualized the discussion section. RH provided the clinical resources for case report. All authors contributed to the manuscript editing, revision, read, and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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# Rapid symptom control in neuroleptic malignant syndrome with electroconvulsive therapy: A case report

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**Introduction:** Neuroleptic malignant syndrome (NMS), thought to arise through dopamine antagonism, is life-threatening. While prompt diagnosis of NMS is critical, it may be obscured by other diagnoses, such as malignant catatonia, with overlapping, life-threatening symptoms. Initiation of dopamine-blocking agents such as antipsychotics and abrupt cessation of dopaminergic medications such as amantadine can precipitate NMS. Once NMS is suspected, deft medical management should ensue. Multiple case reports detail electroconvulsive therapy's (ECT's) effectiveness in the treatment of NMS. While this relationship is well-documented, there is less literature regarding comparative efficacy of ECT in the acute treatment of NMS-like states precipitated by withdrawal of dopamine agonists, such as amantadine.

**Case:** We present a 52-year-old female with schizoaffective disorder bipolar type, with a history of a lorazepam-resistant catatonic episode the prior year that had responded to amantadine. She presented febrile with altered mental status, lead pipe rigidity, mutism, grasp reflex, stereotypy, autonomic instability, and a Bush-Francis Catatonia Rating Scale (BFCRS) of 24, suggesting malignant catatonia versus NMS. There was concern over a potentially abrupt cessation of her amantadine of which she had been prescribed for the past year.

**Interventions:** Organic etiologies were ruled out, and a presumptive diagnosis of NMS was made with central dopaminergic depletion from abrupt dopamine agonist (amantadine) withdrawal as the suspected underlying etiology. After intravenous lorazepam and reinduction of amantadine failed to alleviate her symptoms, urgent ECT was initiated. Our patient received an index series of ECT of seven treatments. After ECT #1 she was no longer obtunded, after treatment #2 her symptoms of mutism, rigidity, stereotypy, and agitation showed improvement, and by ECT #3, the NMS had rapidly dissipated as evidenced by stable vital signs, lack of rigidity, and coherent conversation.

**Conclusion:** Brisk identification of potentially life-threatening NMS and NMS-like states, including malignant catatonia, warrants a trial of ECT. ECT's theoretical mechanisms of action coincide with the theoretical pathophysiology of the conditions. It is a viable and safe treatment option for reducing mortality. With prompt initiation of ECT, we obtained rapid control of a condition with a potentially high mortality.

KEYWORDS

electroconvulsive therapy, neuroleptic malignant syndrome, catatonia, amantadine, case reports, schizoaffective disorder

## Introduction

Neuroleptic malignant syndrome (NMS) is a life-threatening condition characterized by fever, abnormal and widely fluctuating vital signs, "lead-pipe" rigidity, and elevated creatinine kinase (CK) (1). It is thought to arise through dopamine (DA) antagonism. The mortality rate of NMS is reported to be between 5 and 20%, with the rate increasing to up to 70% with complications such as aspiration pneumonia such that prompt diagnosis is critical (2, 3). With high symptom overlap, NMS is phenomenologically and physiologically related to malignant catatonia. The distinction, however, is that NMS is related to effective DA depletion such as antipsychotics (DA antagonists) or the withdrawal or rapid cessation of a dopaminergic agonist (4–6). Perhaps NMS lies on the most extreme continuum of severity of an underlying, diverse condition known as catatonia with its incompletely understood pathophysiological processes (7). Even with rapid cessation of DA agonists, NMS is not always induced, yet milder symptoms of NMS, mood symptoms, or motor abnormalities may be noted. Symptom clusters such as dysphoria, anxiety, fatigue, suicidal thoughts, orthostatic hypotension, and agitation are sometimes described as dopamine agonist withdrawal syndrome (DAWS).

In general, catatonia is often underdiagnosed, a result of its various presentations and variety of subtypes. The classic subtype, stuporous catatonia, is marked by the hallmark features of mutism, staring, immobility, withdrawal, posturing, and waxy flexibility (8). Contrast this to the subtype, excited catatonia, where psychomotor agitation, stereotypies, mannerisms, verbigeration, and echolalia predominate (9). And even more bewildering is periodic catatonia, involving fluctuations between excited and stuporous states; and delirious mania that manifests as typical mania, with signs of delirium, fever, and vital sign derangement (9). Most concerning, however, is malignant catatonia, first described in 1934 by Stauder, that is characterized by delirium, fever, stupor, and a mortality rate of over 50% (10).

Among patients seen on inpatient consultation-liaison psychiatry services, up to 6% may have catatonia (11). Due to the high mortality rates of NMS and malignant catatonia, it is essential to establish the diagnosis early. The variable presentations of catatonia and altered mental status are confounding and require a broad differential diagnosis. Moreover, serotonin syndrome has overlapping features with both catatonia and NMS, including abnormal vital signs and elevated CK (12). Linked to serotonergic activity (rather than DA), it manifests with hyperreflexia rather than muscle rigidity (12). Catatonia can be either primary, arising from an underlying psychiatric etiology such as a mood disorder or schizophrenia. Or it may be secondary to a toxic, metabolic, or neurological process. A useful, validated instrument aiding in the assessment is the Bush-Francis Catatonia Rating Scale (BFCRS) which assists in making the clinical diagnosis. The presence of 2 of 14 screening items is needed for diagnosis (8, 13). And a list of 23 items is provided to scale symptom severity. The DSM-5-TR provides an alternative metric and requires 3 of 12 diagnostic criteria (14). Given only 2 items are needed for a diagnosis of catatonia, BFCRS will be positive in patients with NMS, due to symptom overlap.

Malignant catatonia and NMS are similar conditions. The key differentiator is that NMS is precipitated by dopamine antagonism or by withdrawal of a dopaminergic agent (15). This contrasts with malignant catatonia arising from a primary underlying condition. In this sense, NMS might be considered as having a more iatrogenic origin—such as the addition of a DA antagonist or the removal of a DA agonist. Regardless of whether NMS is considered an iatrogenic malignant catatonia or merely the periphery on a continuum of catatonia, once either is suspected, deft medical management should ensue. ECT affords one of the fastest treatment responses within psychiatry for catatonia and a similarly rapid response is detailed in multiple case reports for the treatment of NMS due to antipsychotic use (15, 16). While its effectiveness is well-documented, there is less literature regarding efficacy or the speed of response to ECT for the acute treatment of NMS when it arises from DA agonist withdrawal, such as amantadine withdrawal.

## Case description

We present a 52-year-old female with schizoaffective disorder bipolar type, cutaneous lupus erythematous, rheumatoid arthritis, chronic kidney disease stage III, and seizure history requiring no antiepileptic medication. She presented to the emergency room febrile, with altered mental status, lead pipe rigidity, mutism, grasp reflex, stereotypies, autonomic dysfunction, tachycardia (110 beats per minute), hypertension (systolic blood pressure of 180 mm Hg). Creatine kinase and white blood cell counts were within normal limits. Within 48 h of admission, she experienced acute hypoxic respiratory failure and unspecific seizure activity requiring intubation. She received 2 mg intravenous lorazepam and a 30 mg/kg loading dose of levetiracetam with 500 mg every 12 h. This was complicated by aspiration, presumed to be from either rigidity or seizure, that led to MRSA pneumonia being treated with intravenous antibiotics. However, motor rigidity and autonomic abnormalities remained unchanged despite resolution of her pneumonia.

EEG monitoring revealed multiple head and arm shaking events; however, the recording did not have an electrographic correlate, wherein non-convulsive seizures were ruled out. Brain MRI was unrevealing. Lupus cerebritis and meningitis were ruled out through serologic testing, urosepsis was ruled out with urinalysis. The patient was subsequently extubated after being deemed able to protect her airway.

Her BFCRS was 24. Her current home medications included hydroxychloroquine 200 mg daily, prednisone 5 mg three times daily, amantadine 100 mg daily, venlafaxine extended release 75 mg daily, and lamotrigine 100 mg nightly. Of concern was her previous catatonic episode 1 year prior that had failed to respond to a four-week course of lorazepam that had been titrated to divided doses of 9 mg daily. However, that previous episode of catatonia remitted rapidly after initiation of amantadine. Unfortunately, further details regarding the treatment course of that episode are unknown.

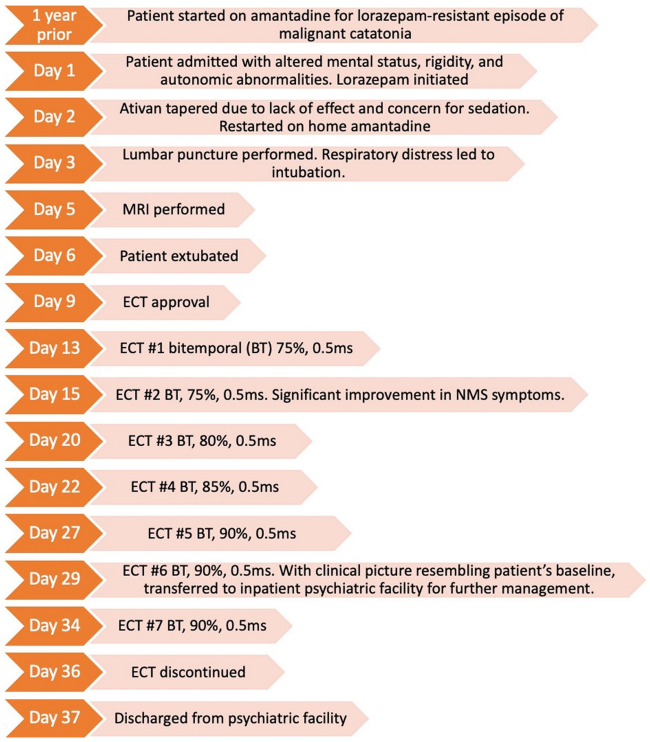
Neuroleptic malignant syndrome vs. malignant catatonia were both high on the differential diagnoses. The emergency room had given a report of a rapid reduction in her amantadine, suggesting the potential of disruption in central dopaminergic activity, such that a presumptive diagnosis of NMS was made. The patient's home amantadine was restarted. However, she showed only minimal, partial improvement in rigidity following amantadine resumption, and continued to exhibit severe catatonic symptoms.

After failing to improve with both intravenous lorazepam 4 mg four times per day and re-initiation of amantadine, an urgent index series of ECT was initiated once legal consent obligations were met. On the morning of her first ECT (now hospital day 12), she remained obtunded and continued to exhibit lead pipe rigidity, mutism, stereotypies, a grasp reflex, tachycardia, and hypertension. Bitemporal electrode placement was selected to afford potentially the fastest response rate (17). ECT stimulus parameters prioritized low frequency over stimulation train duration which offer the most efficient means for seizure induction. The initial total charge dose was 379 mC (0.9A, 0.5 ms, 7.0 s, 60 Hz). Although only theoretical as quality indicators, device seizure quality data is listed for reference: time to peak coherence (6 s) and to peak power (8 s), with the maximum power at 6406 μV (2). Maximum sustained coherence was 91.8%. The seizure abruptly stopped at 31 s with notable post-ictal suppression. All the remaining ECT-induced seizures ranged between 26 and 31 s, and all were deemed efficacious in quality based on seizure morphology.

By 12 h post ECT #1 she was no longer obtunded, becoming alert for the first time since her admission 12 days prior. Her rigidity had also lessened. After ECT #2, her agitation and mutism ceased. She was able to follow commands, state her name, and engage in brief conversation. Her bilateral rigidity was notably improved. The following day post- ECT #2, she reported feeling "much better" have some recollection of her feelings of agitation on the previous days. The remainder of the ECT series (totaling #7) was without complication and well-tolerated. During mid- ECT series, her seizure threshold was suspected to rise based on seizure EEG morphology and duration. This led to subsequent total charge dose titrations with a final charge dose of 454 mC.

After the resolution of the presumptive NMS, our patient manifested symptoms consistent with her long-standing diagnosis of schizoaffective disorder. Despite improved orientation, symptoms included looseness of associations, response to internal stimuli, and auditory hallucinations such that she was transferred to a free-standing community psychiatric hospital for ongoing treatment. It was strongly recommended that she enter a continuation ECT taper, especially given her ongoing psychosis with potential need for an antipsychotic which was concerning given the recent episode of NMS.

## Timeline




## Discussion

The pathophysiology of both catatonia and NMS are yet to be fully elucidated; however, it is thought to be related to a state of gamma-aminobutyric acid (GABA)-dependent dopamine (DA) depletion in various corticostriatal neural circuits (18). These networks include the motor circuit, anterior cingulate, orbitofrontal circuit, lateral hypothalamic connections, and lateral orbitofrontal circuit (18). Dopamine signaling in the striatum and paralimbic cortex is thought to be diminished as a result of reduced GABA-A inhibition of GABA-B (which decreases DA activity) (1). And benzodiazepines, such as lorazepam, a GABA-A agonist, are thought to improve catatonia by acting on this pathway (19). Conversely, reduced GABA-A inhibition of frontal corticostriatal tracts is associated with increased *N*-methyl-D-aspartate (NDMA) receptor activity, which is also thought to play a role in the pathogenesis of catatonia (20). Finally, amantadine and memantine, which antagonize such NMDA receptors, are sometimes used as adjunctive or alternative treatments for catatonia (21).

Patients with a history of malignant catatonia, such as our patient, are predisposed to higher rates of both a recurrence of catatonia and an incidence of NMS (22). Due to the high mortality risks associated with both malignant catatonia and NMS, consideration of ECT is warranted regardless of any ability to distinguish between these two conditions. For our patient, whose symptoms were presumed to be sequelae of dopamine agonist withdrawal (and whose symptoms persisted despite both re-initiation of amantadine and a trial of lorazepam), it was deemed critical to begin ECT for urgent symptom control (23, 24).

For our patient, a DA agonist withdrawal would have created a relative dopamine depletion. The symptoms arising from this

depletion would be expected to respond to ECT (25, 26). It is theorized that ECT is efficacious for the treatment of NMS by increasing dopamine sensitivity and increasing dopamine release, in addition to increasing GABAergic, serotonergic, and noradrenergic transmission (25, 27–31). Limitations of this case report partially lie in the unverifiability in reports regarding her medication compliance, the timing of amantadine cessation, and the degree of her compliance prior to this reported abrupt cessation. However, even had this information been known, it would have mostly aided in diagnostic certainty rather than affording information on the potential efficacy of ECT. It is also unclear how much time was needed after amantadine re-initiation before a response is expected. After 12 days of having resumed amantadine, our patient had shown only an equivocal clinical improvement.

Although it is unknown if ECT was singularly causal in her rapid response, her NMS resolved only after initiation of ECT. It is theoretical that her meager response from amantadine was present with a potentially greater response emerging. Her severe symptomatology had continued despite amantadine re-introduction, yet she had at least not required intubation after the aspiration event. If any positive effects of amantadine were underway or were synergistic with the effects of ECT it was overshadowed by the robustness of her response and would have coincided with precisely the time of the first ECT treatment. It is also possible the effects were solely due to the ECT itself despite only one ECT treatment. Rapid changes occur within the brain during and after only one ECT. Same-day ECT responses are seen when treating catatonia (32); in depression, ECT can rapidly induce a mood change where polarity switches from depression to hypomania have been noted within 1–3 days of ECT of initiation of ECT 33–36.

However, the robustness of response does not aid in clarifying the issue as to whether this may be malignant catatonia instead, or that malignant catatonia and NMS are variations of the same phenomenon. One might even speculate that NMS arising from neuroleptic's DA antagonism is different from NMS arising from DA agonist withdrawal—i.e., various NMS-like states. This is consistent with the idea that catatonia is a continuum. Moreover, case reports have suggested that rapid cessation of amantadine led to neuroleptic induced catatonia (NIC), again suggesting that catatonia and NMS are syndromes along a dopamine blockade continuum (26).

Even though our patient's dose of amantadine was not particularly high (100 mg per day), its abrupt cessation is theoretically high enough to explain her presentation. There are reports of dose reductions of 100 mg every 2 days as unproblematic; however, the authors here suggest that dose reductions of 50 mg every second or third day (or slower), as being more prudent (37). Other reports have cited that even during a 2–3-day amantadine taper, such as with 200 mg or 300 mg, NMS cases have emerged (38, 39). These case reports also mention patients experiencing dopamine agonist withdrawal who have an array of unpleasant mood or motor symptoms yet do meet the full severity of an NMS—again suggesting a continuum.

Another consideration is that our patient's home medication, lamotrigine, played a role in her symptoms. Early animal studies note that chronic treatment with lamotrigine regulates the expression of the inhibitory neurotransmitter GABA-A receptor (40). Moreover, lamotrigine also inhibits voltage-sensitive sodium channels, suppressing the release of glutamate (41). Only a few case reports have implicated lamotrigine as a contributor to NMS (although the underlying pathophysiology was unclear); and we noted only two that reported on its being implicated in isolation from any concurrent atypical antipsychotic use (42–44). These reports describe the occurrence of an NMS-like phenomena that occurred during a lamotrigine titration (or at least during the early weeks of its use), often in augmentation with an antipsychotic. However, our patient had been on lamotrigine for over a year. And, as with the amantadine, the actual medication compliance was unknown such that any contributory effects from lamotrigine for our case are also unknown. Regardless, should lamotrigine have been contributory to an NMS-like clinical picture, it would not have changed our decision to pursue ECT, which notably, increases GABAergic transmission.

Treatment refractory mood disorders typically respond to twice or thrice weekly ECT over a few weeks. The most optimal frequency for treating NMS is less well-established. Yet, given the potentially high mortality rate from NMS, daily ECT might even be justified when available. Our ECT treatments were delivered biweekly using bitemporal ECT electrode placement. It is unclear if more frequent ECT would have hastened her response but given the abrupt dissipation of her symptoms this seems moot.

This case also highlights the utility of ECT in patients who develop NMS secondary to withdrawal of dopaminergic agents, such as levodopa (in Parkinson's Disease) and amantadine. The use of ECT should not be considered exclusive to psychiatric patients should symptoms arise suggesting an NMS-like state for such non-psychiatric patients. Moreover, BFCRS is an excellent tool for catatonia, but an underlying NMS should always be considered in the differential diagnosis given the large symptom overlaps. Given that malignant catatonia and NMS are both conditions with high mortality rates, it is critical to rapidly distinguish them from the problematic, but less pernicious, typical catatonia. This case further reinforces the notion that ECT is a safe and rapidly effective treatment for NMS. Here, ECT was effective in amantadine withdrawal-precipitated NMS, just as it has been shown to be for other NMS-like conditions. For antipsychotic induced NMS cases arising in patients with first order psychotic illnesses, it is likely they will continue to need dopamine antagonist medications. Given the well-documented benefits of a continuation taper of ECT for relapse prevention in mood disorders, it would be prudent to consider this for NMS patients as well. However, such guidelines are not well established.

In 200 words, describe the contribution of your manuscript to the research field. You should frame the research question(s) addressed in your work in the context of current knowledge, highlighting how the findings contribute to progress in your research discipline.

This case highlights the utility of ECT in treatment of NMS precipitated by amantadine withdrawal. ECT afforded rapid symptom reduction. This paper also importantly details the distinction between various forms of catatonia and the necessity of early recognition of malignant catatonia and the related condition, NMS. This case is applicable to physicians in multiple specialties, as many fields may encounter patients at risk for malignant catatonia and NMS, and awareness is paramount to swift intervention.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

BC, RV, and LK wrote the first draft of the manuscript. BC and LK wrote the final draft. All authors contributed to manuscript writing, editing, revision, and approval of the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Electroconvulsive therapy triggers a reversible decrease in brain N-acetylaspartate

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**Introduction:** Based on previous research on electroconvulsive therapy (ECT) we have proposed a model where *disruption, potentiation,* and *rewiring of brain networks* occur in sequence and serve as the underlying therapeutic mechanism of ECT. This model implies that a temporary disturbance of neuronal networks (disruption) is followed by a trophic effect (potentiation), which enables the rewiring of neuronal circuits to a more euthymic functioning brain. We hypothesized that disruption of neuronal networks could trigger biochemical alterations leading to a temporary decrease in N-acetylaspartate (tNAA, considered a marker of neuronal integrity), while choline (a membrane component), myo-Inositol (mI, astroglia marker), and glutamate/glutamine (Glx, excitatory neurotransmitter) were postulated to increase. Previous magnetic resonance spectroscopy studies, reporting diverse findings, have used two different referencing methods - creatine ratios and tissue corrected values referenced to water – for the quantification of brain metabolites. Changes in creatine during ECT have also been reported, which may confound estimates adopting this as an internal reference.

**Methods:** Using MR spectroscopy, we investigated 31 moderately to severely depressed patients and 19 healthy controls before, during, and after ECT or at similar time points (for controls). We tested whether biochemical alterations in tNAA, choline, mI, and Glx lend support to the *disrupt, potentiate, and rewire hypothesis.* We used both creatine ratios and water-scaled values for the quantification of brain metabolites to validate the results across referencing methods.

**Results:** Levels of tNAA in the anterior cingulate cortex decreased after an ECT treatment series (average 10.6 sessions) by 6% ($p$=0.007, creatine ratio) and 3% ($p$=0.02, water referenced) but returned to baseline 6 months after ECT. Compared to after treatment series tNAA levels at 6-month follow-up had increased in both creatine ratio (+6%, $p$<0.001) and water referenced data (+7%, $p$<0.001). Findings for other brain metabolites varied and could not be validated across referencing methods.

**Discussion:** Our findings suggest that prior research must be interpreted with care, as several referencing and processing methods have been used in the past. Yet, the results for tNAA were robust across quantification methods and concur with relevant parts of the *disrupt, potentiate, and rewire* model.

KEYWORDS

depression, electroconvulsive therapy, $^{1}$H-MRS nuclear magnetic resonance spectroscopy, neurometabolites, choline, myoinositol, glutamate

## 1. Introduction

Electroconvulsive therapy (ECT) is a therapy for depression that is mainly used in non-responders to antidepressant pharmacotherapy and in patients requiring fast and effective symptom alleviation (1). The treatment is performed by placing electrodes on the patient's scalp and applying an electrical current to the brain, inducing a seizure. Although it is well established that ECT is an effective treatment for major depressive disorder (MDD) (2) the neurobiological underpinnings of the clinical response are still being investigated.

MR spectroscopy (MRS) is a practical and non-invasive MR-technique that allows investigation of the brain's neurobiology *in vivo*. By exploiting the differences in resonance frequency between molecules certain metabolites can be studied. This gives a unique opportunity to study the neurobiological underpinnings of ECT. Most commonly the hydrogen nucleus (a single proton) is used as origin for the MRS signal, giving the $^{1}$H-MRS spectrum. The total received signal, hence the estimated amplitude and area under the curve, will depend on several factors, including field strength, relaxation effects, and coil properties and loading; several of these are difficult to reliably control for. As such, a stable reference signal is commonly adopted to scale the amplitude and correct for these unknown factors. Though processing pipelines vary, two main referencing methods are used: the metabolite ratio relative to total creatine (/tCr), or water referenced values (/$H_2O$). Both have been used in previous ECT research (3). Since variation in creatine itself has been shown to occur following ECT (4) we have explored both creatine ratios and water referenced metabolite levels. When examining neurobiological underpinnings of ECT, several molecules are of interest - such as N-acetylaspartate (NAA), choline (Cho), myo-Inositol (mI), and glutamate/glutamine (Glx).

The disrupt, potentiate, and rewire (DPR) hypothesis (5) suggests that ECT leads to temporary disruption of neuronal networks, followed by a trophic effect (potentiation), which enables the rewiring of neuronal circuits to a more euthymic functioning brain. It is assumed that in the depressed state, before ECT, the brain has a low plastic potential [as shown in both animal and post-mortem studies, summarized by Ousdal (5)], and it is hypothesized that the temporary disruption created by ECT clinically is seen as post-ictal confusion and, for some, as reduced cognitive performance. This is supported by a meta-analysis which found reduced cognitive functioning 4 days after ECT, but a return to baseline levels or better was seen after 15 days (6). On a neuroradiological level, we hypothesize that disruption is seen as metabolite alterations (3), altered functional connectivity (7), and changed white matter integrity (8). Responding to this disruption, temporary upregulation of neuroplasticity is seen ("potentiate"), reflected in both metabolite changes and increased gray matter volume. During or following this neuroplastic upregulation, previously maladaptive depressive networks may rewire to non-depressed states. Although MRS cannot test the complete DPR-hypothesis, we explored whether metabolite levels measured over the ECT treatment course are as expected under the framework of the DPR- hypothesis.

NAA is the most abundant metabolite in the $^{1}$H-MRS spectrum of the healthy brain. Decreased levels of NAA are seen in brain injury and disease, and in $^{1}$H-MRS, NAA is considered a marker of neuronal integrity (9, 10). $^{1}$H-MRS *total* NAA values (tNAA) are comprised of NAA and closely resonating NAAG, which only amounts to a small part of the signal intensity (10). Maddock and Buonocre have summarized findings for depression, where lower NAA levels have been seen in bipolar depression compared to controls, but not in unipolar depression (11). Several studies have also found lower NAA levels after ECT treatment, as summarized in a recent review (3). NAA could serve as a potential marker of the temporary disruption in the disrupt-potentiate and rewire hypothesis. Equivalent to this theory, NAA decrease has been seen to reverse after successful treatment in epilepsy (12).

Choline is primarily a building block for cell membranes. The choline peak reported in $^{1}$H-MRS at 3.2 ppm consists of several choline compounds: glycerophosphocholine (GPC), phosphocholine (PCh), and free choline, often reported together as total choline (tCho). An increase in choline may reflect both choline synthesis and membrane damage, hence it must be interpreted with care (13). Reviews report increased levels of choline in depression, primarily in the basal ganglia (11, 14), and attribute this to increased membrane turnover. In both a review of depression (15), and an ECT specific review (3), an increase in choline has also been found comparing pre-treatment to post-treatment values. In relation to the DPR-hypothesis, an increase in choline could reflect both disruption (increase due to affection of cell membranes) as well as potentiation and rewiring (increase due to increased membrane turnover).

Primarily three roles are known for mI: as a lipid component for biomembranes, part of an intracellular second messenger system (releasing calcium), and as an osmolyte (10). The antidepressant and mood stabilizer lithium affects Ins levels by blocking its resynthesis. It has therefore been hypothesized that high Ins levels are part of the pathogenesis in bipolar disorder (16, 17), but no consistent Ins alterations have been shown in bipolar patients (11). In depressed patients, $^{1}$H-MRS investigations have not shown higher levels of Ins compared to controls, but rather decreased levels (18–20), which increase with pharmacotherapy (18). Additionally, orally administered Ins has been studied as a potential treatment for depression (21), and a meta-analysis (22) suggested that depressed patients might benefit from Ins. In $^{1}$H-MRS, mI is proposed as a marker for glia cell proliferation (23), and is widely studied as such (16), though this interpretation is disputed - as neural cell lines also have displayed high levels of mI (24). In light of the DPR hypothesis, an increase in mI could reflect

the rewiring and potentiation, due to glial cell proliferation after disruption. In ECT patients, one investigation has shown an increase of mI in the anterior cingulate cortex (ACC) after treatment (25).

Glutamate (Glu) is the main excitatory neurotransmitter in the brain; measured with $^{1}$H-MRS at 3T it is difficult to distinguish from Glutamine (Gln), hence the two are often reported together as Glx – wherein Glu is usually the dominant component due to its substantially higher concentration. Its concentration has been measured to be lower in depressed subjects compared to healthy controls (11, 14). Both neurostimulation and medication have been seen to increase Glu levels in depressed patients (11). However, excessive levels of extracellular Glx are neurotoxic (10). Within the theoretic framework of the DPR hypothesis, excessive Glu release during seizures could be a factor mediating neuronal disruption and thus a change in Glx levels would be expected to be the opposite of a change in tNAA levels.

The total Creatine (tCr) signal in $^{1}$H-MRS originates from Creatine (Cr) and phosphocreatine (PCr). tCr is often assumed to be somewhat stable and is therefore often chosen as an internal concentration reference. However, Cr concentration in the brain may be related to neural activity and/or vascularization and has been shown to vary with intake (26) and in certain conditions and pathologies (27–30), therefore its role as a reference metabolite has been criticized (10, 31). One previous $^{1}$H-MRS investigation in ECT patients has shown an increase in Cr in the ACC related to ECT (4). Both creatine ratios and water referenced metabolites have been used in previous ECT literature, but these referencing methods have not yet been compared in this clinical setting.

### 1.1. Aim and hypotheses

In this investigation, we aimed to investigate metabolite changes during ECT treatment and relate them to the DPR hypothesis. Specifically, we hypothesized that tNAA levels decrease after ECT treatment, due to temporary disruption of neuronal integrity. At 6-month follow-up, tNAA levels return to baseline levels or higher. There is a negative correlation between tNAA and everyday memory impairment. tCho levels increase after ECT due to temporary disruption of cell membranes. This increase from baseline is no longer seen at 6-month follow-up. There is a positive correlation between tCho rise and everyday memory impairment. Baseline mI levels are lower in patients compared to controls and increase during treatment. After the ECT series, and at follow-up, mI levels remain increased for responders indicating potentiation and rewiring. Glx levels at baseline are lower in patients compared to controls. Glx levels increase with ECT and remain increased at 6-month follow-up but have their peak levels after ECT treatment series, possibly as a part of the mechanism behind disruption.

## 2. Materials and methods

This study was approved by the Regional Committee for Medical and Health Research Ethics, REC South East, Norway (2013/1032). The protocol of this study has been published previously (32); here we summarize key points relevant to the analyses in the present work.

### 2.1. Study participants and assessments

Patients referred to ECT treatment at Haukeland University hospital, Norway, between September 2013 to September 2018 were asked to participate in the study. A Montgomery and Aasberg depression rating scale (33) (MADRS) score of minimum 25 and age over 18 years was required to qualify for participation. To control for time effects, age and sex-matched healthy controls (HC) were recruited from the general population in the same area as patients through advertising in public areas. HC could not have a history of psychiatric disease, and MADRS score was taken to document that HC scored below the clinical range (<7). Written informed consent was provided by all participants. The responsible clinician (for patients) or research assistant (for HC) evaluated eligibility for inclusion and the ability to give written informed consent. Subjects who were not able to give informed consent, who were pregnant, or who could not undertake the MRI investigation were excluded. Patients who had undergone ECT treatment during the last 12 months were also excluded. Throughout the treatment course, depression severity was monitored by MADRS. MADRS scores for study purpose were acquired <7 days before participation in the study, and at the same timepoint as MR examinations after treatment (TP3) and at 6-month follow-up (TP4). Remission was defined as a ≥50% reduction of baseline MADRS score and MADRS ≤10. The everyday memory questionnaire (EMQ-28) (34, 35) is a comprehensive, subjective evaluation of everyday memory and was used to assess subjective effects on cognition. The EMQ-28 assesses everyday memory with 28 statements of forgetfulness and their occurrence, ranging from 0 (none) to 8 (more than once a day) leading to a score of maximum 224, indicating the most severe forgetfulness.

### 2.2. ECT procedure

Right unilateral (RUL) electrode placement ECT was performed using a Thymatron System IV (Somatics LLC, Venice, FL, USA). The initial stimulus charge was calculated by an age-based algorithm, where the patient's age in years x5 ≅ stimulus charge in mC. The stimulus was increased during the treatment series due to increase in seizure threshold. All patients were administered anesthesia (thiopental) and neuromuscular blockade (succinylcholine). All patients were hyperoxygenated before and during anesthesia.

### 2.3. MR-acquisition and data analysis

Patients were scanned at four timepoints: 1–2 h before treatment (Baseline), 1–2 h after first treatment (TP2), 7–14 days after completion of ECT series (TP3), and 6 months after ECT series (TP4). HC were scanned at similar time intervals as patients. The study flowchart can be seen in Figure 1.

Imaging and MRS were performed on a 3 Tesla GE Discovery 750 scanner system (Waukesha, WI, USA). A 32-channel head coil was used. For voxel localization, a 3D T1 weighted fast spoiled gradient echo (FSPGR) sequence was used (echo time = 2.9 ms, repetition time = 6.7 ms, inversion time = 600 ms, flip angle 8 degrees, field of view = 25.6, matrix size 256×256, giving an

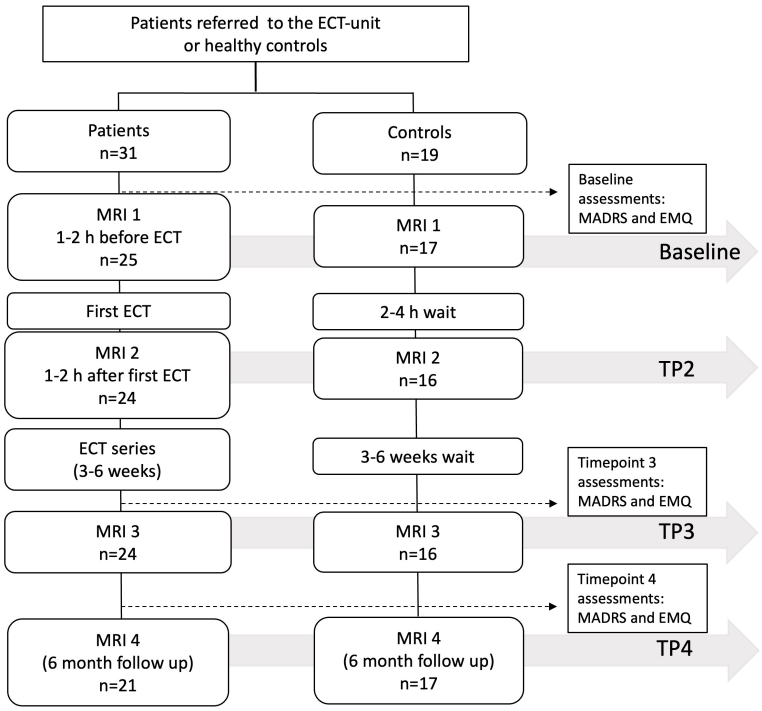


FIGURE 1
Study flowchart. Forty patients and 20 HC were enrolled in the study. Due to missing data, the number of analyzed participants at each timepoint varied as indicated in the figure.

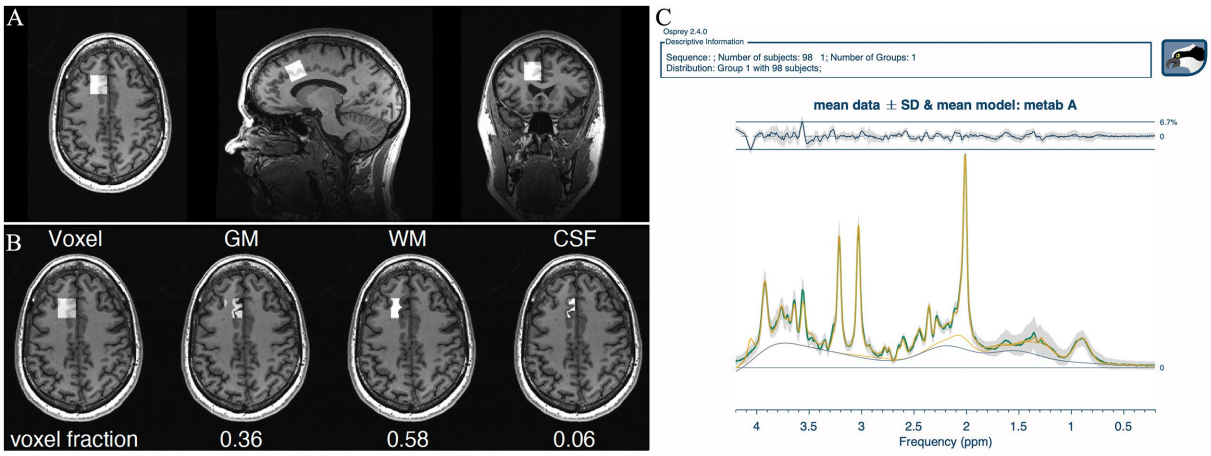


FIGURE 2
Output from Osprey (36). **(A)** Voxel placement in the ACC. **(B)** Voxel segmentation into gray matter, white matter, and CSF. **(C)** Mean spectrum of all patients at all timepoints for visualization of overall quality. Quality metrics: SNR: 48±7, linewidth 5.72±1.08Hz, mean relative amplitude residual 2.86%.

isotropic voxel size of 1x1x1 mm). The single voxel point resolved spectroscopy (SV-PRESS) voxel was placed in the anterior cingulate cortex (ACC), angled to follow the foremost slope of the corpus callosum (Figure 2). Voxel placement alternated between left and right side for every other patient to balance for lateralization effects, as right unilateral ECT creates an anatomically uneven electrical field and volume change (37). Voxel size was 2×2×2 cm (8 mL). Parameters for SV-PRESS were: echo time = 35 ms, repetition time = 1,500 ms, 128 scans, spectral width = 5,000 Hz, number of spectral points = 4,096 points, water suppression method: CHESS. Post-processing, voxel segmentation, and tissue correction were performed using the Osprey software version 2.4.0 (36). The acquired FSPGR acquisition was segmented into CSF, white matter, and gray matter, before adjusting the metabolite concentration to the proportion of gray and white matter in the voxel (38). Metabolite concentrations are reported in institutional units (IU) and presented both as creatine ratios and water referenced values. For further details, see the

table for minimum reporting standards in MRS (39) (Supplementary material S1). All spectra were visually inspected by one reader [VJE], and aberrant spectra were judged for further consensus evaluation by one additional reader [LE or ARC]. If one or more of the metabolite concentration estimates for tNAA, tCho, Glx, mI and tCr were considered extreme outliers (>the 3rd quartile +3 interquartile ranges or < the 1st quartile – 3 interquartile ranges) spectra were flagged and inspected individually. Flagged spectra were excluded if CSF proportion (for water referenced data) seemed incorrect based on visual inspection of the FSPGR acquisition compared to the proportion given in the automatic segmentation. Figure 2 shows the mean $^{1}$H-MRS-spectrum for patients. Metabolite concentrations are reported as mean ± SD.

## 2.4. Statistical analyses

Statistical analyses were performed using the R statistical software, version 4.1.3 (40). All analyses were performed both on the creatine ratio and the water referenced metabolite concentration estimates. Baseline differences between groups were investigated using two-sample's *t*-tests (for age, voxel composition, metabolite levels) or Pearson chi squared tests (for sex).

For longitudinal analyses of patients' $^{1}$H-MRS data the nlme package (41) was used to perform linear mixed effects analyses. Timepoint, sex, age, number of ECT treatments and remission were entered as fixed effects, while participant ID was entered as random effect. The contrast package (42) was used for time-specific comparisons.

Treatment effect and side effect, monitored using MADRS and EMQ-28 respectively, were explored with linear models, comparing delta change between baseline and after treatment. Sex and age were set as fixed effects. Correction for multiple testing was not performed.

# 3. Results

## 3.1. Study group characteristics and participation

Forty patients and 20 HC participated in the study. Due to a scanner update and missing MR data the total number of participants analyzed in this paper was 31 patients and 19 HC, but not all participants had data from all timepoints. This resulted in 25 patients (17 HC) at baseline, 24 patients (16 HC) at TP2, 24 patients (16 HC) at TP 3 and 21 patients (17 HC) at TP4. Because of incorrect segmentation, data from 1 patient was removed after visual inspection. For two patients, a new treatment series was required within 6 months and the follow-up was rescheduled 6 months after start of the second ECT series. For HC, 11 of 19 participants were female, age ranged from 21–69 years (mean 42.26, SD = 15.69). Patient characteristics are given in Table 1. There were no significant differences between patients and HC when comparing age ($t(48) = 0.66$, $p = 0.29$, two samples *t*-test) and sex ($\chi^2$ (0, N = 52) = 1, $p = 1$ Pearson chi squared test). Healthy controls displayed no consistent changes in metabolite concentrations across referencing methods (statistical models and results are given in the Supplementary material S1). Results for patients are listed below.

TABLE 1 Demographic and clinical characteristics of 31 patients referred to ECT.

| Variable | Patients |
|---|---|
| Mean age in years, min-max (SD) | 45.1, 22–77 (13.8) |
| Mean number of ECT treatments in series, min-max (SD) | 10.6, 3–18 (3.9) |
| Mean duration of current depressive episode in weeks, min-max (SD) | 42.8, 3–150 (40.2) |
| Number of remitters* | 12 |
| Medication | |
| Antidepressants | 12 |
| Antipsychotics | 24 |
| Lithium | 5 |
| Benzodiazepines | 0 |
| Diagnosis for referral to ECT | |
| Unipolar, psychotic (F32.3/33.3) | 4 |
| Unipolar non-psychotic (F33.1/33.2) | 21 |
| Bipolar, psychotic (F31.2/31.5) | 0 |
| Bipolar, non-psychotic (F31.3/13.4) | 6 |
| Mean charge of ECT in mC, min-max (SD) | |
| First treatment | 226.1, 76.4–404.1 (82.1) |
| Last treatment | 252.0, 100.4–612.1 (110.16) |

| | Baseline | TP3 | TP4 |
|---|---|---|---|
| Number of participants (female) | 25 (14) | 24 (11) | 21 (10) |
| Mean MADRS (SD) | 34.1 (5.2) | 15.6 (8.9) | 14.2 (8.8) |
| Mean EMQ-28 (SD) | 119 (35) | 111 (29) | 115 (37) |
| Number of remitters* | 10 | 10 | 10 |

Upper part: patients at all timepoints, lower part: patients stratified by timepoint.
*Remission: ≥50% reduction of baseline MADRS score + MADRS ≤ 10.

## 3.2. Clinical outcome and side effect

Patients' MADRS scores decreased from baseline [34.1 (5.2)] to after ECT-series (TP3) [15.6 (8.9), $t(24) = 8.94$, $p < 0.001$, d = 1.79] in all but two patients and remained lower compared to baseline at 6-month follow-up in 20 out of 21 patients (TP4) [14.2 (8.8.), $t(18) = 8.29$, $p < 0.001$, d = 1.90] computed by paired samples *t*-tests. EMQ-28 scores did not differ from baseline 119 (35) to after ECT-series 111 (29) or to 6-month follow-up 115 (37).

## 3.3. Change in metabolite concentrations

For creatine, linewidth (full width at half maximum, FWHM) was in the range of 4.22–10.74 [5.72 ± 1.08 Hz (patients) 5.46 ± 0.67 (HC)]

TABLE 2 Overview of metabolite concentrations.

| Group differences at baseline | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Creatine ratio (IU) | | | | | | | Water scaled (IU) | | | | | |
| | Patients | HC | *p* | % | *t*(df) | *n* | | Patients | HC | *p* | % | *t*(df) | *n* |
| tNAA | 1.41 (0.12) | 1.51 (0.13) | 0.007 | 6.8 | $t(40) = -2.85$ | 50 | tNAA | 16.52 (0.94) | 16.70 (0.77) | 0.52 | 1.2 | $t(40) = -0.64$ | 50 |
| tCho | 0.29 (0.04) | 0.28 (0.03) | 0.26 | 3.5 | $t(40) = 1.14$ | 50 | tCho | 3.17 (0.47) | 2.84 (0.27) | 0.01 | 11.0 | $t(40) = 2.56$ | 50 |
| mI | 0.69 (0.08) | 0.66 (0.09) | 0.36 | 4.4 | $t(40) = 0.93$ | 50 | mI | 7.57 (1.09) | 6.85 (0.91) | 0.03 | 10.0 | $t(40) = 2.25$ | 50 |
| Glx | 1.29 (0.16) | 1.24 (0.18) | 0.35 | 4.0 | $t(40) = 0.94$ | 50 | Glx | 16.18 (1.60) | 14.66 (1.79) | 0.006 | 9.7 | $t(40) = 2.88$ | 50 |
| **Longitudinal changes in patients** | | | | | | | | | | | | | |
| | Creatine ratio (IU) | | | | | | | Water scaled (IU) | | | | | |
| | Baseline | TP3 | *p* | % | *t*(df) | *n* | | Baseline | TP3 | *p* | % | *t*(df) | *n* |
| tNAA | 1.41 (0.12) | 1.33 (0.11) | 0.007 | −5.8 | $t(60) = -2.79$ | 31 | tNAA | 16.52 (0.94) | 16.06 (1.10) | 0.02 | −2.7 | $t(60) = -2.5$ | 31 |
| tCho | 0.29 (0.04) | 0.29 (0.03) | 0.36 | 0 | $t(40) = -0.93$ | 31 | tCho | 3.17 (0.47) | 3.17 (0.36) | 0.54 | −0.1 | $t(60) = 0.62$ | 31 |
| mI | 0.69 (0.08) | 0.68 (0.08) | 0.71 | 1.5 | $t(60) = -0.38$ | 31 | mI | 7.57 (1.09) | 7.71 (1.25) | 0.97 | 1.9 | $t(60) = 0.04$ | 31 |
| Glx | 1.29 (0.16) | 1.22 (0.19) | 0.19 | −5.6 | $t(60) = -1.32$ | 31 | Glx | 16.18 (1.60) | 15.75 (2.65) | 0.42 | −2.5 | $t(60) = -0.82$ | 31 |
| **TP 3 to 4 in patients** | | | | | | | | | | | | | |
| | Creatine ratio (IU) | | | | | | | Water scaled (IU) | | | | | |
| | TP3 | TP4 | *p* | % | *t*(df) | *n* | | TP3 | TP4 | *p* | % | *t*(df) | *n* |
| tNAA | 1.33 (0.11) | 1.41 (0.13) | <0.001 | 5.8 | $t(60) = -4.25$ | 31 | tNAA | 16.06 (1.60) | 17.16 (1.07) | <0.001 | 6.9 | $t(60) = -4.66$ | 31 |

P, patients; HC, healthy controls; *p*, value of *p*; %, percentage change or difference between groups; tNAA, total N-acetylaspartate; tCho, total choline; mI, myo-Inositol; Glx, glutamate + glutamine.

and the signal to noise ratio (SNR) was 22.84–65.53 [48 ± 7 (patients), 49 ± 6 (HC)]. The creatine ratio and water referenced metabolite concentrations for patients and controls at baseline and the percentage change to TP3 for patients are listed in Table 2. For patients, there was no significant change in creatine (tCr/H2O) over time, tested with linear mixed effects models (all $p > 0.6$).

### 3.3.1. tNAA

tNAA/tCr levels at baseline differed between patients 1.41 IU (0.12) and HC 1.51 IU (0.11) computed by a two samples *t*-test $t(40) = -2.85$, $p = 0.007$, d = −0.90. Likewise, tNAA/$H_2O$ levels were lower in patients 16.52 IU (0.94) compared to HC 16.70 IU (0.78), but this was not significant: $t(40) = -0.64$, $p = 0.52$. Longitudinal changes in patients were investigated with a mixed effects model, where timepoint affected both tNAA/tCr levels [$t(60) = -2.79$, $p = 0.007$] and tNAA/$H_2O$ levels [$t(60) = -2.50$, $p = 0.02$] in patients at TP3, resulting in a decrease compared to baseline levels. There were no significant changes in tNAA/$H_2O$ or tNAA/tCr from baseline to any other timepoint. When comparing TP3 to TP4 in the same model tNAA/tCr-levels increased [$t(60) = -4.25$ $p < 0.001$], for tNAA/$H_2O$: [$t(60) = -4.66$, $p < 0.001$]. See Figure 3 for a visualization of longitudinal tNAA levels in patients and HC.

Linear models for tNAA/tCr and tNAA/$H_2O$ levels predicting MADRS or EMQ-28 were not significant for TP1, TP3 or the change between the two. tNAA/tCr and tNAA/$H_2O$ levels at TP3 did not differ between patients who had the voxel on the left versus on the right side compared by a two samples *t*-test.

### 3.3.2. tCho

tCho/$H_2O$ was significantly lower in controls [2.84 IU (0.27)] compared to patients [3.17 IU (0.47)], $t(40) = 2.56$, $p = 0.01$, but this was not seen for tCho/Cre. There were no significant changes in tCho/tCr or tCho/$H_2O$ at any timepoint when compared to baseline, investigated with linear mixed effects models. There were no significant changes in tCho/$H_2O$ or tCho/tCr from baseline to any other timepoint, tested with a linear mixed effects model. Tested with a linear model there was no association between tCho/tCr or tCho/$H_2O$ and EMQ-28 at baseline or when comparing the change from before to after treatment.

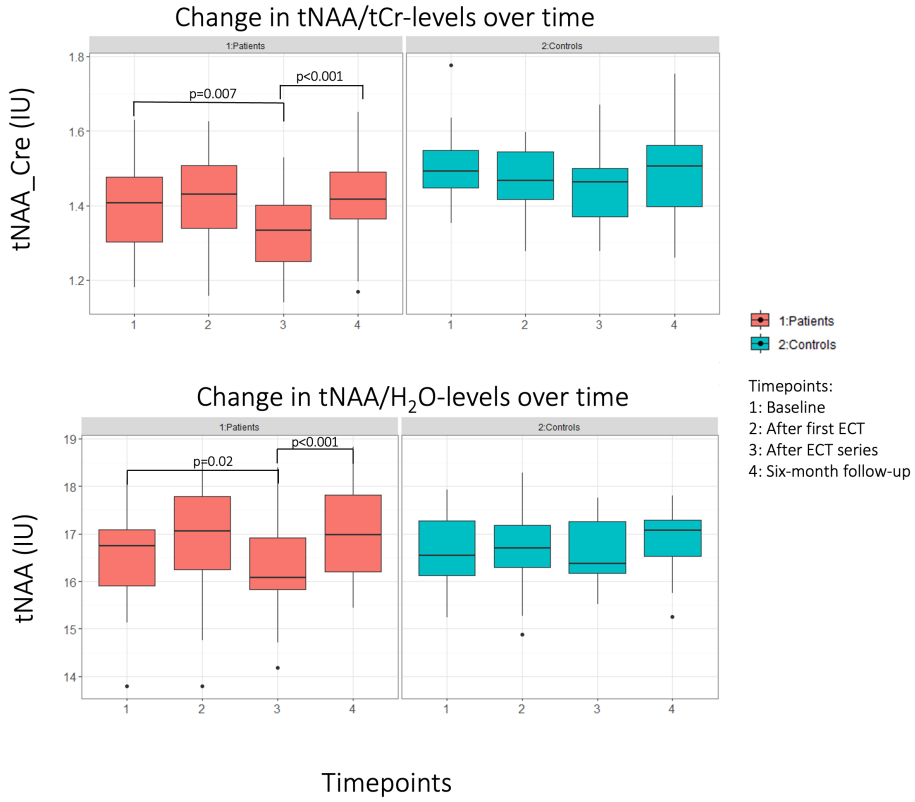


FIGURE 3
Boxplot of change in tNAA levels for patients (red) and HC (blue). Top panel: creatine ratio of tNAA. Lower panel: Water referenced tNAA values.

### 3.3.3. mI

Both mI/tCr and mI/$H_2O$ levels were higher in patients [7.57 IU (1.09), water referenced] compared to controls [6.85 IU (0.91), water referenced] at baseline, but findings were only significant for mI/$H_2O$ [$t(40) = 2.25$, $p = 0.03$]. There were no significant changes in mI/$H_2O$ or mI/tCr from baseline to any other timepoint, tested with a linear mixed effects model. Linear models for mI/tCr and mI/$H_2O$ levels predicting MADRS were not significant for TP1, TP3 or the change between the two.

### 3.3.4. Glx

Patients had higher baseline Glx/$H_2O$ levels [16.18 IU (1.60)] than controls [14.66 IU (11.79)], $t(40) = 2.88$, $p = 0.006$. The same trend was found for Glx/tCr levels: patients [1.29 IU (0.16)], controls [1.24 IU (0.18)], however this was not significant using a two samples $t$-test [$t(40) = 0.94$, $p = 0.35$]. A linear mixed effects model showed no impact of timepoint on Glx/tCr or Glx/$H_2O$.

## 4. Discussion

In this $^1$H-MRS study, we investigated creatine ratios and water referenced estimates of tNAA, tCho, mI, and Glx in 31 patients receiving ECT and 19 healthy controls. Patients were scanned at baseline, after the first ECT, after the ECT treatment series, and at six-month follow-up. HC, not receiving ECT, were scanned at similar time points. Our findings showed that ECT causes a reversible decrease in tNAA. Though the direction of the change in metabolite concentration mainly was the same across referencing methods (either increase, decrease, or no change) neither tCho, mI, or Glx displayed a significant change across referencing methods. No changes were found in any of the metabolites at the timepoint 2 h after the first ECT treatment. Possible explanations for this could be that: one single ECT treatment is not sufficient to induce metabolite changes on a level detectable with MRS or delay in detectable metabolite turnover. In the following paragraphs, we interpret our findings according to the DPR-hypothesis.

### 4.1. Disruption

We hypothesized that MRS correlates of disruption could be seen as a decrease in tNAA (a marker of neuronal integrity), an increase in tCho (membrane component), and an increase in Glx (mainly glutamate, excitatory neurotransmitter). We found a significant decrease in the patients' tNAA levels from baseline to after the ECT series, in both creatine ratio and water referenced data. This finding is concordant with findings from several previous studies (4, 43–47).

Choline is present in cell membranes and has previously been reported to increase after ECT (47–49). An increase in choline during and after ECT treatment, especially if NAA decrease is also seen, is often understood as disruption of cell membranes. In our sample, the longitudinal change in choline was not consistent across quantification methods, and neither method yielded statistically significant change.

We did not find a change in Glx concentration during the ECT treatment series. Contrary to the findings summarized in two reviews (11, 14) and our hypothesis, but in accordance with another study (50), we could not find any group differences when comparing patients and healthy controls at baseline. However, Glx is a pooled measure of glutamate and glutamine, two metabolites that are challenging to distinguish with a scanner strength of 3T. Hence, a subtle change in glutamate may not necessarily be reflected in our results.

## 4.2. Potentiation and rewiring

An increase in mI (glial proliferation marker) was hypothesized to coincide with the alleviation of depressive symptoms and would support potentiation (increased plasticity) and rewiring. Similarly, an increase in NAA or a return to baseline after the first decrease (disruption), could also be interpreted as either end of the disruptive effect or rewiring through axonal recovery after neuronal disturbances, as reviewed by Burtscher and Holtås where such a mechanism was suggested for epilepsy (51). Previously, an increase in mI has been reported in the ACC in patients treated with ECT (25). The increase was seen within one week after ECT and was interpreted as an increase in glial functioning. In our sample, we found no change in mI for any timepoint, hence the hypothesized change suggestive of potentiation or rewiring was not found. For tNAA and using either referencing method, we found an increase from after-treatment series to six-month follow-up, when the metabolite concentration was no longer different from baseline values. Though this finding might not directly imply potentiation and rewiring, our finding suggests that ECT-induced neuronal *disruption* is reversible over time.

## 4.3. Metabolite concentrations in relation to effect and side effects of ECT

Linear models for tNAA levels predicting MADRS were not significant, suggesting that the disruptive effects of the treatment could not alone explain the effect of the ECT on depressive symptoms. Linear models for mI levels predicting MADRS were not significant for TP1, TP3, or the change between the two. Other hypotheses, though not ECT-specific, have argued that both increased and reduced levels of mI might play a role in the alleviation of depressive symptoms. However, a sample studied by Njau et al. (25) could not associate the change in depression score with mI levels, and we could not find a correlation between mI levels and MADRS. Contrary to our hypothesis, mI levels were higher in patients than controls at baseline, but this was not seen for both referencing methods, and should therefore be interpreted with care.

We also hypothesized a correlation between subjective memory complaints and both tNAA-levels (increase in memory complaints due to reduced neuronal integrity: lower levels of tNAA) and tCho-levels (increased memory complaints due to disruption of cell membranes: higher levels of tCho). Linear models for tNAA levels predicting EMQ-28 were not significant, and we found no association between tCho and EMQ-28 at baseline or when comparing the change from before to after treatment. EMQ-28 is a measure of subjective everyday memory, and the correlation to depression severity seems uncertain, as both correlation and no correlation have been found (52, 53). Although the ecological validity for measuring the subjective experience may be higher for EMQ-28, it may be regarded as a measure of metamemory, i.e., what the patient reports that they forget, rather than actual forgetfulness.

## 4.4. Limitations

Our study is based on results from 31 patients and 19 healthy controls. A larger sample size would increase statistical power and possibly allow the quantification of more subtle changes in metabolite concentrations. A larger sample size would also allow for subgroup analysis based on patient heterogeneity (i.e., diagnoses, medication, comorbidity, duration of current episode etc.). Such analyses may explain results that are now interpreted as conflicting. Previous investigations have mainly been of smaller samples. Consortia like the global ECT-MRI research collaboration [GEMRIC, (54)] may give an opportunity for pooled data analysis with a larger sample size in the future.

It can be reasoned that psychotic or elderly patients who have the largest effect of ECT (55, 56) also may display the largest neurobiological changes during and after ECT. However, these groups only constitute a smaller fraction of the studied sample, as they are challenging to include in studies. Reasons for this may be that these patients carry a greater burden of disease and might therefore also not be motivated and able to give informed consent, and hence also have a greater rate of attrition.

During the statistical analysis, correction for multiple testing was not performed. The significance of the results must therefore be interpreted accordingly. Correction for multiple testing has some weaknesses as it can reduce statistical power and introduce type II errors. Hence, true differences may remain undiscovered. Additionally, the number of tests performed may be difficult to establish, as complex models yield several *p*-value, but are only one model. Our investigation was hypothesis-driven, and two referencing methods were used, strengthening results that are significant across referencing methods.

Due to the large voxel localized in the ACC region, a heterogeneous tissue composition including both gray and white matter are measured. Although Osprey (36) was used to derive tissue- and relaxation-corrected concentration estimates according to the Gasparovic method (38), reliable measurements of either gray or white matter only are not feasible. While depression has been suggested to be a disorder of brain networks (57), our study only investigated the ACC. Findings in ACC regions have been suggested as biomarkers of treatment response; larger baseline subgenual cingulate volume was found to predict response in ECT (58), and pretreatment ACC functional activity predicted response to antidepressant medication (59). However, the hippocampus and amygdala are structures known to display the largest volumetric changes following ECT (5). Both the amygdala and hippocampus are connected with the ACC, either directly or indirectly (60), and these structures also have larger gray matter fractions than the ACC. Accordingly, areas such as the amygdala and hippocampus may also display larger metabolite changes. Future MRS studies of these areas could therefore lead to better insight into ECT response in depression.

In previous MRS investigations of ECT, findings have been inhomogeneous. This could in part be due to differences in the choice

of referencing method. Hence, we have used both water referenced results as well as the creatine ratio for the quantification of brain metabolites in our sample. Still, this approach does not reflect the whole variety of different MRS post processing pipelines that have been used in previous research. A more methodological comparison between methods is out of the scope of this article.

## 5. Conclusion

Using both creatine ratio and water reference for MRS-data quantification, our study indicates a decrease in tNAA levels after ECT. This was reversed to pre-ECT levels 6 months after ECT. This finding lends support to temporary disruption as suggested in the "disrupt, potentiate, and rewire" hypothesis. Longitudinal changes in mI, tCho, or Glx levels were not consistent across quantification method, and we did not find any correlation between tNAA or tCho and effect or side effects of ECT. For future research, MR-spectroscopy investigations with voxel placement in areas that have an even stronger implication in the setting of depression, and which are more affected by ECT, such as the hippocampus and amygdala, may further shed light on the disrupt, potentiate, and rewire hypothesis. Other methods, such as Diffusion Tensor Imaging and resting state functional MRI may be better to assess neuronal potentiation and rewiring. Furthermore, larger sample sizes and multi-site investigations are important to improve our understanding of brain metabolites and their role in the neurobiological underpinnings of ECT.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by The Regional Committee for Medical and Health Research Ethics, REC South East, Norway (2013/1032). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

VE: formal analysis, writing original draft, and writing-review and editing. LO and LE: conceptualization, supervision, methodology, and writing-review and editing. UK: conceptualization, methodology, and writing-review and editing. KO: conceptualization, supervision, and writing-review and editing. AC: software, formal analysis, and writing-review and editing. JH: conceptualization and writing-review and editing. FR: methodology and writing-review and editing. CB-J: methodology, statistical analysis, and writing-review and editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1155689/full#supplementary-material

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# Deep brain stimulation programming for intractable obsessive–compulsive disorder using a long pulse width

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**Introduction:** Around 25% of patients with obsessive–compulsive disorder (OCD) do not respond to medication or psychotherapy, producing significant impairment and treatment challenges. Deep Brain Stimulation (DBS) has been shown in multiple blinded trials to be a safe and durable emerging option for treatment-refractory OCD. Intraoperative device interrogation offers a theoretical anchor for starting outpatient DBS programming; however, no definitive post-operative programming algorithm for psychiatrists exists currently.

**Case:** Here we present a 58-year-old female with childhood-onset, severe, intractable OCD with multiple failed trials of psychotherapy, medication, and electroconvulsive therapy. After interdisciplinary evaluation, she underwent bilateral electrode implantation targeting the anterior limb of the internal capsule, nucleus accumbens (ALIC/NAc). Intraoperative interrogation afforded sparse information about a preferred lead contact or current density target. Subsequent outpatient interrogation consisted of systematic and independent mapping using monopolar cathodic stimulation with constant current. Modulating bipolar and triple monopolar configurations, amplitude, and pulse width all failed to induce observable effects. Given negligible interrogation feedback, we created an electrical field through the ALIC bilaterally, using the three most ventral contacts to create triple monopoles, with a long pulse width and moderate amperage.

**Conclusion:** Three months post-programming, the patient reported significant improvement in OCD symptoms, particularly checking behaviors, with response sustained over the next several months. As with our case, the majority of DBS lead contacts do not induce affective or physiological markers in patients, complicating programming optimization. Here, we discuss an approach to titrating various stimulation parameters and purported mechanisms of physiological markers in DBS for OCD.

KEYWORDS

**deep brain stimulation, intractable OCD, psychiatric deep brain stimulation, anterior limb of the internal capsule, monopolar settings, case reports deep brain stimulation, case reports**

# Introduction

Structural and functional neural circuit mapping of OCD is some of the most robust in the psychiatric literature, with strong evidence for aberrant hyperconnectivity in cortico–striato–thalamo–cortical (CSTC) circuitry, known as the frontostriatal model (1, 2). Recent research has also shown the involvement of other neural networks at interplay with the CSTC circuit (3, 4). Despite the strength of this work, treatment for OCD remains suboptimal, with upwards of one-third of patients not fully responding to psychotherapy and psychopharmacology (5, 6). Furthermore, intractable OCD, in which multiple treatment regimens have failed, affects up to 10% of patients (7). Historically, partial response for such cases was obtained through the use of psychosurgical capsulotomy, in which the anterior limb of the internal capsule (ALIC) was ablated to disrupt frontostriatal circuits during the 1940s and 1950s (8, 9). The initial rationale behind Deep Brain Stimulation (DBS) was to create a reversible lesion similar to a capsulotomy (10, 11).

For bilateral ventral caudate/ventral striatum (VC/*VS*) DBS lead placement, the ventromedial region of the nucleus accumbens (NAc) is stimulated through the most ventral contact, with the middle two contacts stimulating the ventral portion of the ALIC. This configuration results in similar targets to a ventral capsulotomy, though the VC/*VS* target has moved posteriorly over time due to refinement in targeting methods, resulting in better clinical outcomes (9, 12). Results from a double-blind controlled trial of DBS for OCD showed comparable efficacy to psychosurgery, greater response rates, and decreased symptom severity as a function of more recent posterior lead placement versus its antecedent DBS targets (9, 13).

In addition to its clinical promise, DBS is likely to be cost-effective over long-time periods, especially when a rechargeable internal pulse generator (IPG) is used (14). However, overall access to DBS remains an issue for many patients with intractable OCD like ours due to inconsistent coverage by insurers, who frequently incorrectly cite the treatment as experimental (11, 15). DBS for OCD is evidence-based treatment under a humanitarian device exemption (HDE) status by the FDA, versus experimental treatments which fall under an investigational device exemption (IDE) (11, 15). There is currently a call by leaders in the field to expand access to this treatment, both by increasing the number of DBS-trained psychiatrists comfortable with the management of these patients and through expanded insurance access (11). Of note, the lack of insurance coverage for DBS for OCD violates 2008 mental-health parity laws, which require equal coverage for medical and mental health conditions by major insurers, and notably, DBS is covered by major insurers for neurological conditions like dystonia, which also falls under an HDE (15). This case report describes a method we used to evaluate and adjust different stimulation parameters. We also examined their potential mechanisms of physiological side effect and response to stimulation and how these related to her clinical outcomes.

# Case

## Patient information & clinical findings

Our patient is a 50 y.o. female who presented for neurosurgical evaluation for a 35-year history of intractable OCD. Her symptoms began following a childhood trauma, and her obsessions centered on safety. She described intrusive thoughts of harming others, checking rituals, and feelings of incompleteness. She no longer could drive or leave her house alone due to these symptoms. She worked in a complex healthcare occupation previously but left her job due to excessive time spent in documentation due to OCD symptoms. Previous treatment trials included psychotherapy, various psychopharmacological trials (including SSRIs, atypical antidepressants, atypical antipsychotics, and benzodiazepines), and electro-convulsive therapy.

## Diagnostic assessment

This patient was evaluated at the University of Florida Center for Movement Disorders and Neurorestoration as a collaboration of the departments of Psychiatry, Neurology, and Neurosurgery. Prior to recommending surgery, a risk versus benefit analysis was performed by a multidisciplinary team (psychiatrist, psychologist, neurologist, and functional neurosurgeon), which reviewed all past treatments, procedures, and evaluations to ensure the appropriateness of the candidate. Psychiatric diagnoses were based on a review of medical records and clinical interviews.The patient met DSM-V criteria for OCD with an Obsessive Compulsive Scale (Y-BOCS), with a history of treatment-refractory OCD symptoms since age 15 causing suffering and functional impairment. Her symptomatology was supported by a Y-BOCS of 36 at the time of the initial DBS consultation, indicating extreme severity (scores 32–40). Previous psychotherapy, pharmacological, and electroconvulsive therapy trials were deemed adequate, and she was deemed a potential candidate for deep brain stimulation therapy to treat her debilitating, medication-refractory OCD symptoms.

While she was deemed a surgical candidate at this time, the next 7 years were spent on medication optimization because her insurance would not cover the procedure. Upon changing insurance, the patient was again deemed a surgical candidate after repeat evaluation by a multidisciplinary team. She underwent successful bilateral VC/*VS* Medtronic device implantation and initial device programming occurred over a 3-month period. Her medication regimen was fluvoxamine 100 mg 3 times per day, olanzapine 10 mg at night, and clonazepam 1 mg 3 times per day, and remained unchanged over the following year throughout DBS implantation and optimization.

## DBS implantation

The anatomical target was the same for both the left and right sides. The DBS targeting utilized a stereotactic CT scan fused with MRI and morphed to a deformable atlas and was deemed successful. Although coordinates are less meaningful in such individual cases due to high patient-to-patient variability, we have included a patient-specific figure showing the lead position (Figures 1–3). Additionally, it should be noted that variability in DBS settings across leads may be explained by the variability of lead implantation within the targeted brain area. After implantation, there was no difference in the positions of the left and right leads.

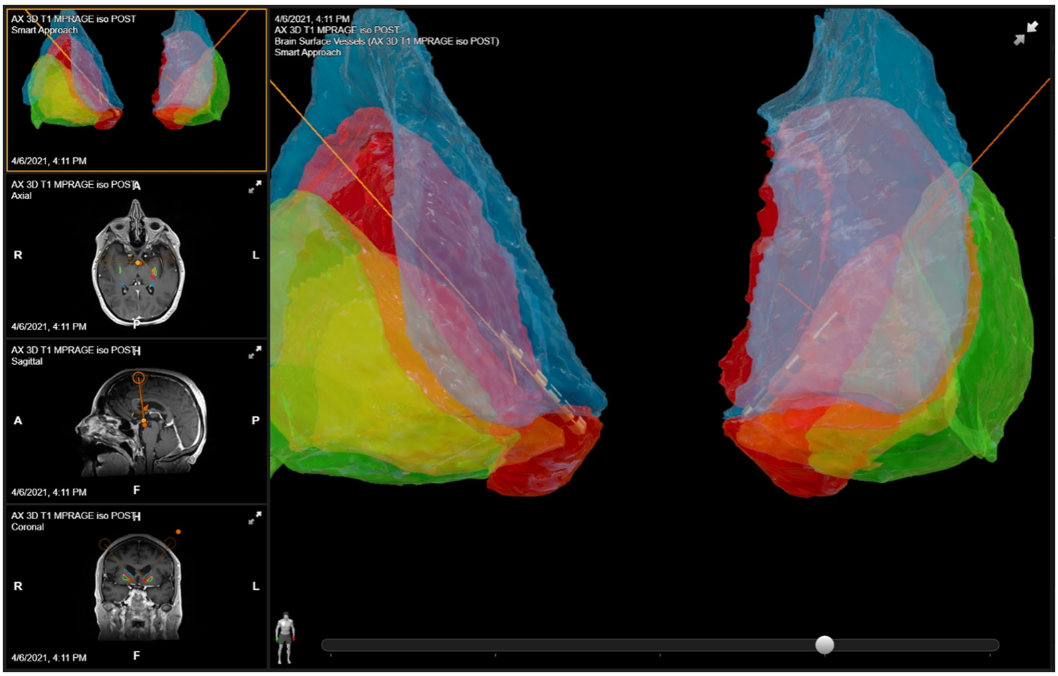



FIGURE 1
DBS lead placement. Images were generated using patient-specific anatomical mapping algorithm lead localization software in *BrainLAB Elements* (Pink: internal capsule, Orange: GPi, Green: Putamen, Blue: Caudate).

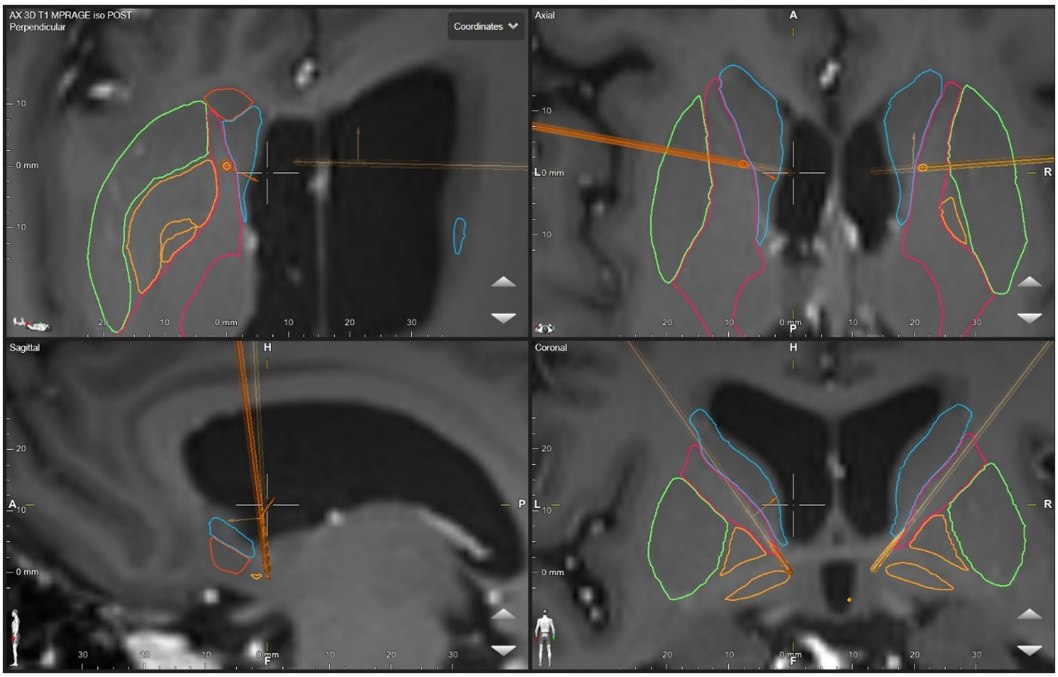



FIGURE 2
DBS lead placement. Images were generated using patient-specific anatomical mapping algorithm lead localization software in *BrainLAB Elements* (Pink: internal capsule, Orange: GPi, Green: Putamen, Blue: Caudate).

## Therapeutic interventions

At 2 months post-implantation, we attempted an initial systematic, exploratory, trial-and-error approach, assessing the effects of various stimulation parameters predominately through variation in amperage amplitude across various contacts. Frequency was held constant throughout at 135 Hz. Although

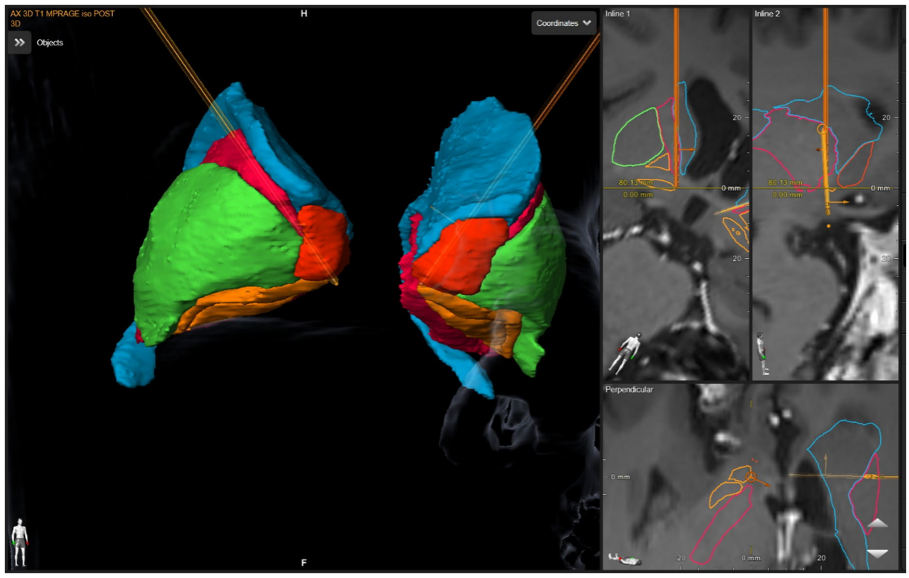



FIGURE 3
DBS lead placement. Images were generated using patient-specific anatomical mapping algorithm lead localization software in *BrainLAB Elements* (Pink: internal capsule, Orange: GPi, Green: Putamen, Blue: Caudate).

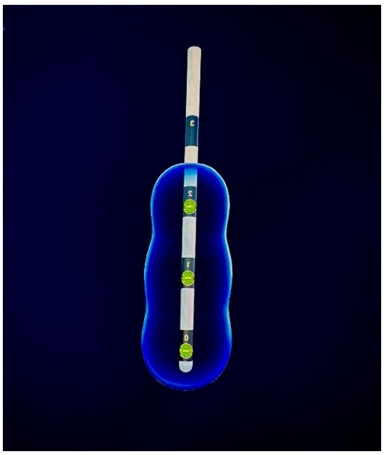


FIGURE 4
Triple monopolar settings.

monopolar stimulation lacks precision, it allows for a larger electrical field spread across the targeting region. For our purposes this broader, less precise, field would be of benefit for exploring regions that might elicit an acute positive emotional or affective response such as feelings of euphoria, mirth, or smile.

Monopolar interrogation consisted of testing all eight contacts (4 each, bilaterally) individually and systematically at 135 us, 190 us, 210 us, and 260 us. For each given pulse width, amperage was titrated upwards in 0.5 mA increments every 60 s. At longer pulse widths of 210us and 260us, she reported side effects– feeling "clammy and sweaty" and nauseated at the most ventral, right contact at 4.0 mA. We noticed no affective stimulus response elicited by the DBS stimulation.

Double monopolar settings were interrogated, and we used a similar titration pattern, pairing the two most ventral contacts, then pairing the middle contacts, holding the frequency at 135 Hz again. No stimulus effects, i.e., no mirth or smile were noted with any settings. Consistent with monopolar interrogation, the most ventral pair on the right induced side effects of "clamminess" and feeling "hot" at 3.3 mA. And for the left ventral most contact, "hot flashes" and "nausea" occurred at 3.5 mA. No euphoria, smile nor mirth was noted.

Her symptoms remained unchanged at her follow-up approximately 1 month later. Dose optimization continued, now with triple monopolar interrogation using the three most ventral contacts, holding both pulse width (260 µs) and frequency (135 Hz) constant (See Figure 4). Again, no mirth or smile resulted from any setting changes. On the left, mild nausea was noted at 3.2 mA and resolved at 2.5 mA. On the right, mild nausea at 2.3 mA resolved at 2.0 mA. Again, there was no stimulation-induced euphoria, smile, or mirth for any parameter settings. Given that she was now 5 months post-implantation, that a broad electrical field theoretically covered at least the ventral portion of the ALIC, minimal side effects were noted, and the presumption that further interrogation would be unlikely to uncover any mirth response, these settings were held and considered optimized.

At a return visit 5 months later, the patient reported a robust improvement in her quality of life, a "25% reduction in OCD" symptoms, and even more so for her checking behaviors. Some days she experienced "no symptoms" and felt "like myself, minus the OCD." She also reported experiencing a 4–5 h per day reduction in compulsive behaviors. She also reported the symptoms of depression were absent, and that her mood was "good." A repeat Y-BOCS had not been performed for this visit. During this visit it was noted that for the left lead, the pulse width had been inadvertently set at 250 µs rather than 260 µs, a finding deemed

inconsequential given her marked improvement such that pulse width was continued with this slight asymmetry, still using long pulse width bilaterally. Her device battery life was at 28%, and an elective repair indication notification was present. She was eager to schedule battery replacement surgery given her response. She opted for a rechargeable battery and had the IPG replacement performed at an outside hospital closer to her home where the IPG was changed to a Boston Scientific, device type– Vercise Genus. Final settings were as follows: Left C+, 0−, 1-, 2- @ 2.7 mA, 250 μs, 135 Hz, Right C+, 0-, 1-, 2- @ 2.3 mA, 260 μs, 135 Hz.

### Follow-up and outcomes

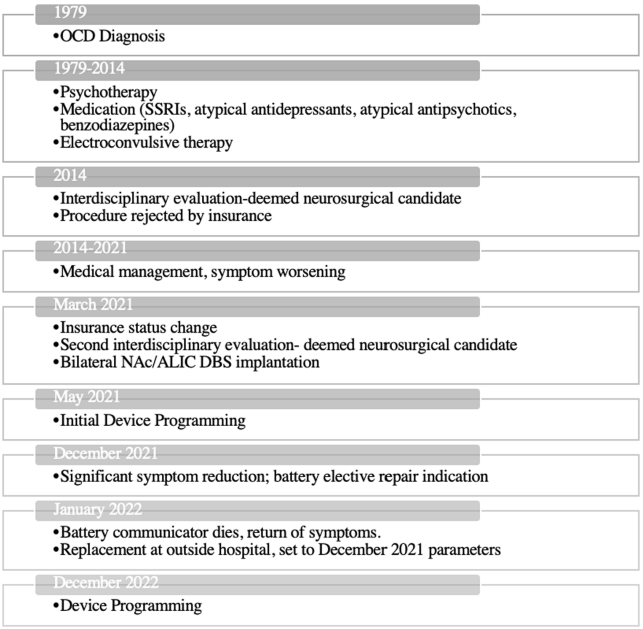
After her IPG replacement, she also transferred her programming care to an outside team closer to her home. Immediately after the replacement, her new provider changed her device settings from our initial optimization, reducing the longer pulse width. The patient reported they had concerns about the battery consumption due to her prior settings. New settings were: bilateral triple monopoles at the three most ventral contacts, 7.5 mA, 136 Hz, and 150 μs. However, one month after her settings had been changed the patient reported a return of depression and a significant worsening of OCD symptoms. This persisted for several months, and she contacted us requesting a DBS programming consultation. She reported her symptoms were now "debilitating," with OCD compulsions lasting several hours daily, and that she was in bed for hours at a time with thoughts of suicide beginning to return.

We resumed her DBS programming and began transitioning her settings to her previous parameters in an attempt to replicate the previous response. At the time of this writing, we have continued with the use of triple monopoles bilaterally, and over the next 3 months will transition her settings to a longer pulse width, monitoring for side effects. Vecise Neural Navigator 4 software indicates her most recent settings (9.0 mA, 200 us, 136 Hz) will increase her daily charging time from only 20 to 30 min.

Our goal was to gradually transition her back to her previous optimized settings. During the transfer of care to our clinic, we reintroduced the longer pulse-width settings. However, it had previously taken several weeks to adjust some of those settings. While increasing the pulse width, she experienced hot flashes and nausea that persisted beyond 200 us. As a result, we kept her at 200 us. Her overall dosing was lower than what was currently being used, so we adjusted her amperage as it had minimal effect on the nausea at 200 us pulse width. Two weeks later suicidal thoughts had diminished. After her follow-up 2 months later, her depression and OCD symptoms remained unchanged. So, we targeted a longer pulse width again.

During one of her early optimization trials, we noted that nausea would dissipate by lowering the frequency to around 99-105 Hz. We leveraged this and lowered her frequency at the 2nd follow-up visit after returning to our care; this allowed us to achieve a longer pulse width (260us) without side effects or nausea. Communication with the patient over the next 2 months revealed that her depressive symptoms were subsiding with the longer pulse width. She reported that her suicidal ideation had completely disappeared, and she was now out of bed. She described her residual depression as dysphoria arising specifically from her OCD symptoms. However, her OCD symptoms remained unchanged.

### Timeline




## Discussion

### Target overview

Although the ALIC/NAc is the general region of DBS placement for the treatment of OCD, the precise targets and mechanism of action are still unresolved. Complicating matters is that device interrogation for psychiatric disorders lacks the immediate objective feedback seen in the treatment of motor disorders given the phenomenological nature of psychiatric illnesses. This adds to uncertainty, not only about the region to be targeted but also about whether the correct target has even been stimulated. Despite a precise lead placement, the ALIC with or without the addition of the NAc remains a broad and vague target. Moreover, the induced electrical field within it can vary significantly with only slight variations of lead placement or stimulation parameter change. For example, subtle stimulation changes at the most ventral lead may potentially encroach not only into the NAc but may spread to other unintended areas. Therein, DBS programming must also consider stimulation effects, including any induced acute side effects–in addition to merely creating an electrical field within the ALIC.

One case report noted a non-response for depressive and obsessive symptomatology when solely the NAc was stimulated, yet noted a response after the ventromedial caudate nucleus contacts were activated (16, 17). Furthermore, a study of stimulation versus sham-induced side effects of DBS for OCD noted mood effects with acute stimulation of both the dorsal and the ventral ALIC, as well as the NAc, with worsened mood associated with most ventral lead (nearer NAc), and the middle contact (within ALIC) associated with improved mood (18). Recent literature suggests that in ALIC/NAc lead placement, stimulation may spread to multiple targets such as the associated bed nucleus of stria terminalis (BNST), and "off-target" effects may contribute to response variation (19). This is likely the case for our patient who had an ALIC/NAc lead placement, and whose

most ventral contact likely has current spread into the NAc and beyond.

Locating the ideal target or temporally linking an associated stimulation to the target is complicated by the potential for a lag in the emergence of any stimulation effect. Moreover, to minimize surgical time, per-operative exploration settings often sample fewer and more assertive amplitude configurations than in the outpatient setting. This unrefined sampling provides only a rapid, yet rough, overview of theoretically beneficial or problematical settings. Per-op settings are often not congruent to those sampled during an outpatient visit where there is more time allocation for subtle or delayed effects during the interrogation. These post-op settings allow for smaller, incremental stimulation adjustments to note any effects on patient comfort (i.e., dysphoria or panic) or safety (i.e., emerging mania). Or any emergence of a change in affect that may be quite subtle. Problematically, the kinetics of such limbic effects are dependent on the brain target, and the order or intensity of the stimulation. And a previous stimulation may, to some unknown degree, influence the effects of the next confounding the causal link. This could lead to misinterpretation of any noted or unseen per-op and post-op stimulation effects where these effects have not been explored within similar conditions. Such conditions may also include the environmental setting, order in which contact stimulation is trialed, use of unilateral or bilateral leads, configuration settings, rapidity of amplitude changes, etc., all of which may induce significant differences in the observed clinical effects. Moreover, the induced and observed stimulation effects do not neatly overlay an observed clinical effect. Despite these issues, the association of potential efficacy seen in those patients manifesting a stimulation-induced mirth response led to our systematic search for the same. Although high amplitude doses are not the goal to establish efficacy, too low of an amplitude could result in an inadequate electrical field. As such, even with diminished feedback by a mirth response, titrating to a higher amplitude dosing just beneath any noted side effects would at least assure a maximum tolerated dose was utilized.

## Stimulation-induced euphoria, mirth, smile

Controlling the electrical field shape and intensity is important for proper targeting, and for reducing side effects. The transition towards the use of constant current (versus voltage) for newer devices, diminishes any fluctuations in amperage arising from variation in impedance, thus affording a reduced side effect profile (20, 21). However, it has also been shown that stimulation effects such as mirth, smile response, mood change, or even panic might serve as a beacon for optimizing contact selection and current density parameters, and might suggest higher efficacy. The prognostic value of such stimulation effects intraoperatively or during outpatient programming is currently unknown.As occurred with our patient, two-thirds of DBS lead contacts do not induce notable simulation effects on mood, smile, or produce side effects such as other physiological responses, that would have ideally served as potential biomarkers for dose optimization (12, 18). Moreover, stimulation-induced side effects also serve as a natural limiting factor for amplitude settings, i.e., current density.

Additionally, the interpretation of these subtle subjective emotional changes, i.e., stimulation effects, may be further obscured by the direct effects of stimulation producing an affective marker, during DBS programming. For example, previous work has postulated that involuntary facial muscle movement may be disrupted for OCD patients at the level of the basal ganglia and may be independent of mood-related epiphenomena (22). Several cases of unilateral programming inducing a contralateral smile have been reported, which is suspected to arise from the direct stimulation of limbic-motor loops (18, 23). This phenomenon has been hypothesized to be a predictor of OCD response (24). The smile response is often not an isolated motor event. It may spread bilaterally and later become euphorigenic (12). Studies have further aimed to differentiate between the mechanisms of euphoria and "context-dependent mirth" in DBS (24). One such study mapped euphoria to an array of regions, including the STN, NAc, medial temporal cortex, and hypothalamus, with a greater role for the NAc in euphoria than context-dependent mirth (24).

As with the muscles of facial expression involved in smiling, dysregulation occurs in the behavioral circuitry for laughter in OCD patients, and intraoperative stimulation of laughter has been similarly thought to be a predictor of DBS response (22, 24). During programming optimization, this must be interrogated promptly, as habituation of the laughter response occurs after device activation. This laughter may involve a process occurring at the level of NAc and be related to the loss of novelty response (24). This may be distinct from DBS-induced impulse dysregulation or mania which are both thought to possibly arise from ventromedial STN stimulation affecting limbic areas (21). Though the subtle distinction between spontaneous and context-dependent smiling and laughter relate to their respective neural pathways, whether these contacts are the most optimum targets remains unknown.

During the exploration phase for our patient, we noted no such mirth or smile response. The search for such a marker was part of the rationale for the increasing pulse widths, that were beneath the amplitude for any uncomfortable side effects.

## Stimulation-induced autonomic side effects

Stimulation side effects may place natural constraints on contacts or parameter dosing. This was the case for our patient as we continued to expand the amplitude of her parameters settings up to the side effect threshold (for her, feeling "clammy" or "hot"). Such autonomic phenomena are sweating, sensations of heat and cold, and increased heart rate and breathing occurring, possibly due to autonomic fiber activation associated with the hypothalamus, *via* current spread through amygdalofugal pathways (12, 18). Additionally, amygdala projections and hypothalamic and autonomic fibers in the same circuit terminate on the frontal cortex, where they may elicit a panic response (18). Other commonly seen negative effects of programming are sleep disruption or restlessness (5). In addition to anxiogenic effects, acute dysphoria, and depression have been observed with contacts placed within substantia nigra in Parkinson's Disease (PD) patients (21). Finally, current spread into the anterior hypothalamus or pathways involving the temporal lobe may be responsible for nausea (7, 18). Irrespective of the stimulation effect as a potential marker of efficacy or merely an unpleasant side effect, the extent to which acute side effects and stimulation response serve as a response predictor have not been verified.

## Battery consumption

It is well-documented that DBS for OCD patients typically requires settings with high power consumption. To minimize psychiatric and surgical risks, preserving the battery life is especially critical for patients without a rechargeable IPG. Without a known marker for optimization, preservation of battery charge is an important consideration, but too conservative an approach might lead to underdosing. In earlier studies, the large current density requisite for treating OCD patients led to the need for battery replacement within 6–12 months (10). This was consistent with the energy consumption of our patient. With battery depletion, relapse is imminent. And the time frame required for spontaneous resolution of mood phenomena arising from device termination, as well as recommendations for settings for DBS tapering are currently unknown and present potential future areas of research (5, 25).

## Parameter selection

While numerous parameter combinations may generate the same charge density, minimizing side effect profile and charge depletion has taken precedence historically. Modifying variables such as current, voltage, amplitude, pulse width, and frequency should attempt to allow for a wider DBS therapeutic window. More precisely, it is an attempt to widen the difference between the minimum stimulation, usually amplitude (of current or amperage) required to produce adverse effects, and the amplitude required to produce a beneficial effect (17, 21). Perhaps the most common and simple approach to increasing charge density is increasing the amplitude of the voltage or the current.

Early seminal trials continue to guide parameter selections, such as the monopolar survey commonly using 130 Hz, 90–210 μs (10, 25). These parameters have natural ceilings for charge density for brain tissue at 30 $\mu C/cm^2$ (25, 26). The use of constant current streamlines programming due to reduced variation in impedance. For example, impedance may be increased at the brain tissue: electrode interface due to increased electrode and IPG encapsulation, which alters the electric field and increases resistance (20, 27). However, there is still a lack of data on parameter variation and anatomical impact (19).

Pioneering work on DBS for essential tremor provided a broad range of frequency parameters (28). At present, frequency typically ranges between 100 and 145 Hz, with some programming work showing 130 Hz as an ideal trade-off between power consumption and clinical efficiency (12, 21). A cross-over study on DBS for treatment-resistant depression found a response advantage with no difference in side effect profile for 130 Hz vs. 20 Hz (29). Previous studies have noted that with the commonly used pulse width of 130 μs, voltages over 5.5 V tend to increase the side effect profile (30). For our patient, we continued with the fairly standard use of 130 Hz. We then began systematically increasing the amplitude of amperage across an array of pulse widths, including longer ones.

However, pulse width selection is highly variable in many studies, with clinical improvement using both short and long pulse widths, including reports of 450 μs in dystonia (17). Additionally, in a study evaluating 26 parameters in DBS for PD, the voltage was the most important factor, and more specifically, maximizing voltage amplitude while minimizing pulse width afforded the most energy-equivalent symptom reduction (31). Most early studies utilized pulse widths ranging between 90 and 210 μs (25). For our patient, we selected a long pulse width as it had been well tolerated during the optimization phase and seemed to allow for an adequately broad therapeutic window. Despite our attempts to elicit stimulation effects (such as mirth or smile), such effects were never elicited. We continued settings with the well-tolerated longer pulse width in the event there was the potential for more current spread across the ALIC and to avoid potentially suboptimal dosing. Three months later, these settings coincided with a notably robust response.

# Conclusion

Our systematic optimization approach resulted in a positive response from the patient. Using long pulse widths, we increased settings to the highest tolerable threshold before side effects were noted. Although this helped assure we had increased the settings as high as was tolerable to avoid under-dosing, higher doses do not necessarily equate with efficacy. Fortunately, the high battery consumption issues plaguing such DBS cases have been mitigated with rechargeable batteries. However, in this single case, the contribution of efficacy arising from the effects of micro lesioning during lead implantation, or the placebo effect is unknown. Yet, her severe symptomatology remained durable past 6 months of optimization, the durability beyond this has not yet been assessed. It is also unclear whether reintroducing her previously optimized settings will return her to a remitted state. For our patient, leveraging the higher pulse width over amplitude, coincided with response, and seems a viable strategy. We offer this as our approach to this particular case. However, with such vast parameter options, and high anatomical variability between individuals and their lead placement, individualized optimization may take a different parameter formulation for others– depending on side effects and response.

# Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

# Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

# Author contributions

BC and EB wrote the first draft of the manuscript. BC conceptualized the discussion section. KP provided clinical resources for the case report. LK helped write and edit manuscript drafts. All authors contributed to the article and approved the submitted version.

# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Electric field distribution predicts efficacy of accelerated intermittent theta burst stimulation for late-life depression

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**Introduction:** Repetitive transcranial magnetic stimulation (rTMS) is a promising intervention for late-life depression (LLD) but may have lower rates of response and remission owing to age-related brain changes. In particular, rTMS induced electric field strength may be attenuated by cortical atrophy in the prefrontal cortex. To identify clinical characteristics and treatment parameters associated with response, we undertook a pilot study of accelerated fMRI-guided intermittent theta burst stimulation (iTBS) to the right dorsolateral prefrontal cortex in 25 adults aged 50 or greater diagnosed with LLD and qualifying to receive clinical rTMS.

**Methods:** Participants underwent baseline behavioral assessment, cognitive testing, and structural and functional MRI to generate individualized targets and perform electric field modeling. Forty-five sessions of iTBS were delivered over 9 days (1800 pulses per session, 50-min inter-session interval). Assessments and testing were repeated after 15 sessions (Visit 2) and 45 sessions (Visit 3). Primary outcome measure was the change in depressive symptoms on the Inventory of Depressive Symptomatology-30-Clinician (IDS-C-30) from Visit 1 to Visit 3.

**Results:** Overall there was a significant improvement in IDS score with the treatment (Visit 1: 38.6; Visit 2: 31.0; Visit 3: 21.3; mean improvement 45.5%) with 13/25 (52%) achieving response and 5/25 (20%) achieving remission (IDS-C-30 < 12). Electric field strength and antidepressant effect were positively correlated in a subregion of the ventrolateral prefrontal cortex (VLPFC) (Brodmann area 47) and negatively correlated in the posterior dorsolateral prefrontal cortex (DLPFC).

**Conclusion:** Response and remission rates were lower than in recently published trials of accelerated fMRI-guided iTBS to the left DLPFC. These results suggest that sufficient electric field strength in VLPFC may be a contributor to effective rTMS, and that modeling to optimize electric field strength in this area may improve response and remission rates. Further studies are needed to clarify the relationship of induced electric field strength with antidepressant effects of rTMS for LLD.

KEYWORDS

late-life depression, accelerated intermittent theta burst stimulation, neuronavigation, induced electric field, ventrolateral prefrontal cortex

# 1. Introduction

A significant percentage (10–15%) of the aging population experiences major depressive disorder, known as late-life depression (LLD), with negative impacts on functioning and quality of life (1). Mild cases can be addressed with education and counseling, while moderate to severe cases of LLD may require antidepressant medication or somatic therapies which can cause systemic and cognitive side effects (2). In particular, electroconvulsive therapy (ECT) is associated with risk of anterograde and retrograde memory loss (3), potentially compounding the cognitive deficits associated with neurodegenerative conditions, chronic medical conditions, and cerebrovascular disease. Efficacious treatments for LLD without risk of cognitive impairment are needed.

Repetitive transcranial magnetic stimulation (rTMS) is a FDA-approved therapeutic option for treatment-resistant depression that may be effective for LLD (4, 5). By generating electric currents in cerebral cortex through electromagnetic induction, rTMS is able to alter connectivity within and between large-scale brain networks involved in emotion regulation (6). When administered using various protocols such as 10 Hz, 1 Hz, or intermittent theta burst stimulation (iTBS), rTMS has demonstrated rates of up to 70% response and 40% remission in naturalistic studies (7, 8).

## 1.1. Atrophy in late-life depression may affect rTMS efficacy

Unfortunately, increased age has been associated with diminished rates of response and remission in multiple studies since the initial demonstrations of rTMS for depression (5). A 2022 systematic review of seven randomized trials and seven uncontrolled trials of rTMS for LLD [found significant variability in response rates (6.7–54.3%)] as well as parameters utilized (9). Suspected causes of reduced efficacy include vascular damage to structural white matter pathways along which rTMS effects propagate (10); the presence of common comorbidities in late-life depression, such as anxiety disorders (11), that are associated with lower remission rates with rTMS (12); and age-related cortical atrophy, which may require higher intensities of magnetic field strength to achieve adequate penetration. An early study of high frequency left dorsolateral prefrontal cortex (DLPFC) rTMS in LLD found the antidepressant response rate was greater in patients <65 years of age compared to those >65 (56% vs. 23%) (13), with the authors concluding that structural brain changes in persons with LLD contribute to reduced efficacy. Two more studies found no significant effect of rTMS treatment compared to placebo in persons with LLD (14, 15). Nahas et al. (16) showed that adjusting stimulation parameters for frontal atrophy resulted in an antidepressant effect in 27% of participants. Jorge et al. (17) performed a randomized sham-controlled trial of rTMS in persons with vascular depression and found that age and frontal gray matter atrophy were negatively correlated with response (16). Even in more contemporary studies using higher pulse counts, longer treatment durations and greater intensities, rTMS efficacy for LLD may be significantly diminished, such as in a recent small double-blinded rTMS trial that found 0% response in 10 patients receiving left unilateral excitatory stimulation alone (18). Heuristics to counteract effects of asymmetric atrophy such as adjusting motor threshold-based stimulation intensity according to scalp to cortex distance at the prefrontal target have been proposed and utilized (19, 20), but do not fully account for the effects of gyral thinning and sulcal widening on the induced electric field, and have generally not been used above the maximum stimulation intensity of 120% resting motor threshold.

## 1.2. Current targeting methods do not address electric field dose

Recent advances in accessibility of computational finite element modeling for use in noninvasive brain stimulation have enabled rapid calculation of the predicted induced electric field ($|E|$) of rTMS and correlation of its distribution and intensity with clinical and physiological outcomes. This capability provides a means for accurately and precisely assessing the effects of generalized and local atrophy on efficacy of rTMS in LLD. Electric field modeling has been used extensively in studies of the motor system, with strong correlations demonstrated between motor cortex $|E|$, coil-to-cortex distance, and motor threshold (21–23). There have been fewer clear results regarding $|E|$ in the DLPFC for treatment of depression. A rTMS modeling study conducted in 121 patients from the Human Connectome Project database demonstrated high rates of inter-individual variability in $|E|$ and its distribution, as well as in networks stimulated when rTMS is delivered to generic targets such as F3 (24). In a study of rTMS for smoking cessation by Caulfield et al. (25), $|E|$ in the prefrontal cortex was shown to be significantly diminished compared to the motor cortex, with higher levels of stimulation needed in the prefrontal cortex (133% of motor threshold) to achieve the same $|E|$ obtained in the motor cortex at 100% of threshold. A study by Deng et al. (26) of electric field strength in the middle, superior, and inferior frontal gyri of the DLPFC in 26 depressed patients receiving rTMS at F3 did not find a correlation with clinical outcomes. A recent study by Zhang et al. (27) of 12 patients receiving 3 weeks of left iTBS/right cTBS for depression found that the normal component of the electric field, not the tangential component or overall magnitude, was significantly correlated with antidepressant response. Finally, a comparison study was conducted by Deng et al. (28) between four targeting methods (5 cm rule, Beam F3, MRI-guided, and electric field-optimization) using pilot data from ten adolescents receiving 30 daily sessions of 10 Hz rTMS. Significant correlation was observed between $|E|$ in the DLPFC and antidepressant response in patients receiving a full course of treatment. Of the above methods,

the 5 cm rule method yielded the weakest field strength, and the Beam F3 method demonstrated significant variability.

To date, computational modeling has not been used to assess the relationship of |*E*| to clinical benefit with rTMS in an aged population. Therefore, we proposed and conducted a pilot study of accelerated fMRI-guided iTBS for patients with LLD and hypothesized that greater |*E*| measured at the personalized target would be associated with greater antidepressant response.

## 2. Methods

This was an unblinded, single-arm, prospective cohort study of accelerated fMRI-targeted iTBS conducted in 25 patients aged 50 and older with a diagnosis of major depressive disorder. This protocol was reviewed and approved by the UNM Health Sciences Center Human Research Review Committee (HRRC #19–531).

### 2.1. Recruitment

Recruitment took place through the UNM Treatment Resistant Depression Clinic, Geriatric Psychiatry Clinic, TMS Service, and ECT Service. All participants from the various clinics were referred for consideration of rTMS treatment for major depression, having failed various therapeutics such as oral antidepressants, esketamine, ECT, or traditional rTMS. Participants were screened *via* phone for inclusion and exclusion criteria.

### 2.2. Inclusion/exclusion criteria

To be enrolled in the study, participants met the following inclusion criteria: 1) ages 50–79, 2) diagnosis of major depressive disorder of at least 6 months' duration preceding study entry, confirmed by two independent board-certified psychiatrists according to DSM-5 criteria, 3) four or more adequate trials of antidepressants in the current episode, and 4) score of 10 or higher on the Quick Inventory of Depressive Symptomatology (16 item) (Self-Report) (QIDS-SR-16) at time of study entry. Exclusion criteria included: 1) history of seizure, 2) history of a major neurocognitive disorder or central nervous system disorder diagnosis, 3) implanted ferromagnetic material or contraindication to obtaining MRI, 4) pregnancy, 5) current incarceration, 6) inability to complete the protocol, 7) medical instability resulting in hospitalization or emergency department visit within the past month, and 8) psychotropic medication change or treatment with electroconvulsive therapy within the month preceding study entry.

### 2.3. Visit 1 assessment

After screening and consent, participants underwent demographic survey (age, sex, socioeconomic status, educational attainment, ethnicity, race, and handedness); assessment of depression history and treatment; mood and anxiety symptom assessment with the Inventory of Depressive Symptomatology for Clinicians (IDS-C-30, primary outcome measure); Generalized Anxiety Disorder-7 (GAD-7); Snaith-Hamilton Assessment of Pleasure Seeking for Clinician Administration (SHAPS-C); Temporal Experience of Pleasure Scale (TEPS); and the Behavioral Inhibition System/Behavioral Approach System Scale (BIS/BAS). Select domains of cognition were assessed with the Delis-Kaplan Executive Function Scale (DKEFS), Wechsler Adult Intelligence Scale (WAIS), and Hopkins Verbal Learning Test-Revised (HVLT). These instruments were chosen in line with prior study protocols combining imaging and neuromodulation (29, 30).

### 2.4. MRI

At the baseline visit, participants underwent structural and resting-state functional magnetic resonance imaging (MRI) on a 3 T Siemens Prisma scanner. High-resolution $T_1$- and $T_2$-weighted structural images and two 6-min runs of resting-state functional MRI (rsfMRI) were obtained. For structural scans: repetition time (TR) = 2,530 milliseconds (ms), echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, Inversion time (TI) = 1,200 ms, flip angle = 7.0°, slices = 192, field of view = 256, matrix 256 × 256, voxel size = 1.0 × 1.0 × 1.0 millimeter (mm). For resting-state scans: TR = 480 ms (multiband acceleration factor of 8), TE = 29 ms, flip angle (FA) = 75°, slices = 192, voxel size = 2.0 × 2.0 × 2.0 mm. The $T_1$ was preprocessed by parcellating with Freesurfer 6.0.0 and then aligned to rsfMRI data (31). The rsfMRI was preprocessed using AFNI's recommended pipeline (example 11) afni_proc.py with AFNI 20.2.18 (32). The first four volumes of each run were dropped and each run was aligned and despiked, slice time corrected, distortion corrected, warped to Montreal Neurological Institute (MNI) space, blurred with a 4 mm full width at half maximum (FWHM) Gaussian kernel, and scaled to a mean of 100. Nuisance signals were regressed and outlying volumes censored, and the runs were concatenated.

### 2.5. Targeting

Resting-state fMRI analysis and determination of neuronavigation targets were based on the published method of Ning et al. (33). The use of resting-state fMRI to identify targets within the DLPFC is built on a growing body of lesion and imaging work demonstrating the SgCC as a critical region mediating depressive symptomatology (34, 35). fMRI studies particularly by Fox et al. (36, 37) have shown that the degree of intrinsic anticorrelated activity between the DLPFC and SgCC at the target is a predictor of response to rTMS. More recent studies have demonstrated that distance of the stimulated target from the maximum anticorrelated target correlates with response to treatment (36, 38, 39). Our seed region was defined using the Brainnetome atlas region corresponding to the SgCC (187, 188), and the bounding search region within the DLPFC in each hemisphere was created from Brainnetome regions (15, 16, 19, 20, 21, 22) making up Brodmann areas 9 and 46 (40). Functional connectivity was measured by correlating time-series data from the pre-processed resting-state fMRI data for the seed region with each voxel in the search regions. A mask was created with the maximum anticorrelated voxel in the search region. Structural $T_1$ images and the functional mask were then exported to the Localite neuronavigation system for registration during stimulation sessions.

## 2.6. Stimulation

The 25 participants each received a total of 45 sessions (five sessions/day, nine weekdays) of iTBS to the cortical target with a MagPro X100 equipped with a Cool-B70 coil (Magventure Inc., Alpharetta, GA). The right DLPFC was chosen as the initial target region given its potential efficacy for depressive and anxious symptoms (41, 42), and based on earlier work showing that iTBS to this area can improve cases of depression that do not respond to iTBS to the left DLPFC (43). Co-registration of the MRI data in the Localite neuronavigation system was performed with head landmarks at the nasion and bilateral tragus. The mask with the functional target was overlaid on the structural images and projected orthogonally to the nearest scalp surface for coil positioning. Coil rotation at the scalp projection was specified as 45° from midline, with the coil handle pointing posteriorly. Coil tilt was maintained tangential to the plumb line from scalp projection to brain target. Deviation from target during iTBS was monitored and the coil repositioned for any displacements greater than three millimeters. In each session, 1800 pulses were delivered in 60 trains of 10 triplet bursts (pulse frequency 50 Hz, burst frequency 5 Hz), 2 s train duration, and 8 s intertrain interval in accordance with recently published accelerated iTBS protocols by Cole et al. (44). Pulses were delivered at 120% of resting motor threshold (RMT), defined as the minimum amount of energy to obtain five out of 10 motor evoked potentials with peak to peak amplitude of at least 50 uV in the abductor pollicis brevis muscle on electromyography, in accordance with parameters from the iTBS noninferiority study by Blumberger et al. (45). If patients could not tolerate 120% of RMT due to scalp discomfort, the highest tolerable stimulation intensity up to 120% RMT was delivered. Each iTBS session was separated by 50 min, based on prior work demonstrating this time frame as the optimal recovery time between sessions for accelerated protocols (46).

## 2.7. Visit 2 and 3 assessments

After 15 sessions participants repeated all behavioral assessments as this corresponds to the timeframe for mid-course evaluation in a typical clinical rTMS course. They then received 30 more sessions. If there was minimal improvement (<10%) noted in IDS-C-30 score at Visit 2 or development of intolerable side effects, the participant was switched to stimulation of the left hemisphere for the remainder of treatment, in line with clinical practice. The day following completion of the 45th session, participants repeated behavioral assessments and cognitive testing (Visit 3). At 1 month and 2 months following the protocol, the subjects were contacted by phone and assessed with the IDS-C-30.

## 2.8. Statistical analysis

Means and standard deviations for demographics and baseline behavioral and cognitive measures were calculated in SPSS Statistics 26 (IBM; Armonk, NY). Repeated-measures analyzes of variance and effect sizes expressed as partial eta squared ($\eta_p^2$) were calculated for Visit 1, 2, and 3 behavioral and cognitive outcomes using R v. 4.1.3 (R Foundation; Vienna, Austria).

## 2.9. Electric field modeling

Using the T1 and T2 weighted images within Simulation of Non-Invasive Brain Stimulation (SimNIBS) (47) a segmented 10-tissue head model was created and a simulated coil placed at the personalized target of each participant. The modeled coil orientation was defined as tangential to the scalp and rotated 45° from midline with the coil handle pointing posteriorly. A model based on a quasi-static approximation of Maxwell's equations was then solved for the vectorwise induced electric field (E), which is then scaled by the actual intensity of the individual stimulation delivered (% of maximum device output). To simplify calculations and the emphasis of directionality of the electric field, the magnitude of the induced electric field was calculated(|E|). This induced electric field measure was averaged in each parcellated region across the whole brain using the Human Connectome Project multimodal atlas parcellation (48) (HCP-MMP) for each subject to create regional induced electric field measures. Electric field analysis was restricted to areas that received significant field magnitude [defined as any area above half of the maximum brain average field ($|E_{max}|/2$) or above half of the maximum induced standard deviation ($|E_{max,sd}|/2$)], based on the entire cohort's |E|. This restricted the analysis to 11 regions in the HCP-MMP atlas. Due to segmentation issues only 23 of 25 participants' electric fields were included in the analysis.

# 3. Results

## 3.1. Baseline characteristics

Baseline characteristics of the study population are displayed in Table 1. The participants were predominantly female (22 of 25, 88%) and Caucasian (23 of 25, 92%), consistent with composition of the referring clinics. Comorbid psychiatric diagnoses (e.g., generalized anxiety disorder, GAD; posttraumatic stress disorder, PTSD) were present in 44% of participants. Treatment resistance was high, with participants on average having trialed nine medications prior to study entry, and 32% having previously trialed ECT.

## 3.2. Side effects

The most common reported side effects were scalp discomfort (68%), headache (48%), fatigue (40%), and sleep disruption (36%). All 25 participants completed all assessments for Visits 1, 2, and 3, and no participants discontinued involvement in the study. The average intensity of stimulation tolerated was 114.9% of RMT, with five subjects not able to tolerate the full dose of 120% of RMT.

## 3.3. Depression

Table 2 contains means and standard deviations for each behavioral and cognitive measure as well as *p* values and effect sizes. Assumptions of normality and sphericity were met for the primary outcome measure of depressive symptoms, the IDS-C-30, and most behavioral and cognitive secondary outcome measures. For certain

TABLE 1 Demographic and clinical characteristics of the study population ($N = 25$).

| Variable | Value |
|---|---|
| Age, years | 65 ± 7 |
| Sex | |
| Male | 3 (12) |
| Female | 22 (88) |
| Education (years) | 6.5 ± 1.4 |
| BMI | 29.6 ± 7.3 |
| Ethnicity | |
| Non-Hispanic | 23 (92) |
| Hispanic | 2 (8) |
| Race | |
| Caucasian | 23 (92) |
| Other | 2 (8) |
| Comorbid psychiatric diagnoses | |
| None | 14 (56) |
| GAD | 9 (36) |
| PTSD | 6 (24) |
| Other | 2 (8) |
| Episode duration (months) | 202.0 ± 196.5 |
| Lifetime duration (years) | 42.7 ± 15.7 |
| History of ECT | |
| Yes | 8 (32) |
| No | 17 (68) |
| Test of premorbid function scaled score | 108.5 ± 21.7 |
| Family history | |
| Yes | 21(84) |
| No | 4(16) |
| Number of failed antidepressant trials | 9.3 ± 6.0 |

Values are number (%) or mean ± standard deviation.

secondary outcome measures such as the GAD-7, Letter Fluency, and Color Word Score where assumptions of sphericity were not met, Greenhouse–Geisser correction was applied to the repeated measures ANOVA results. Mean depression scores for the entire cohort as measured by the IDS-C-30 improved significantly from Visit 1 to Visit 3 (Visit 1: 38.6 +/− 9.31; Visit 2: 31.0 +/− 10.2; Visit 3: 21.3 +/− 10.4; $F(2,48) = 62.88$, $p = < 0.0001$, $\eta_p^2 = 0.72$) (Figure 1). Clinical response, defined as > = 50% improvement in depression score, was achieved in 13 out of 25 subjects (52%) by Visit 3, and remission, defined as IDS-C-30 = < 12, was achieved in 5 out of 25 subjects (20%). Post-hoc t-tests with Bonferroni correction confirmed significant decreases in depression scores between Visit 1 and 2 ($t(24) = 5.90$, $p < 0.0001$), Visit 1 and 3 ($t(24) = 9.64$, $p < 0.00001$), and Visit 2 and 3 ($t(24) = 6.41$, $p < 0.00001$). An exploratory analysis of long-term effects was undertaken with follow-up IDS-C-30 assessment *via* phone call to all participants at 1 month and 2 months after treatment. Two participants were not able to be reached for 1 month assessment; at three-month follow-up, five participants were not able to be reached; these were the only missing data points in the cohort. Mean IDS-C-30 scores and standard deviations at one-month follow-up were 22.4 +/− 15.0. At three-month follow-up, mean IDS-C-30 score and standard deviation were 25.5 +/− 12.3.

## 3.4. Switching

A total of six patients switched to left hemisphere treatment during the protocol due to lack of at least 10% improvement in the IDS-C-30 at Visit 2. Of the subjects that switched, by Visit 3 none met criteria for remission, two met criteria for response, two met criteria for partial response (25–50% improvement), and two patients did not respond (Visit 1: 38.8 +/− 9.24; Visit 2: 38.7 +/− 9.69; Visit 3: 26.0 +/− 9.72).

## 3.5. Anxiety

Generalized anxiety symptoms as measured by the GAD-7 declined significantly from Visit 1 to Visit 3 ($F(1.57, 37.6) = 12.74$, $p < 0.001$, $\eta_p^2 = 0.35$) (Figure 2). Behavioral inhibition as measured by the BIS/BAS demonstrated improvement with treatment ($F(2,48) = 11.9$; $p < 0.0001$; $\eta_p^2 = 0.33$) (Figure 3).

## 3.6. Anhedonia

There were significant improvements observed in anhedonia symptoms from Visit 1 to Visit 3 as measured by the TEPS ($F(2,48) = 7.85$, $p = 0.001$, $\eta_p^2 = 0.25$) and the SHAPS-C ($F(2,48) = 10.47$, $p < 0.001$, $\eta_p^2 = 0.3$) (Figure 2). Behavioral approach as measured by the BIS/BAS also demonstrated significant changes, with increases in Reward Responsivity ($F(2,48) = 7.21$; $p = 0.002$; $\eta_p^2 = 0.23$) and Drive ($F(2,48) = 4.51$; $p = 0.016$; $\eta_p^2 = 0.16$) (Figure 3). After Bonferroni correction for multiple comparisons, the findings for the Drive subscale were no longer significant.

## 3.7. Cognition

There were no significant changes in any of the cognitive domains tested, including short term memory (HVLT-R), attention (WAIS), and executive function (DKEFS) from Visit 1 to Visit 3 (see Table 2).

## 3.8. Target distribution

The DLPFC target search region in Figure 4A and spatial distribution of the right DLPFC targets as well as their associated efficacy at Visit 2 and Visit 3 are displayed in Figures 4C,D. Also portrayed in Figure 4B are the cortical position of scalp location F4, as well as the right anterolateral anticorrelated network connectivity target identified by Siddiqi et al. *via* aggregative analysis of multiple imaging and brain stimulation data sets (35, 49). Degree of anticorrelation of the DLPFC targets with the SgCC was not significantly associated with change on the IDS-C-30 ($r = -0.002$; $p = 0.28$); however, anticorrelation between the DLPFC targets and SgCC showed a moderate positive correlation with increasing age

TABLE 2 Means and standard deviations (in parentheses) for primary and secondary behavioral outcome variables and cognitive assessments at Visits 1, 2, and 3.

| | Visit 1 | Visit 2 | Visit 3 | *F* | df | *p* | $\eta_p^2$ |
|---|---|---|---|---|---|---|---|
| IDS-C-30[a] | 38.64 (9.31) | 30.96 (10.2) | 21.28 (10.41) | 62.88 | 2,48 | **<0.0001** | 0.72 |
| GAD-7 | 9.72 (5.46) | 9.00 (4.81) | 5.6 (4.81) | 12.74 | 1.57,37.6 | **<0.001** | 0.35 |
| TEPS | 60.44 (11.23) | 65.52 (11.37) | 68.16 (11.10) | 7.85 | 2,48 | **0.001** | 0.25 |
| SHAPS-C | 38.8 (9.05) | 34.80 (8.31) | 32.32 (8.91) | 10.47 | 2,48 | **<0.001** | 0.3 |
| BAS drive | 8.80 (2.81) | 10.20 (2.47) | 10.00 (2.24) | 4.51 | 2,48 | **0.016** | 0.16 |
| BAS fun seeking | 8.80 (2.55) | 9.48 (2.31) | 9.24 (2.42) | 1.95 | 2,46 | 0.15 | 0.07 |
| BAS reward resp | 14.80 (2.12) | 15.44 (1.64) | 16.32 (1.93) | 7.21 | 2,48 | **0.002** | 0.23 |
| BIS | 24.20 (3.15) | 23.88 (3.87) | 22.52 (3.50) | 11.9 | 2,46 | **<0.0001** | 0.33 |
| DKEFS | | | | | | | |
| Letter fluency total correct scaled score | 12.17 (3.57) | 12.6 (3.27) | 12.52 (3.45) | 2.19 | 1.6,36.7 | 0.14 | 0.087 |
| Category fluency total correct scaled score | 11.35 (3.34) | 11.36 (3.11) | 11.24 (4.14) | 0.07 | 2,44 | 0.935 | 0.003 |
| Category switching total correct scaled score | 11.39 (3.64) | 12.00 (3.42) | 12.46 (3.28) | 1.49 | 2,42 | 0.24 | 0.066 |
| Category switching accuracy scaled score | 11.04 (3.70) | 11.80 (3.16) | 12.04 (3.16) | 1.26 | 2,42 | 0.29 | 0.057 |
| Color-word condition 1 color scaled score | 8.96 (3.83) | 9.12 (2.99) | 9.60 (3.20) | 2.23 | 2,44 | 0.12 | 0.092 |
| Color-word condition 2 word scaled score | 9.48 (3.19) | 9.12 (2.44) | 9.04 (2.75) | 0.22 | 2,44 | 0.81 | 0.01 |
| Color-word condition 3 inhibition scaled score | 9.70 (3.90) | 10.12 (2.98) | 10.20 (3.48) | 0.84 | 1.44,31.76 | 0.41 | 0.037 |
| Color-word condition 4 inhibition switch scaled score | 10.18 (3.26) | 10.28 (2.94) | 10.60 (3.11) | 0.54 | 1.45,30.45 | 0.53 | 0.025 |
| Color-word composite scaled score | 9.48 (3.38) | 9.28 (2.51) | 9.64 (2.72) | 1.04 | 1.55,34.11 | 0.35 | 0.045 |
| HVLT | | | | | | | |
| Total recall correct T score | 46.63 (13.37) | 49.40 (8.35) | 47.84 (11.34) | 0.90 | 2,46 | 0.41 | 0.038 |
| Delayed recall correct T score | 48.17 (11.50) | 49.60 (9.17) | 49.00 (10.57) | 0.21 | 2,46 | 0.81 | 0.009 |
| Retention T score | 52.71 (13.22) | 50.04 (9.97) | 51.00 (10.68) | 0.40 | 2,46 | 0.67 | 0.017 |
| Recognition discrimination index T score | 47.63 (7.92) | 46.44 (9.95) | 46.60 (10.79) | 0.35 | 2,46 | 0.71 | 0.015 |
| WAIS | | | | | | | |
| Digit span scaled score | 11.76 (2.61) | 11.33 (2.35) | 12.18 (2.35) | 0.96 | 2,18 | 0.40 | 0.097 |

[a]Indicates primary outcome measure.
IDS-C-30, Inventory of Depressive Symptoms-30-Clinician; GAD-7, Generalized Anxiety Disorder-7; TEPS, Temporal Experience of Pleasure Scale; SHAPS-C, Snaith-Hamilton Pleasure Scale-Clinician; BAS, Behavioral Approach System; BIS, Behavioral Inhibition System; DKEFS, Delis-Kaplan Executive Function System; HVLT, Hopkins Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale.

($r = 0.39$, $p = 0.05$), i.e., anticorrelation magnitude decreased as age increased.

## 3.9. Electric field distribution

The average induced electric field for all participants was distributed broadly across the right frontal lobe, with regions of greatest $|E|$ found in the middle frontal gyrus and inferior frontal gyrus (Figure 5A). $|E|$ at the target ($|E_{target}|$) for each patient was not significantly associated ($p > 0.1$) with change in IDS score, nor was $|E_{target}|$ correlated with the simulated electric field magnitude at the motor cortex (scalp location C3). In whole-brain analysis, negative correlations were observed between $|E|$ and change in IDS-C-30 between Visit 1 and 2 and Visit 1 and 3 (i.e., higher field magnitude associated with greater reduction in IDS score and antidepressant benefit) in anterior and lateral regions, i.e., Brodmann areas 10, 47, and 45 (Figures 5B,C). Positive correlation between $|E|$ and change in IDS-C-30 (i.e., higher field magnitude associated with less reduction or even increase in IDS score) was observed in posterior dorsolateral, dorsomedial, and motor regions. Of all areas meeting criteria for inclusion in electric field analysis, only posterior rostral Brodmann area 47 (p47r; Figure 5D) was significantly associated with change in IDS-C-30 score. The degree of correlation was moderate between $|E|$ in p47r and change in IDS-C-30 from Visit 1 to 2 ($r = -0.41$, $p = 0.05$). In participants who received all 45 stimulation sessions to the right hemisphere, the degree of correlation was strong between $|E|$ in p47r and change in IDS-C-30 from Visit 1 to 3 ($r = -0.56$, $p = 0.02$) (Figure 6). After controlling for false discovery rate, $p_{fdr} = 0.12$.

# 4. Discussion

In this open-label, single-arm pilot study, accelerated fMRI-guided iTBS significantly improved depressive and anxious symptoms in 25 patients with LLD. The protocol itself was well-tolerated, with no participants discontinuing treatments early. The most common side effects were scalp discomfort, mild headache,

sleep disruption, and fatigue. There were no serious adverse events and no significant changes on any of the cognitive measures obtained, indicating that accelerated iTBS at clinical stimulation intensities (110–120%) is a safe form of neuromodulation even in a population at increased risk of cognitive side effects. A very large effect was observed in the primary outcome measure, the IDS-C-30, with a mean 17-point reduction in depressive symptoms observed by the end of 45 iTBS sessions over 9 days, equating to a 52% response rate and 20% remission rate. Large effects on generalized anxiety levels and anhedonia symptoms were also demonstrated in the cohort. Our results highlight the rapidity of clinical benefit seen with accelerated protocols (44), in which response and remission can be achieved in 10 days or less compared to six to eight weeks with traditional once-daily clinical rTMS.

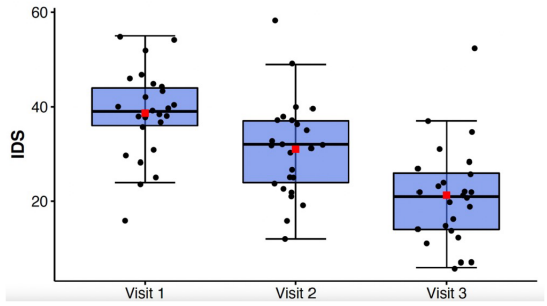


FIGURE 1
Box-whisker plot of IDS-C-30 scores at study Visits 1, 2, and 3. Center box lines indicate medians, red squares indicate means. Shaded box areas indicate 25th–75th percentile values. Bars indicate 1.5x interquartile range.

## 4.1. Utility of right iTBS for depression

This is the first rTMS study for LLD to target the right DLPFC with iTBS, an excitatory paradigm, and the first to use individualized fMRI guidance to the right DLPFC. The response rate of 52% is comparable to those described in uncontrolled non-accelerated studies of rTMS to the left DLPFC in general adult populations (7, 8), adding to the growing evidence base supporting targeting the right DLPFC with iTBS as an effective alternative strategy for treating depression (43, 50). These positive results run counter to a long-standing theory of hemispheric asymmetry of emotion regulation in the rTMS literature which posits that neuromodulation of the right DLPFC should be inhibitory in nature (i.e., 1 Hz) to be effective for depression (51). Recent work synthesizing results from multiple imaging and neuromodulation cohorts supports a conceptualization of the hemispheres as having relatively symmetric anticorrelated nodes in the DLPFC with similar relationships to depressive symptoms and treatment response to rTMS (35). Based on our clinical experience, up to 50% of patients will fail to respond to left DLPFC stimulation alone, highlighting the need for an accelerated iTBS protocol in the right hemisphere with an acceptable rate of benefit.

## 4.2. Clinical and stimulation factors influencing efficacy

Our remission rate of 20% was lower than described by Cole et al. (44) in the SAINT protocol study delivering accelerated fMRI-guided iTBS to the left DLPFC. They achieved 84% remission in an uncontrolled single-arm design and 79% remission in the active group in a subsequent double-blind trial (52). We believe our lower remission rate reflects several potential factors that may have relevance for wider use of accelerated protocols. First, the SAINT protocol

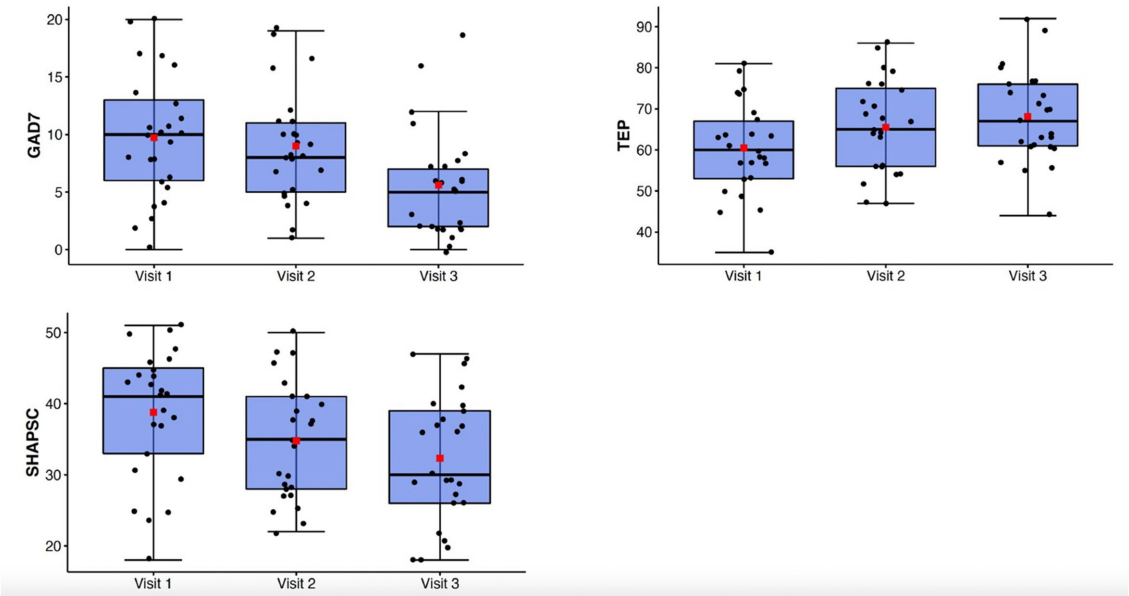


FIGURE 2
Top: box-whisker plots of GAD-7, TEPS, SHAPS-C at study Visits 1, 2, and 3. Center box lines indicate medians, red squares indicate means. Shaded box areas indicate 25th–75th percentile values. Bars indicate 1.5x interquartile range.

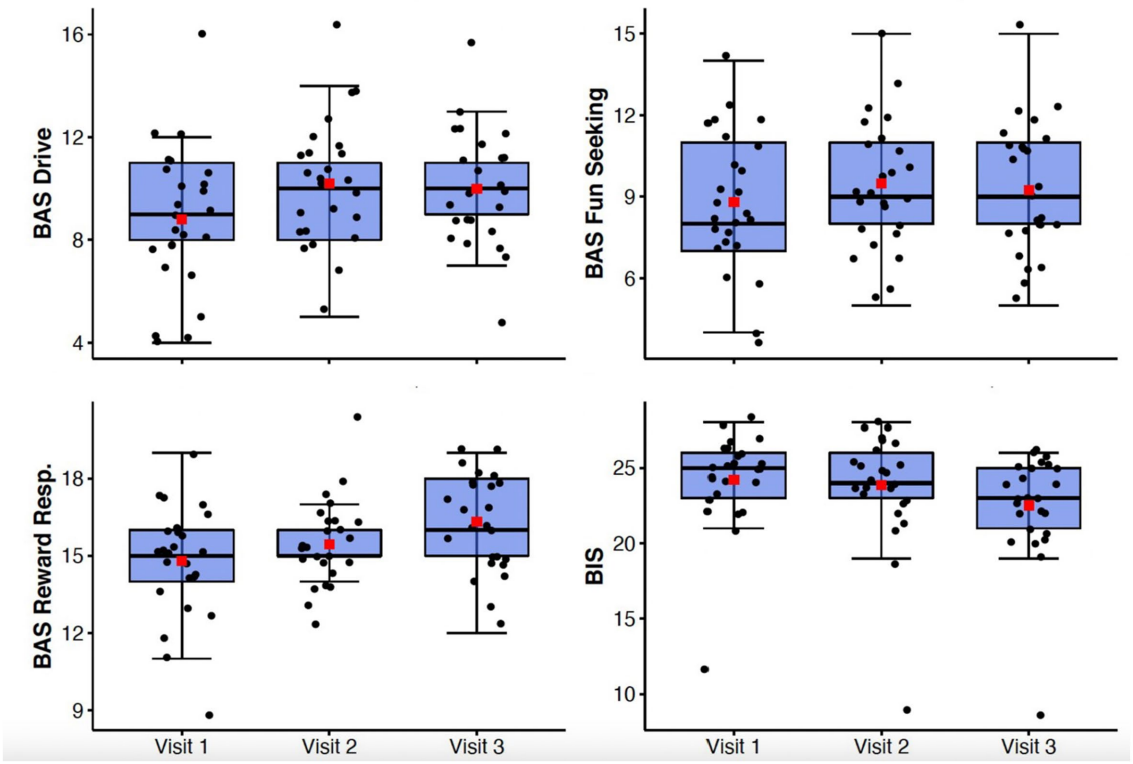


FIGURE 3
Box-whisker plots of BIS/BAS subscale scores at study Visits 1, 2, and 3. Center box lines indicate medians, red squares indicate means. Shaded box areas indicate 25th–75th percentile values. Bars indicate 1.5x interquartile range.

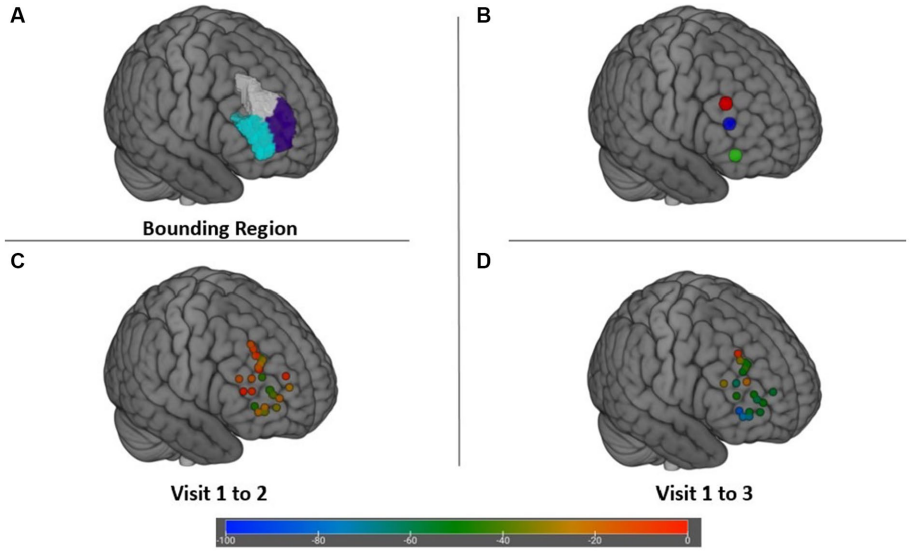


FIGURE 4
**(A)** Bounding search region within the DLPFC for targets maximally anticorrelated with the SgCC. **(B)** Cortical locations of scalp target F4 (X + 47 Y + 34 Z + 38) (red), depression network connectivity target from Siddiqi et al. (35) (X + 48 Y + 38 Z + 23) (blue), and posterior Brodmann area 47 (X + 46 Y + 43 Z-3) (green). **(C)** Change in IDS-C-30 from Visit 1 to Visit 2 achieved at each target. **(D)** Change in IDS-C-30 from Visit 1 to Visit 3 for participants receiving all 45 sessions to the right DLFPC.

delivered 50 sessions of iTBS in 5 days at 90% of motor threshold, whereas our protocol was 45 sessions over 9 days at 120% of motor threshold; the number, pace of acceleration, and dose of treatments may have had effects on the overall rate of clinical response, and not simply on the rapidity of improvement. Second, the SAINT protocol enrolled a younger population of adults (average age 45 vs. 65 in our

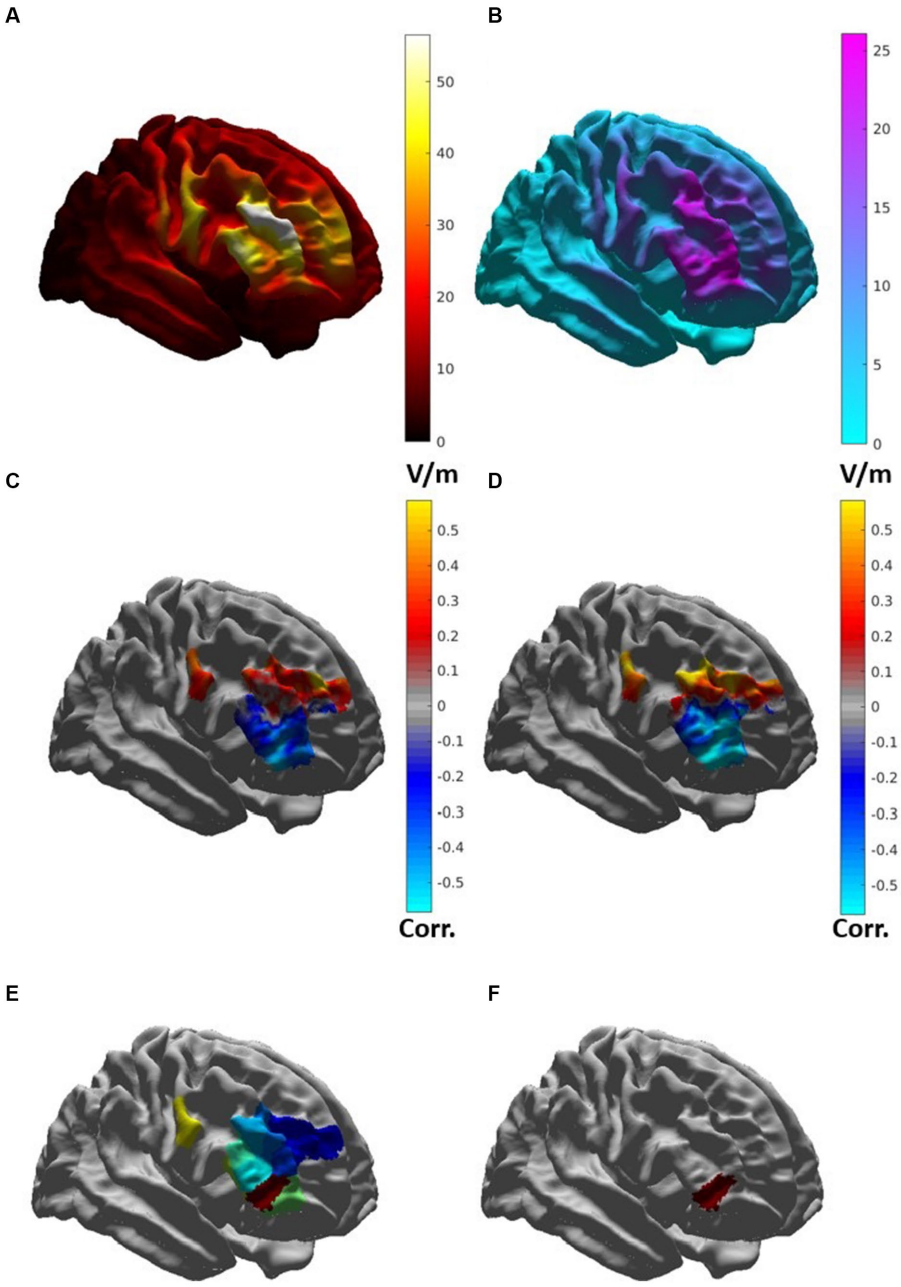


FIGURE 5
**(A)** Map of average induced electric field magnitude |*E*| (in V/m) for 23 patients. **(B)** Map of standard deviation of |*E*| (in V/m), indicating areas with high degree of variability. **(C)** Map of correlation between |*E*| and change in IDS-C-30 from Visit 1 to Visit 2 in brain regions included for analysis. Cool colors indicate areas of negative correlation, warm areas indicate areas of positive correlation. **(D)** Map of correlation between |*E*| and change in IDS-C-30 from Visit 1 to Visit 3 in participants receiving all 45 sessions to the right DLFPC. **(E)** HCP-MMP regions included for electric field analysis. **(F)** Posterior rostral Brodmann area 47 (p47r).

study), with lower average number of medication trials (5 vs. 9) and fewer ECT-experienced patients (0% vs. 32%). There was a high degree of comorbidity in our cohort, with 44% of participants with a secondary psychiatric condition, especially anxiety disorders. Each of these factors has been independently associated with lower rates of response and remission (7, 16, 17). Third, our protocol targeted the right DLPFC with iTBS, a less studied paradigm for depression than left iTBS, 10 Hz, or right 1 Hz inhibitory approaches. While right DLPFC iTBS has been shown to have benefit for patients who fail to respond to left side stimulation (43, 50), its approximate effect size for depression is not yet established, thus it is a possibility that iTBS to the right DLPFC is overall less efficacious for depression compared to the left DLPFC.

A fourth factor that may have contributed to lower response and remission rates is the accuracy of the functional targeting method used in our study. The maximum anticorrelated target in the DLPFC is theorized to be the subregion through which rTMS may most robustly modulate SgCC activity, which has been extensively linked to

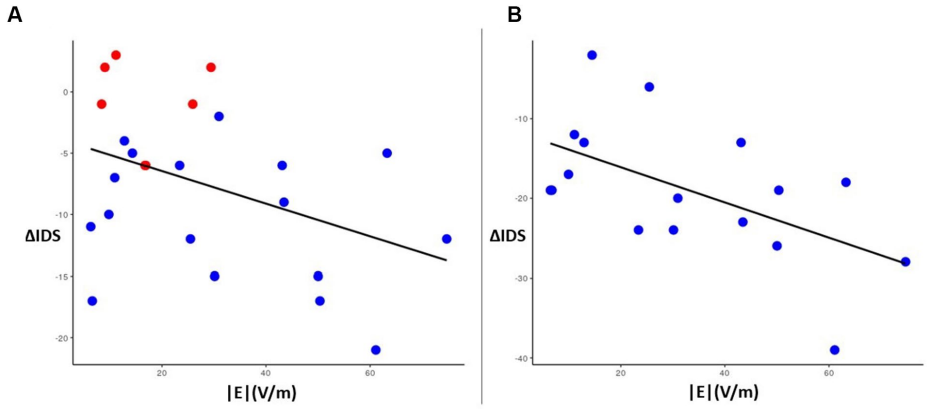


FIGURE 6
Left: correlation plot of magnitude |*E*| (x-axis) in region p47r with change in IDS-C-30 score (y-axis) between Visit 1 and Visit 2 for all participants ($N = 23$) ($r = -0.41$, $p = 0.05$). Red dots indicate the six participants who switched from right side to left side stimulation for Visit 2 to Visit 3. Right: correlation plot of |*E*| (x-axis) in region p47r with change in IDS-C-30 score between Visit 1 and Visit 3 for participants receiving all 45 sessions to the right DLFPC ($N = 17$) ($r = -0.56$, $p = 0.02$).

depressive symptomatology (34, 36). Several algorithms for targeting have been published, with varying degrees of incorporation of normative data sets and varying findings with regard to stability of targets (33, 44, 53). The voxel-based method utilized in this study has been critiqued for the level of variability in its generated targets, with clustering and network connectivity analyzes currently being more favored (33, 53). It is possible that using one of these alternative methods may have obtained better outcomes. However, there has not been a head-to-head trial of one fMRI-based targeting method versus another, nor has there been a definitive controlled trial of fMRI-based targeting versus scalp-based targeting. In addition, a recently published network connectivity target for depression in the right hemisphere obtained from multiple imaging and neuromodulation datasets (35, 49) (Figure 4B) fell within our target bounding region (Figure 4A) and near the center of the average induced electric field (Figure 5A), suggesting that while our targets may have been distributed diffusely through the bounding region, they were likely not inaccurate in general. The fMRI targeting pipeline used in our pilot study was selected based on its feasibility of implementation using published information; its use of freely available software; its basis on each patient's scan results and not group averages to compute the maximum anticorrelated node within the specified bounding region; and its ability to generate targets within 24 h of image acquisition. That there are multiple available targeting methods for fMRI-guided rTMS with different strengths and weaknesses highlights the need for studies comparing clinical efficacy of these methods.

## 4.3. Antidepressant effects in VLPFC

Of importance to the discussion of efficacy is our demonstration that |*E*| magnitude associates with clinical outcome for rTMS, the first such study in the right hemisphere. Greater |*E*| magnitude in anterior dorsolateral and ventrolateral regions was associated with greater antidepressant effect and was mirrored by the finding that greater |*E*| in posterior DLPFC was associated with less benefit. This anterior–posterior gradient agrees with theoretical work (35, 38) that posits an anterolateral anticorrelated node adjacent to correlated regions, with clinical benefit increasing the closer the target is to the anticorrelated node. We believe our findings provide evidence indicating that delivery of sufficient |*E*| to the functionally anticorrelated target is necessary for clinical response.

In addition, we note that the most impactful electric field effects on antidepressant outcome were not found in the targeted DLPFC, but in Brodmann area 47 (BA 47), a region categorized as ventrolateral prefrontal cortex (VLPFC), inferior frontal gyrus (IFG), and pars orbitalis. BA 47 has been implicated in language processing (54), emotion perception and regulation (55), social cognition (56), and resilience (57), and functions as a key node in a ventral emotion regulation network (58). Reduced gray matter volume and altered connectivity of the VLPFC have been implicated in suicidality in late-life depression (59). As a target for neuromodulation, it has been suggested the VLPFC may have more direct white matter connections to the SgCC and thus may be a more effective target for modulating SgCC activity (60) compared to the DLPFC (61, 62). Sydnore et al. (63) found that in-scanner rTMS to the VLPFC demonstrated engagement with both the SgCC and the amygdala, with direct white matter connections through the uncinate fasciculus. Likewise, Wu et al. (60) recently reported that positron emission tomography imaging in 19 patients receiving accelerated iTBS to the left DLPFC demonstrated that baseline hypometabolism in the left IFG was associated with clinical improvement, and that more anterolateral targeting results in significant electric field strength in the IFG. As stimulation targets for rTMS have moved more anteriorly and laterally over time, the VLPFC/IFG region may be increasingly exposed to induced electric fields, and may contribute to the increasing efficacy that has been seen with later targets (64).

## 4.4. Importance of electric field modeling in LLD

Our findings highlight the emerging importance of electric field modeling for rTMS for LLD, especially for ensuring adequate dose.

The induced electric field from each magnetic pulse engages axon bodies of neurons in gyral crowns and creates lasting physiological effects based on duration, frequency, and field strength (65). If field strength is inadequate, as is seen with rTMS at less than 80% RMT, there may be insufficient neuronal tissue stimulated to create neuroplastic network effects. Likewise, if the strength is excessive, it may lead to adverse effects such as seizure. While a dose–response relationship between electric field magnitude and clinical efficacy has not yet been established, our data suggests that in BA 47, 30 V/m was the threshold below which non-response tended to occur. As only a minority of participants received field intensities at or above this threshold, insufficient dosing may be a further explanation for the lower response/remission rate observed in our study. Placement of the coil closer to this region would increase the dose, as would utilizing electric field modeling to optimize for scalp to cortex distance, coil orientation and local anatomic effects on distribution and strength of $|E|$ given specific gyral and sulcal patterns (25, 66, 67). Especially in LLD, where a large proportion of patients may have significant prefrontal atrophy, electric field modeling may enable delivery of prefrontal stimulation at doses of $|E|$ that more closely resemble the electric field intensities obtained at motor cortex during threshold determination, and maximize clinical efficacy while maintaining safety limits related to cortical excitability.

Electric field modeling also enables more precise steering of $|E|$ to deliver stimulation to the intended target alone. If a coil is not located optimally over the target, the induced field may still "find" the target nearby and achieve the desired clinical effect if greater $|E|$ with broader distribution is used. This may explain the benefits seen with deep rTMS for LLD, which is delivered with a H-coil that achieves both deeper and broader stimulation over both hemispheres and may stimulate VLPFC in addition to DLPFC (68). However, increased $|E|$ and distribution may have negative implications for focality and anti-therapeutic stimulation of surrounding areas (47). Although generally considered more focal than deep TMS, the spatial distribution of $|E|$ with a figure-8 coil over the DLPFC still extends to adjacent cortex regions and can unintentionally stimulate nodes that participate in different networks (67). In our study this tradeoff was observed: while peripheral $|E|$ in the neighboring VLPFC was more beneficial for depression outcome, greater field distribution in the posterior DLPFC was less beneficial, confirming what has been posited by connectivity targeting analyzes regarding an anterior–posterior gradient of effect. We believe this argues for use of modeling to ensure $|E|$ is directed not only toward the therapeutic target but also away from non-therapeutic or anti-therapeutic regions.

## 5. Limitations

Limitations of this study include its small size, the lack of a sham control group, and a study population skewed toward female Caucasian patients. We did not adjust stimulation intensity for coil to cortex distance in the prefrontal lobe to account for possible frontal lobe atrophy, as all stimulations were intended to be delivered at the maximum allowable safe dose of 120% of RMT. Further work using electric field modeling will likely justify dosing at higher intensities without compromising safety.

## 6. Conclusion

In this open-label, single-arm trial, accelerated fMRI-guided iTBS to the right DLPFC was feasible and effective for treating late-life depression, although not as effective as recent trials of accelerated fMRI-guided TMS to the left DLPFC, possibly due to hemispheric lateralization, age-related effects, treatment resistance, target selection methods, or inadequate dosing. Induced electric field intensity in posterior BA 47 was correlated with antidepressant response, suggesting the importance of generating sufficient electric field strength in anterolateral zones to achieve clinical benefit. Further study of the spatial distribution and magnitude of the induced electric field at the cortical and subcortical level are needed to determine optimal dosing and delivery of rTMS for LLD.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by University of New Mexico Health Sciences Center Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

BG, JY, SH, AP, ED, BH, TO, ML, CA, CO, DB-W, and DQ were responsible for protocol administration and data collection. TJ, JU, and TO were responsible for data analysis and figure design. DQ, DF, JM, CA, BH, JY, and AV were responsible for literature review, study design, data curation, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Preliminary data from this study was previously presented at the American Association of Geriatric Psychiatry Annual Meeting, Orlando, FL, March 18–21, 2022.

## Publisher's note



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# Improvement of working memory in older adults with mild cognitive impairment after repetitive transcranial magnetic stimulation – a randomized controlled pilot study

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Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that could improve cognitive function. It is being developed as a non-pharmacological intervention to alleviate symptoms of cognitive deterioration. We assessed the efficacy of rTMS in improving cognitive functioning among people with Mild Cognitive Impairment (MCI) in a partially-blinded, sham-controlled randomized trial. Out of 91 subjects screened, 31 participants with MCI (mean age 70.73; SD = 4.47), were randomly assigned to one of three groups: (A) Active rTMS; (B) Active rTMS with Computerized Cognitive Training RehaCom; and (C) Sham control. The study evaluated cognitive function using the DemTect, FAS, and CANTAB tests before and after the stimulation. The following treatment protocol was applied: 2000 pulses at 10 Hz, 5-s train duration, and 25-s intervals at 110% of resting MT delivered over the left Dorsolateral Prefrontal Cortex (DLPFC) five times a week for 2 weeks. After 10 sessions of high-frequency rTMS, there was an improvement in overall cognitive function and memory, assessed by the DemTect evaluation, with no serious adverse effects. Analysis of differences in time (after 10 sessions) between studied groups showed statistically significant improvement in DemTect total score (time by group interaction $p = 0.026$) in favor of rTMS+RehaCom. The linear regression of CANTAB Paired Associates Learning revealed significant differences in favor of rTMS+RehaCom in three subtests. Our study shows that 10 sessions of rTMS over the left DLPFC (alone as well as combined with Computerized Cognitive Training) can have a positive impact on cognitive function in people with MCI. Further research should investigate the underlying mechanism and determine the optimal parameters for rTMS, which will be important for its efficacy in clinical settings.

KEYWORDS

**mild cognitive impairment, transcranial magnetic stimulation, resting-state functional MRI, computerized cognitive training, cognitive function, dorsolateral prefrontal cortex**

# 1 Introduction

Mild cognitive impairment (MCI) is a term used to describe an early stage of memory loss or other cognitive ability loss in individuals who otherwise maintain independent performance in most activities of daily living. It is perceived as a transitional state between normal aging and dementia. According to Petersen's MCI classification, it comprises four clinical subtypes: (i) single-domain amnestic MCI; (ii) multiple-domain MCI; (iii) single-domain non-amnestic MCI; and (iv) multiple-domain non-amnestic MCI (1). These subtypes indicate differences in clinical outcomes. Both amnestic MCI (i, ii) are more likely to convert into Alzheimer's disease (AD), while non-amnestic MCI conditions (iii, iv) are instead more likely to convert into other types of dementia, such as vascular dementia or Lewy body dementia (2, 3).

Most often, patients initially notice a decline in the memory regarding daily activities, recent personal experiences, new information, etc., called everyday memory. Their observations are confirmed by neuropsychological assessment since individuals with MCI typically show impairment in delayed recall tasks, involving encoding and retrieval of information (3). Such cognitive deficits are responsible for a decrease in quality of life (QOL) (4, 5) and make them more susceptible to the occurrence of psychiatric conditions such as depression, irritability, and apathy when compared to older adults without cognitive impairment (6). The relationship between cognitive and neuropsychiatric disorders is a complex phenomenon, as cognitive disorders can be a consequence of confrontation with declining cognitive performance, but they can also precede cognitive disorders as in the case of Parkinson's disease (7) or result from fear of potential impairment (not necessarily already present). In addition, cognitive impairments can mask other disorders, e.g., a depressive disorder and disappear after appropriate pharmacotherapy (8). Since pharmacological treatment for MCI has exhibited no significant effect on cognitive deterioration symptoms (9) establishing the efficacy of nonpharmacological interventions (e.g., cognitive, physiological, dietary, psychosocial, and noninvasive brain stimulation methods) in slowing the transition from MCI to dementia is playing a leading role in aging research (10).

Transcranial magnetic stimulation (TMS) emerges as a noninvasive electrophysiological method of central nervous system stimulation with the potential to enhance cognitive functioning. During TMS electric current is generated in the therapeutic coil, which subsequently generates a magnetic field responsible for a change of electrical field in the brain cortex. A magnetic pulse delivered by the coil penetrates the skin and skull bone in a non-invasive and generally well-tolerated and safe way. Subsequently, due to numerous connections with many other structures, the stimulus spreads into further regions and functional brain networks (11). Single and paired-pulse protocols are most frequently used for research purposes, i.e., to investigate cortical excitability and reactivity, while repetitive TMS (rTMS) is usually employed in treatment protocols (12). Low-frequency rTMS (≤1 Hz) causes inhibition of cortical excitability, whereas high-frequency rTMS (5-20 Hz) leads to increased excitability (13).

So far, the most commonly used cortical target for the therapeutic application of rTMS in MCI or AD-type dementia was the Dorsolateral prefrontal cortex (DLPFC) (3). The DLPFC is involved in such cognitive functions as everyday memory, working memory (14), and executive function (15). Studies involving functional magnetic resonance imaging (fMRI) have shown that high-frequency rTMS increases cortical excitability of the left and right DLPFC before memory tasks, and these changes are associated with the increased metabolic activity of the right DLPFC (16). Even though rTMS studies on cognitive functions have been conducted for more than 10 years, there are still some controversies regarding its efficacy in improving general cognitive functioning (3), the potential mechanism of the improvement of cognitive performance (17), the level of cognitive deterioration for which rTMS is effective (MCI/AD) (9), and the possibility of enhancing its potential via cognitive training pre/post/during the intervention (18).

A 2022 study by Esposito et al. (10) showed significantly increased semantic fluency ($p = 0.026$) and visuospatial ($p = 0.014$) performances after rTMS in the treated group but not in the sham group. These results are in line with a 2023 literature review on noninvasive brain stimulation in Primary Progressive Aphasia by Papanikolau (19), which points toward the application of rTMS having a positive effect in improving symptoms, such as verb production, action naming, phonemic-verbal fluency, grammatical comprehension, written spelling, and semantic features. On the contrary, the results from a 2023 random-effects meta-analysis by A. Miller et al. (20) demonstrated that rTMS significantly improved global cognitive function relative to control groups ($p = 0.017$), however no significant effects were found for individual cognitive domains. Discrepancies regarding cognitive training are also evident, as some studies report its reinforcing effect on stimulation efficacy (21), while others show that an enhanced synergistic effect does not occur when both interventions are used simultaneously (22).

The purpose of the study was to answer the aforementioned concerns emerging in the evaluation of the effects of rTMS. Firstly, it aims to assess the efficacy of rTMS over the left DLPFC in enhancing general functioning as well as selected cognitive domains of elderly patients. General cognitive functioning, which is a primary outcome of the study, is measured by the DemTect total score. Selected cognitive domains (secondary outcome measures) were assessed by the FAS verbal fluency test and a very sensitive computerized measurement of cognitive function, the Cambridge Neuropsychological Test Automated Battery (CANTAB). Secondly, the study is meant to determine whether the incorporation of Computerized Cognitive Training directly after the rTMS sessions may enhance its efficacy in improving cognitive performance. Based on previous research we can suspect that rTMS can lead to long-lasting after-effects in the brain, and therefore it is thought to be able to induce adaptive structural and functional changes to the brain, called neuroplasticity (23). Because both rTMS and cognitive pieces of training can enhance adaptive plastic mechanisms (24), our focus was to determine if a synergistic positive effect could result from the combination of both approaches, as it was suggested by Birba et al. (21). Results of the study are reported in accordance with "Consolidated Standards for Reporting Trials (CONSORT)" guidelines and recommendations.

# 2 Materials and methods

The study was designed as a partially-blinded sham-controlled randomized trial. Patients as well as raters were blinded regarding the type of treatment (active or sham coil). The participants who

performed computerized cognitive training are considered partially-blinded, since they were aware that they were training cognitive functions via RehaCom software. Unblinding was permissible only in case of adverse symptoms that threaten the health of the participant. The person applying the stimulation was unblinded due to technical considerations and was not involved in any rating activities. Two independent data entry personnel entered data separately. Any discrepancies between their entries were resolved by referring back to the source data. This double data entry process allowed to identify and rectify data entry errors effectively. To maintain consistency and facilitate data analysis, we employed a standardized coding system for variables and data categories. Access to the research data was restricted to authorized personnel only. The research protocol was reviewed and approved by the Bioethical Committee at Wroclaw Medical University (KB-400/2018/2506). The trial was registered at ClinicalTrials.gov (NCT05730296).

## 2.1 Participants

The recruitment process was carried out through media advertisements and community settings, between January 2020 and December 2022. Interested patients were scheduled for an appointment with a psychologist who provided them with all the information about the study design and rTMS itself. During the appointment, the psychologist carried out a cognitive examination at T1 (before stimulation) and helped those participants who needed some assistance to fill out a paper form application for the clinical trial, providing their contact details and socio-demographic information. Finally, the patients who completed the application form were contacted and examined by a psychiatrist who assessed their mood and anxiety symptoms and verified the inclusion and exclusion criteria.

The inclusion criteria for the study were: (i) absence of other psychiatric disorders (i.e., depression, anxiety disorders), which may affect cognitive performance (GDS-15, 15-item Geriatric Depression Scale; HAM-A 14, 14-item Hamilton Anxiety Scale); (ii) MCI diagnosis according to Petersen's criteria such as (a) subjective memory impairment over 1–2 years, (b) objective declined memory performance assessed by Montreal Cognitive Assessment Scale, (MoCA) with score between 19–26, (c) preserved general cognitive function based on the initial interview, (d) minimal impairment in activities of daily living based on the initial interview, (iii) age between 55 and 80 years, (iv) given informed consent to participate in the study and commitment to participate in individual sessions according to the treatment protocol.

The exclusion criteria for the study were divided into two groups: specific TMS contradictions and specific MRI contradictions. The former include (i) a positive history of epileptic seizures or a positive family history of epilepsy, (ii) magnetic or ferromagnetic implants, both electronic (e.g., heart/brain stimulators) as well as mechanical (e.g., bone anastomoses) within the head and neck, (iii) previous stroke or head injury with identified neurological deficits, (iv) increased intracranial pressure or a positive history of increased intracranial pressure, (v) occurrence of significant pathologies in the cerebrum area (tumors, hydrocephalus, strokes). The latter include (i) claustrophobia, and (ii) magnetic or ferromagnetic implants, both electronic (e.g., cardiac/brain stimulators) as well as mechanical (e.g., bone anastomoses) within the head and neck.

The patients who completed the psychological and psychiatric evaluation progressed to receive a structural MRI to exclude contraindications to stimulation. All MR examinations were carried out on a 3 Tesla MR scanner (Ingenia Philips Best Netherlands) equipped with 45 mT/m 200 T/m/s gradients and a 32-channel head coil. All patients underwent brain MRI two times: before TMS (structural imaging followed by resting-state functional MRI) and after TMS sessions (only resting-state functional MRI). Structural imaging was performed to search for brain pathologies that could exclude patients from the study and consisted of standard MR sequences such as axial T2-weighted imaging, 3D FLAIR, DWI, and SWI.

## 2.2 Intervention

Patients included in the study were randomized and assigned into one of three groups using the Sealed Envelope online software application:

A. rTMS active group
B. rTMS+RehaCom active group
C. sham control group

The randomization was stratified by age at baseline. Single pulse stimulation was used to find the motor hotspot, using an electromyography (EMG) signal recorded from the flexor digitorum superficialis (with an electrode located on the index finger). The resting motor threshold (MT) was determined afterward, similarly based on the EMG signal. After MT determination (defined as % of the device output needed to elicit a motor response in ≥50% of the attempts), the stimulation point (target) was set, by moving the coil 6 cm to the front from the determined hotspot. The following treatment protocol was applied (in both active and sham groups): 2000 pulses at 10 Hz, 5-s train duration, and 25-s intervals at 110% of resting MT delivered five times a week for 2 weeks (10 sessions). For the control group, we used a sham coil generating a minimal magnetic field affecting only adjacent tissues (scalp). PowerMag 100 lab device (Mag&More, Munich, Germany) applied in this research, along with active and sham coils of the figure of eight, provided by the same manufacturer. The high frequency (hf) rTMS protocol was ascertained based on previous research (3).

For participants who were allocated to the rTMS+RehaCom group, we employed the software RehaCom (25), which is a modular, interactive program designed to train cognitive abilities. The system includes procedures to train and improve attention, memory, visuospatial processing, and executive functions. The therapist's interface allows for the introduction and retrieval of personal and clinical information of the patients, the design of individual subprograms, including the individualized level of difficulty, and the collection of data. The training plan was standardized, as each participant performed a different set of exercises each day, programmed in advance by the experimenter for 10 days of stimulation. The training was performed under the supervision of specialists for 30 min just after each TMS session.

## 2.3 Measures

At the stage of the inclusion to the study, symptoms of cognitive decline were diagnosed using the Montreal Cognitive Assessment test and Clinical Dementia Rating Scale. Additionally, symptoms of anxiety and depression, which may negatively affect cognitive functions, were assessed by the 14-item Hamilton Anxiety Scale and the 15-item Geriatric Depression Scale, respectively. Next, the severity of cognitive decline was assessed at two points in time: T1 – before stimulation, and T2 – at the end of stimulation, using the DemTect test for general cognitive functioning (primary outcome) and CANTAB with the Verbal Fluency Test FAS for selected cognitive domains (secondary outcome).

### 2.3.1 Inclusion measurements

*MoCa (Montreal Cognitive Assessment)* is a screening tool created to identify cognitive impairment. Ziad Nasreddine created this assessment in 1996 as an alternative to the Mini-Mental State Examination. MoCA is a recommended test for MCI detection (26). The cut-off point for MCI is ≤26. MoCA assesses several cognitive domains: orientation, memory, naming, visuospatial functions, vigilance, language, abstract thinking, and alternating trial-making (27).

*CDR (Clinical Dementia Rating Scale)* is a clinical tool for dementia assessment, developed at Washington University School of Medicine. It estimates six cognitive domains: Memory, Orientation judgment, Community Affairs, Home and Hobbies, and Personal Care (28). In addition to the rating for each domain, an overall CDR score may be calculated through the use of the algorithm. In this study, the 0.5 over score was used as a cut-off for MCI.

*GDS-15 (15-Item Geriatric Depression Scale)* is a screening tool used to assess depression symptoms. Of the 15 items, 10 (question numbers 2, 3, 4, 6, 8, 9, 10, 12) indicate the presence of depression symptoms when answered positively, while the rest (1, 5, 7, 11, 13) indicate depression when answered negatively. Scores of 0–4 are considered normal; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression. The GDS was found to have a 92% sensitivity and an 89% specificity when evaluated against diagnostic criteria (29). To be included in the study patients needed to score < 7.

*HAM-A 14 (14-Item Hamilton Anxiety Scale)* is a scale widely used by clinicians for patients' anxiety rates. It was originally published by Max Hamilton in 1959. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical ailments related to anxiety) (30). This scale allows us to estimate the extensiveness of anxiety and is still widely used in clinical settings. The cut-off score in the study was <8.

### 2.3.2 Study outcomes measurements

*DemTect (Demenz-Test)* is a brief (8–10 min), easy-to-administer screening test for dementia comprising five short subtests (10-word list repetition, number transcoding, semantic word fluency task, backward digit span, delayed word list recall) (31). Its transformed total score (maximum 18) is independent of age and education. DemTect allows one to decide whether cognitive performance is age adequate (13–18 points), suggests MCI (9–12 points,) or dementia (8 points or below) (32).

*Verbal Fluency FAS Test* is a measure of phonemic word fluency, which is a type of verbal fluency. Verbal fluency facilitates information retrieval from memory. Successful retrieval requires executive control over such cognitive processes as selective attention, internal response generation, self-monitoring, and self-control. In FAS, by requesting an individual to orally produce as many words that begin with the letters F, A, and S as possible, phonemic fluency is assessed, within a prescribed time, usually 1 min (33).

*CANTAB (the Cambridge Neuropsychological Test Automated Battery)* was created to assess cognitive deficits in patients with neurodegenerative diseases or brain damage (34). Studies show that this tool is a reliable and valid clinical assessment. What is more, its method of administration is exceptionally standardized, which results in fewer variations due to experimenter change or error (35). The Alzheimer battery used in this study estimates cognitive functions in seven domains: Motor Screening Task (MOT): 2 min, Reaction Time (RTI): 3 min, associate learning (PAL): 8 min, Spatial Working Memory (SWM): 4 min, Pattern Recognition Memory (PRM): 4 min, Delayed Matching to Sample (DMS): 7 min and Rapid Visual Information Processing (RVP): 7 min. It takes 35 min to complete the Alzheimer's battery.

## 2.4 Statistical analysis

The Shapiro–Wilk test and visual assessment were used to analyze the normality of the data. Demographic characteristics at baseline were compared using the Fisher exact test for independent samples (gender, place of residence, education, work, marital status) and the Kruskal-Wallis tests (age, MoCA, HAM-A, GDS scores). Analysis of changes between T1 T2 in FAS, DemTect, and CANTAB was performed using ng Wilcoxon signed-rank test for paired data. Additionally, multivariate mixed models were used to assess differences over time between groups. The level of statistical significance was set at 0.05. Calculations were made using the R for Windows package (version 4.2.2.).

# 3 Results

## 3.1 Consort diagram flow

Out of 81 subjects screened by a psychologist, 42 did not fulfill the enrollment criteria. Among the subjects left, 39 proceeded to get an MRI. One person was excluded from the study at this point due to radiological contradiction, yielding a total number of 43 participants excluded from the study. Next, 38 participants were enrolled in the study and randomly assigned into one of three groups: (A) Active rTMS ($n = 13$); (B) Active rTMS with Computerized Cognitive Training RehaCom ($n = 13$); and (C) Sham control ($n = 12$). Six patients dropped out of the study during the first few sessions and these individuals were excluded due to their inability to follow the procedure protocol. The causes of drop-out were as following: anxiety reaction during stimulation (2 people), Change in personal situation (2 people), 1 day-lasting headache after stimulation (one person). One person resigned before the first rTMS session due to emergency heart

surgery, with a total of 1 people who could not participate in the entire stimulation process. In the end a total number of 31 participants finished the protocol. The CONSORT diagram flow of the study design can be found in Figure 1.

## 3.2 Characteristics of the studied group

All of the participants lived in a big city. Above 63% of patients in every group were married. The vast majority had middle or higher

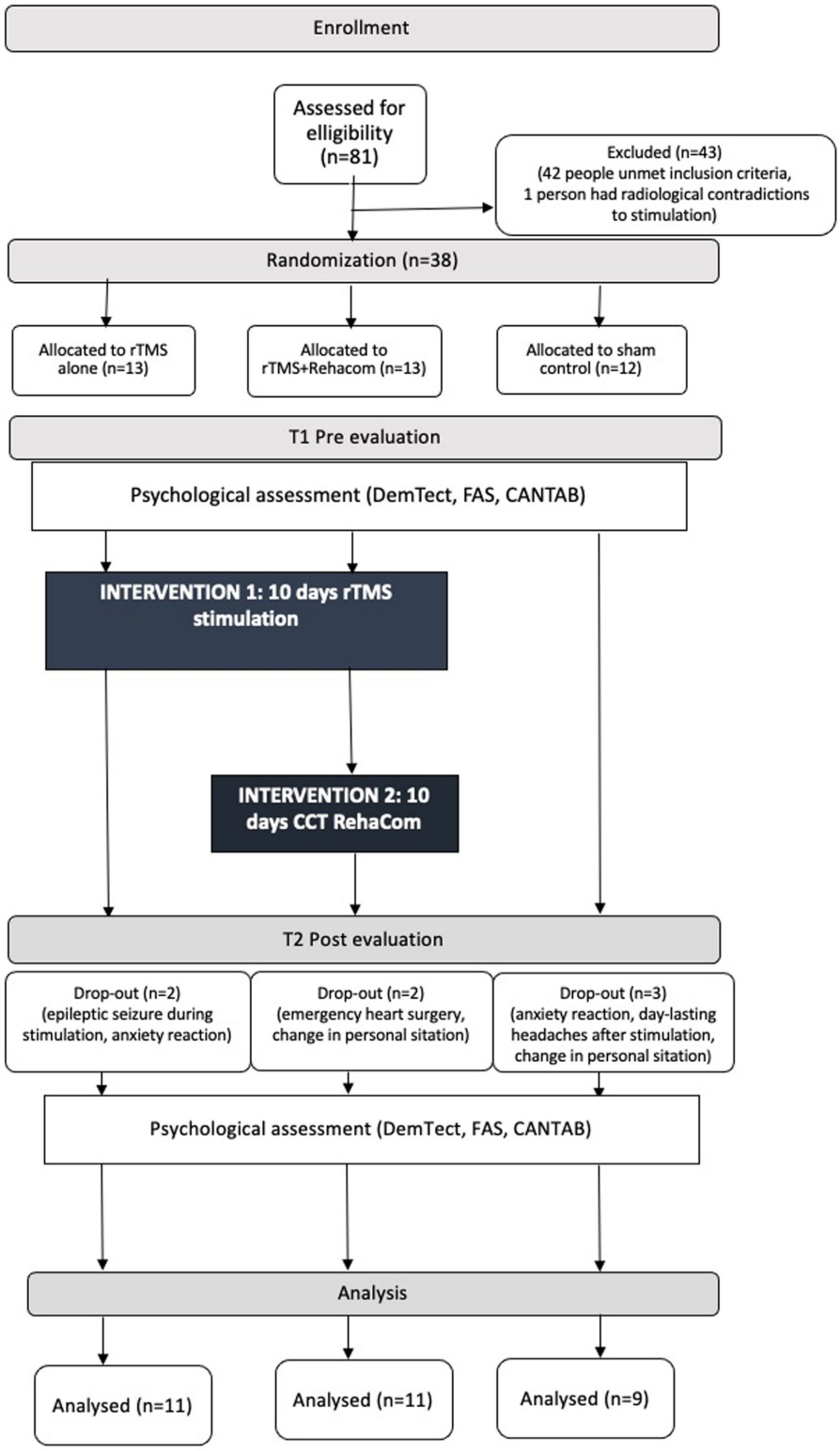


FIGURE 1
The consort diagram flow of the study.

education and were retired. More than half of the participants were men. At baseline, groups were homogeneous in terms of global cognitive status and in terms of severity of anxiety and depressive symptoms, failing to meet the criteria for a diagnosis of either disorder. Furthermore, there were no significant differences between the randomized groups regarding the severity of cognitive deterioration at baseline (T1) measured with DemTect, FAS, and CANTAB. Detailed clinical and demographic characteristics as presented in Table 1. Specific data [M (SD)] on CANTAB and, FAS, DemTect scores in T1 and T2 due to their multiplicity are given in Supplementary Table S1.

## 3.3 Tolerability and safety

rTMS at 10 Hz with 110% of the MT was relatively well tolerated. However, one patient experienced an epileptic seizure during the first session of rTMS, which significantly increased the rate of serious adverse effects in our study to 4.5%. The patient was subsequently counted as drop-outs of the study. 6 patients in the control group and 12 in both experimental groups analyzed together reported some side effects after the intervention, which included headache, insomnia, pain in the area of stimulation, and a burning sensation on the scalp. The number of adverse effects in the experimental and control groups was similar. As stimulation progressed, patients reported fewer adverse effects. For the analysis of TMS side effects, the experimental groups were combined, as we did not expect any somatic side effects caused by computerized training (see Table 2). These side effects did not require medical intervention other than the occasional administration of analgesics.

## 3.4 Linear regression for main outcome variables

A comparison of the efficacy of rTMS alone and rTMS+RehaCom in active and sham stimulation conditions was performed using linear regression with an interaction term. The subtests and total scores of DemTect, FAS, and CANTAB were used as outcome measures.

Analysis of differences in time between studied groups showed evidence for a statistically significant improvement in DemTect total score [time by group interaction $p = 0.026$, T1 mean score (SD) = 11.82 (1.66), T2 mean score (SD) =13.18 (1.72)] in favor of rTMS+RehaCom (Table 3). Moreover, the detailed analysis of individual subtests of the DemTect scale indicates an upward trend towards the significant difference between groups measured over time (T1 vs. T2) in immediate recall DemTect; the sham group performed almost significantly poorer than experimental groups ($p = 0.068$), losing on average 1.34 points in T2, while experimental groups performed better in T2 (rTMS: 1.38 points, RehaCom 1.36 points) (see Figure 2). This trend is most likely responsible for a statistically significant change in the overall DemTect score. There were no statistically significant differences betwee T1, T2 in FAS scores in experimental groups in comparison to a control group (see Table 3 with linear regression model).

The linear regression of CANTAB Paired Associates Learning, which assesses visual memory and new learning, revealed significant differences in favor of rTMS+RehaCom in three subtests. In *palta 4*, which measures the total number of attempts made (but not necessarily completed) by the subject during the assessment

TABLE 1 Baseline characteristics of the participants.

| Characteristics | rTMS | rTMS+RehaCom | Sham | *p*-value |
|---|---|---|---|---|
| | (*n* = 11) | (*n* = 11) | (*n* = 9) | ($p < 0.05$) |
| Age (mean, SD) | 70.73 (±4.47) | 70.64 (±3.14) | 71.62 (±5.71) | 0.932[a] |
| Men (*n*, %) | 6 (54.5) | 7 (63.6) | 8 (88.9) | 0.308[b] |
| Education level (*n*, %) | | | | 0.122[b] |
| University | 4 (36.4) | 4 (36.4) | 1 (11.1) | |
| Secondary | 6 (54.5) | 7 (63.6) | 8 (88.9) | |
| Elementary | 1 (9.1) | 0 (0.00) | 0 (0.00) | |
| Marital status (*n*, %) | | | | 0.761[b] |
| Widowed | 2 (18.2) | 1 (9.1) | 0 (0.0) | |
| Divorced | 2 (18.2) | 1 (9.1) | 1 (11.1) | |
| Married | 7 (63.6) | 9 (81.8) | 7 (77.8) | |
| Single | 0 (0.0) | 0 (0.0) | 1 (11.1) | |
| Town dweller (*n*, %) | 11 (100.0) | 11 (100.0) | 9 (100.0) | >0.999[a] |
| Retirement (*n*, %) | 10 (90.9) | 10 (90.9) | 8 (88.9) | >0.99[a] |
| GDS 15 (mean, SD) | 4.00 (1.26) | 4.00 (1.55) | 4.44 (0.73) | 0.440[a] |
| MoCA (mean, SD) | 24.82 (1.17) | 23.82 (2.71) | 24.56 (1.74) | 0.561[a] |
| HAM-A 14 (mean, SD) | 5.36 (3.26) | 6.00 (2.57) | 5.11 (2.98) | 0.868[a] |
| CDR | 0.5 | 0.5 | 0.5 | |

Values are given as means (SD) or *n* (%). rTMS: experimental rTMS alone group, rTMS + RehaCom: experimental group with Computerized Cognitive Training RehaCom. sham, sham control group; MoCA, Montreal Assessment Cognitive Scale; DemTect, Demenz Scale; GDS-15, Geriatric Depression Scale; HAM-A 14, Hamilton Anxiety Rating Scale; CDR, Clinical Dementia Rating Scale. [a]Kruskal Wallis test.
[b]Fisher's test.

TABLE 2 Side-effects after rTMS.

| Side-effects | Session number | 1 | *p* value | 5 | *p* value | 10 | *p* value |
|---|---|---|---|---|---|---|---|
| | Group | *n* (%) | ($p < 0.05$) | *n* (%) | ($p < 0.05$) | *n* (%) | ($p < 0.05$) |
| Seizure | rTMS | 1 (4.5) | 1[a] | 0 (0) | 1[a] | 0 (0) | 1[a] |
| | Sham | 0 (0) | | 0 (0) | | 0 (0) | |
| Insomnia | rTMS | 0 (0) | 0.29[a] | 0 (0) | 0.29[a] | 0 (0) | 1[a] |
| | Sham | 1 (11.1) | | 1 (11.1) | | 0 (0) | |
| Burning scalp | rTMS | 4 (18.2) | 0.61[a] | 2 (9.1) | 0.56[a] | 1 (4.5) | 0.50[a] |
| | Sham | 2 (22.2) | | 2 (22.2) | | 1 (11.1) | |
| Headache | rTMS | 3 (13.6) | 0.61[a] | 0 (0.0) | 1[a] | 1 (11.1) | 1[a] |
| | Sham | 2 (22.2) | | 0 (0) | | 0 (0) | |
| Scalp pain | rTMS | 4 (18.2) | 1[a] | 2 (9.1) | 1[a] | 1 (4.5) | 1[a] |
| | Sham | 1 (11.1) | | 0 (0) | | 0 (0) | |

Values are given as *n* (%). rTMS, experimental groups; sham, sham control group. [a]Fisher's test.

containing a total of 4 shapes to recall, and in *palte 4* and *paltea 4*, both of which count the total number of attempts made (but not necessarily completed) by the subject during the assessment of a total of 4 shapes to recall [*palta 4* time by group interaction $p = 0.030$, T1 mean score (SD) = 2.90 (1.20), T2 mean score (SD) = 1.89 (0.93), *palte 4* and *paltea 4* time by group interaction $p = 0.027$, T1 mean score (SD) = 6.10 (4.15), T2 mean score (SD) = 2.56 (3.47)]. In each subtest, rTMS+RehaCom group obtained lower scores in T2. Also in Pattern Recognition Memory, which is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm, statistical analysis showed a significant difference in favor of rTMS+RehaCom *prmpci subtest*, evaluating the number of correct patterns selected by the subject in the immediate forced-choice condition [*prmpci* time by group interaction $p = 0.023$, T1 mean score (SD) = 78.03 (11.35), T2 mean score (SD) = 83.33 (12.91)]. The linear regression on CANTAB Spatial Working Memory, assessing retention and manipulation of visuospatial information, showed a significant difference in favor of the rTMS alone group in the *swms 6* strategic thinking subtest [time by group interaction $p = 0.008$, T1 mean score (SD) = 3.80 (0.92), T2 mean score (SD) = 4.56 (0.73)]. The linear regression performed for other subtests from the CANTAB battery yielded no significant differences in the studied groups between T1 and T2. Due to the amount of data, this information is not included in Table 3.

## 4 Discussion

This study investigated the effects of rTMS (alone as well as combined with Computerized Cognitive Training) over the left DLPFC on cognitive functions in MCI individuals. Cognitive performance at T1 and T2 was evaluated by paper-based (DemTect, FAS) and computer-based (CANTAB) tools. Our study indicates that the administration of 10 sessions of rTMS along with computer-based cognitive training has the potential for significant cognitive improvement among MCI participants that was observed in DemTect total score and several CANTAB subtests in a partially-blind, randomized sham-controlled study. Results from the CANTAB showed that participants received higher scores in T2 in subtests assessing visual memory, new learning, and visual pattern recognition, most associated with working memory. For the other examined cognitive functions (verbal fluency, delayed memory, reaction time) no statistically significant improvements after the rTMS sessions were found. Based on these results the conclusion can be drawn, that 10 sessions of 10 Hz rTMS at 110% MT followed by cognitive training improve working memory.

The recent data of ASL perfusion and resting-state functional magnetic resonance imaging (rs-fMRI) showed that patients with cognitive impairments including MCI show abnormalities in regional cerebral blood flow, which were mainly located in the left posterior cingulate cortex (PCC), the left and right dorsolateral prefrontal cortex (DLPFC), the left inferior parietal lobule (IPL), the right middle temporal gyrus (MTG), the left middle occipital gyrus (MOG), and the left precuneus (PCu) (36). The fact that in our study patients improved mainly in terms of working memory, while almost no significant changes in long-term memory and other cognitive variables were observed, can be interpreted in the light of the previous studies regarding changes in the activity of neural networks after TMS stimulation within the DPLFC. The DLPFC together with the lateral posterior parietal cortex (lPPC) and the Central Executive Network (CEN), regulates executive functions such as working memory and cognitive flexibility (37). Previous studies have shown that TMS within the DLPFC increases activity within CEN and decreases activity within the oppositely correlated Default Mode Network (DMN). The DMN is primarily composed of the dorsal medial prefrontal cortex (mPFC), PCC/PCu, and angular gyrus and is responsible for slow-flowing thoughts, which may explain the improvement in working memory obtained in our study (38).

Another way of describing executive cognitive functions is the Executive Control Network (ECN) consisting of: the DLPFC related to working memory and attention; the inferior parietal lobule (IPL) related to bottom-up attention and episodic memory; the middle frontal gyrus (MFG) related to executive ability; and the middle temporal gyrus (MTG) related to language function (32). The findings imply the effect of rTMS applied to the left DLPFC may have both direct and indirect effects on brain regions activating the working memory-associated network such as connections to the prefrontal and limbic systems. Research by Xiao et al. showed that iTBS applied over the left DPLFC significantly enhanced the brain function connection

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TABLE 3 Linear mixed model analysis results (T1, T2).

| Tool | Interaction description | Linear mixed model analysis – interaction effect | | | Effect size |
|---|---|---|---|---|---|
| | | Beta | 95% CI | *p*-value | $\eta^2$ |
| Swms 6 | T1 | – | – | – | 0.001 |
| | T2 | −0.591 | −1.261, 0079 | 0.083 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.700 | −1.386, −0.014 | **0.046** | 6.121e-04 |
| | sham | −0.278 | −0.982, 0.427 | 0.432 | |
| | T2 * rTMS +RehaCom | 1.346 | 0.375, 2.318 | **0.008** | 0.130 |
| | T2 * sham | 0.591 | −0.394, 1.576 | 0.234 | |
| Palta 4 | T1 | – | – | – | 0.008 |
| | T2 | 0.455 | −0.472, 1.383 | 0.322 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | 0.08 | −0.210, 1.830 | 0.117 | 8.756e-04 |
| | sham | 0.132 | −0.916, 1.181 | 0.801 | |
| | T2 * rTMS +RehaCom | −1.505 | −2.851, −0.160 | **0.030** | 0.019 |
| | T2 * sham | −0.233 | −1.596, 1.129 | 0.727 | |
| Palte 4 | T1 | – | – | – | 0.044 |
| | T2 | 1.296 | −1.689, 4.281 | 0.380 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | 3.032 | −0.16,4 6.229 | 0.063 | 0.052 |
| | sham | −0.401 | −3.685, 2.883 | 0.807 | |
| | T2 * rTMS +RehaCom | −4.933 | −9.265, −0.601 | **0.027** | |
| | T2 * sham | −1.074 | −5.463, 3.316 | 0.619 | 0.045 |
| Paltea 4 | T1 | – | – | – | 0.025 |
| | T2 | 1.296 | −1.689, 4.281 | 0.380 | |
| | rTMS | – | – | – | 0.055 |
| | rTMS+RehaCom | 3.032 | −0.164, 6.229 | 0.063 | |
| | sham | −0.401 | −3.685, 2.883 | 0.807 | |
| | T2 * rTMS +RehaCom | −4.933 | −9.265, −0,601 | **0.027** | 0.190 |
| | T2 * sham | −1.1 | −5.5, 3.3 | 0.6 | |
| Prmpci | T1 | – | – | – | 0.012 |
| | T2 | −10.379 | −19.966, −0.792 | **0.034** | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −10.38 | −20.723–1.550 | **0.024** | 0.134 |
| | sham | 2.499 | −7.582, 12.580 | 0.621 | |
| | T2 * rTMS +RehaCom | 15.681 | 2.286, 29.076 | **0.023** | 0.091 |
| | T2 * sham | 8.527 | −5.576, 22.629 | 0.231 | |
| F | T1 | – | – | – | 0.056 |
| | T2 | 0.364 | −0.184, 0.911 | 0.184 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | 0.455 | −2.474, 3.383 | 0.753 | 0.028 |
| | sham | −0.646 | −3.733, 2.441 | 0.672 | |
| | T2 * rTMS +RehaCom | 0.000 | −0.774, 0.774 | >0.99 | 0.061 |
| | T2 * sham | −0.475 | −1.290, 0.341 | 0.243 | |

*(Continued)*

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TABLE 3 (Continued)

| Tool | Interaction description | Linear mixed model analysis – interaction effect | | | Effect size |
|---|---|---|---|---|---|
| | | Beta | 95% CI | *p*-value | $\eta^2$ |
| A | T1 | – | – | – | 0.101 |
| | T2 | 1.091 | −0.136, 2.318 | 0.079 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.27 | −3.065, 2.519 | 0.844 | 0.056 |
| | sham | −1.2 | −4.115, 1.771 | 0.424 | |
| | T2 * rTMS +RehaCom | −0.27 | −2.008, 1.463 | 0.750 | 0.053 |
| | T2 * sham | −1.1 | −2.920, 0.738 | 0.232 | |
| S | T1 | – | – | – | 0.118 |
| | T2 | 1.455 | −0.334, 3.243 | 0.107 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | 0.273 | −3.869, 4.414 | 0.894 | 0.021 |
| | sham | −1.404 | −5.869, 3.000 | 0.518 | |
| | T2 * rTMS +RehaCom | −1.091 | −3.620, 1.439 | 0.385 | 0.030 |
| | T2 * sham | −0.232 | −2.899, 2.434 | 0.860 | |
| FAS total | T1 | – | – | – | 0.204 |
| | T2 | 2.909 | 0.538, 5.280 | **0.018** | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | 0.455 | −8.064, 8.973 | >0.914 | 0.038 |
| | sham | −3.222 | −12,201, 5.757 | 0.469 | |
| | T2 * rTMS +RehaCom | −1.364 | −4.716, 1.989 | 0.412 | 0.042 |
| | T2 * sham | −1,798 | −5.332, 1.736 | 0.306 | |
| Demtect 1 | T1 | – | – | – | 0.010 |
| | T2 | 1.182 | −0.634, 2.998 | 0.198 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.091 | −1.908, 1.725 | 0.920 | 0.012 |
| | sham | 0.758 | −1.157, 2.672 | 0.431 | |
| | T2 * rTMS +RehaCom | 0.182 | −2.386, 2.750 | 0.888 | 0.079 |
| | T2 * sham | −2.515 | −5.222, 0.192 | 0.068 | |
| Demtect 2 | T1 | – | – | – | 0.065 |
| | T2 | 0.000 | −0.149, 0.149 | >0.999 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.182 | −0.433, 0.069 | 0.151 | 0.111 |
| | sham | −0.222 | −0.487, 0.042 | 0.097 | |
| | T2 * rTMS +RehaCom | 0.182 | −0.229, 0.393 | 0.089 | 0.125 |
| | T2 * sham | 0.00 | −0.223, 0.223 | >0.999 | |
| Demtect 3 | T1 | – | – | – | 0.020 |
| | T2 | 0.182 | −2,938, 3.302 | >0.906 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.636 | −4.470, 3.197 | 0.740 | 0.072 |
| | sham | −1.141 | −5.183, 2.900 | 0.573 | |
| | T2 * rTMS +RehaCom | 0.091 | −4.505, 4.321 | >0.967 | 0.052 |
| | T2 * sham | −2.515 | −7.166, 2.136 | 0.277 | |

*(Continued)*

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TABLE 3 (Continued)

| Tool | Interaction description | Linear mixed model analysis – interaction effect | | | Effect size |
|---|---|---|---|---|---|
| | | Beta | 95% CI | *p*-value | $\eta^2$ |
| Demtect 4 | T1 | – | – | – | 0.010 |
| | T2 | 0.00 | −0.352, 0.352 | >0.999 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.55 | −1.227, 0.136 | 0.113 | 0.130 |
| | sham | −0.61 | −1.324, 0.112 | 0.096 | |
| | T2 * rTMS +RehaCom | 0.27 | −0.224, 0.770 | 0.271 | 0.081 |
| | T2 * sham | −0.11 | −0.635, 0.413 | 0.411 | |
| Demtect 5 | T1 | – | – | – | 0.125 |
| | T2 | 0.545 | −0.612, 1.703 | 0.343 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −0.636 | −2.254, 1.081 | 0.459 | 0.016 |
| | sham | −0.283 | −2.093, 1.528 | 0.754 | |
| | T2 * rTMS +RehaCom | 0.273 | −1.364, 1.910 | 0.735 | 0.004 |
| | T2 * sham | 0.121 | −1.604, 1.847 | 0.887 | |
| Demtect total | T1 | – | – | – | 0.161 |
| | T2 | 0.273 | −0.791, 1.337 | 0.604 | |
| | rTMS | – | – | – | |
| | rTMS+RehaCom | −2.000 | −4.160, 0.160 | 0.069 | 0.052 |
| | sham | −0.838 | −3.115, 1.438 | 0.460 | |
| | T2 * rTMS +RehaCom | 1.727 | 0.223, 3.223 | **0.026** | 0.241 |
| | T2 * sham | −0.38 | −1.970, 1.202 | 0.624 | |

Values are given as Beta coefficient. Bolding indicates a statistically significant score ($p \leq 0.05$). rTMS, experimental rTMS alone group; rTMS + RehaCom, an experimental group with Computerized Cognitive Training RehaCom; sham, sham control group; FAS, Verbal Fluency Test FAS; DemTect, Demenz Test; Swms6, Palta 4, Palte 4, Paltea 4, Prmpci – subtest from the Cambridge Neuropsychological Test Automated Battery in which Linear Mixed Model Analysis with Interaction Effect was statistically significant.

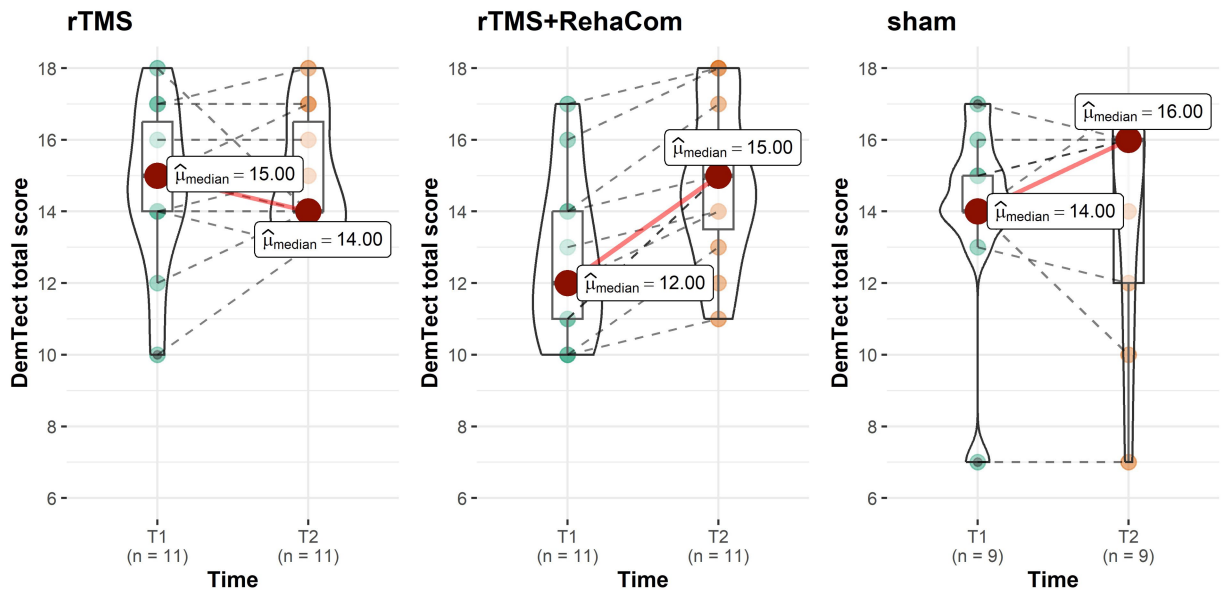


FIGURE 2
The DemTect total scores (T1 T2).

between the left DLPFC and the left IPL within Alzheimer's Disease patients, compared to healthy controls (39). In conclusion, previous literature provides vital data indicating the beneficial effect of TMS within the DLPFC on neural networks related to working memory and attention, which contrasts with the relative lack of reports on the positive effect of TMS on other cognitive functions – which was also demonstrated in our study regarding MCI patients.

Interestingly, the enhancement of working memory was noticed only in the rTMS group that also received computer-based cognitive training, which may suggest that rTMS enhances cognitive performance as long as it is combined with an extra procognitive intervention. The obtained results can be interpreted in two ways: either rTMS has an additive effect on the efficacy of cognitive training, or it is the computerized cognitive training itself that led to improved performance, not rTMS. The former standpoint is supported by the fact that both methods change brain activity, so we can suspect that when combined, they may lead to a greater degree of enhancement of cognitive function. Behind this hypothesis is the fact that rTMS is increasingly treated as an adjunctive method for treating mental, emotional, and behavioral disorders, which contributes to strengthening the effect of the first-line therapies (40–43).

In favor of the second position is the fact that cognitive training, having its level tailored to the needs and capabilities of the trainee and taking into account tasks related to the daily life of the subjects, contributes to the improvement of the cognitive performance of MCI patients, as reported by some systematic reviews (44, 45). Computerized Cognitive Training RehaCom applied in the present study is a comprehensive system of software that allows training specific aspects of attention, concentration, memory, perception, and activities of daily living. Its most notable advantages are that, first, it has high ecological validity (its tasks resemble the challenges we face in our daily lives increasing the possibility of transfer of training to contexts beyond the trained tasks), and second, the system is auto-adaptive (the level of these tasks is appropriate to the baseline and to the progress, the patient is making). Therefore, the improvement in working memory might be a result of the implementation of well-designed cognitive training, rather than just rTMS. Cognitive training is also associated with well-documented changes in brain activity in the frontal and parietal cortex and basal ganglia, as well as changes in dopamine receptor density (46). RehaCom training may have potentiated the effect of the rTMS in this study.

Finally, it is worth noting that the study did not assess mood before and after stimulation (but it did measure the presence of depressive symptoms, to exclude subjects whose cognitive impairment may have resulted from depressive disorders). Since the left DLFPC is also stimulated in depression treatment protocols using rTMS (18, 38, 47) we cannot rule out that to some extent the improvement in working memory performance may have been related to the mood improvement.

## 4.1 Limitations of the study

Our study has several limitations. First of all, it involved a relatively small group of participants (n = 31), divided into three study groups, which poses a significant limitation on the generalizability of the results and impacts the conclusions as well as the power of the performed statistical analysis. Secondly, it lacks a fourth study group, participants undergoing cognitive training alone, making it impossible to clearly answer the question of whether computerized training or rTMS is responsible for the improvement in participants' cognitive performance. Thirdly, the study was partially blinded, since participants from rTMS+RehaCom group were aware that they are training cognitive functions via RehaCom software. Fourthly, despite the exclusion of all but the amnestic MCI subtype, the preliminary analysis of collected neuroimaging data (MRI) suggested the group remained heterogeneous in terms of neuronal deficits. These finding doubt on the possibility of establishing one common protocol for MCI patients, without previous extensive and expensive MRI testing, even when accounting for the MCI subtype. Finally, the study did not include a mood assessment after the intervention. Knowing that the same rTMS protocols over left DLPFC lead to positive clinical outcomes in patients with depression, we cannot eliminate the possibility that to a small extent (those with depressive symptoms were excluded from the study) the improvement in working memory performance might be an indirect consequence of improved affect, the assessment of depressive symptoms at the time of enrollment in the study ensures that participants without moderate to severe depressive symptoms participated in the study.

## 4.2 Implications of research

Based on the results of this study, some implications for future research can be pointed out. There is a need for more studies comparing the rTMS effect with and without additional cognitive stimulation (like memory training). Furthermore, studies comparing the sole effect of cognitive stimulation to combined treatment with rTMS are needed to establish significant clinical implications. Finally, larger studies comparing directly different TMS protocols in MCI treatment are required to determine the most efficient modality of TMS (also including modern variants like theta-burst stimulation or deep TMS). It would be valuable to focus on the effect on various cognitive functions, not exclusively on the memory modality. In addition, future research should focus on the analysis of the mechanism of action of TMS in participants with cognitive impairments, including cognitive reserve and brain network changes.

# 5 Conclusion

This study provides evidence that 10 rTMS sessions combined with individualized computerized cognitive training improve working memory in MCI patients. The area targeted in the study was DLPFC. The exact mechanism of action of rTMS remains unknown, but a prevalent theory involves the induction of long-term potentiation such as plasticity. Enhanced plasticity may make the brain more receptive to cognitive training. These results support the development of noninvasive interventions for persons at risk of dementia, especially since causal treatment is not available to date.

# Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

AS, DS, and JR were involved in the conceptualization of the study and study design. AS, DS, and JM conducted the data analyses. AS, DS, TW, JM, MM, BB, AZ, KF-P, and JR collaborated on the interpretation of findings and placement in context. The manuscript was drafted by AS. TW, KF-P, AZ, MM, and BB were responsible for editing and refining of the manuscript's content. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1196478/full#supplementary-material

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# Effect of transcranial direct current stimulation and narrow-band auditory stimulation on the intraoperative electroencephalogram: an exploratoratory feasibility study

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**Introduction:** During general anesthesia, frontal electroencephalogram (EEG) activity in the alpha frequency band (8–12 Hz) correlates with the adequacy of analgesia. Transcranial direct current stimulation (tDCS) and auditory stimulation, two noninvasive neuromodulation techniques, can entrain alpha activity in awake or sleeping patients. This study evaluates their effects on alpha oscillations in patients under general anesthesia.

**Methods:** 30 patients receiving general anesthesia for surgery were enrolled in this two-by-two randomized clinical trial. Each participant received active or sham tDCS followed by auditory stimulation or silence according to assigned group (TDCS/AUD, TDCS/SIL, SHAM/AUD, SHAM/SIL). Frontal EEG was recorded before and after neuromodulation. Patients with burst suppression, mid-study changes in anesthetic, or incomplete EEG recordings were excluded from analysis. The primary outcome was post-stimulation change in oscillatory alpha power, compared in each intervention group against the change in the control group SHAM/SIL by Wilcoxon Rank Sum testing.

**Results:** All 30 enrolled participants completed the study. Of the 22 included for analysis, 8 were in TDCS/AUD, 4 were in TDCS/SIL, 5 were in SHAM/AUD, and 5 were in SHAM/SIL. The median change in oscillatory alpha power was +4.7 dB (IQR 4.4, 5.8 dB) in SHAM/SIL, +2.8 dB (IQR 1.5, 8.9 dB) in TDCS/SIL ($p$ = 0.730), +5.5 dB in SHAM/AUD ($p$ = 0.421), and -6.1 dB (IQR -10.2, -2.2 dB) in TDCS/AUD ($p$ = 0.045).

**Conclusion:** tDCS and auditory stimulation can be administered safely intraoperatively. However, these interventions did not increase alpha power as administered and measured in this pilot study.

KEYWORDS

EEG, alpha power, transcranial direct current stimulation, auditory stimulation, neuromodulation

## Introduction

Postoperative pain is a nearly universal symptom experienced by patients (1–3), and it has been linked to poor wound healing, lengthier hospital stays, higher healthcare costs, and development of postoperative pain and cognitive disorders (4–7). Providing more adequate analgesia to patients undergoing surgery has potential protective benefits against these complications (8, 9).

Continuous frontal electroencephalography (EEG) monitoring during anesthesia provides metrics that strongly correlate with the adequacy of analgesia, specifically activity in the alpha frequency band (8–12 Hz), thought to reflect thalamocortical oscillations (10–12). Noxious stimulation decreases the strength of alpha oscillations (11, 13), and administration of both opioids and sedatives with analgesic effects increases alpha power (11, 14–16). These observations suggest that alpha power is an objective indicator of the degree of noxious stimulation and the adequacy of analgesia, so techniques of directly boosting this frequency band may have benefits in the intraoperative setting (11, 13).

Recent studies have demonstrated nonpharmacological techniques of neuromodulation, including transcranial direct current stimulation (tDCS) and narrow-band auditory stimulation (17–22). Given the importance of maintaining alpha oscillations in the intraoperative setting to mitigate negative consequences in emergence and recovery post-surgery, it is conceivable that neuromodulation targeting this frequency can be beneficial in multimodal analgesia.

tDCS is an extensively investigated technique of non-invasive brain stimulation that is utilized in a variety of clinical settings including psychiatry, neurology, and pain medicine (23–31). It delivers a battery-powered, low-intensity direct current at 1 to 2 milliamps (mA) via scalp electrodes to the cortical tissue (24). The current flow results in changes to the extracellular *milieu* changing the resting membrane potential of the proximal neurons of the electrode configuration (23–25). Application over the dorsolateral prefrontal cortex is hypothesized to promote thalamocortical oscillations, resulting in the observed increased alpha activity (Supplementary Figure 1) (17). Animal models have demonstrated tDCS can quicken emergence and recovery from volatile anesthesia, indicating potential perioperative utility (27, 32). Most recently, a clinical study demonstrated reduced anxiety in patients who received tDCS in the 24 hours prior to surgery (33).

Acoustic stimulation is a form of sensory entrainment capable of modulating EEG patterns: it has been shown to entrain slow EEG waves during sleep (34), and gamma-band synchronization entrained to external 40-Hz sounds has been previously described (35–37). As a modality already studied primarily in the form of music's effect on perioperative anxiolysis, auditory stimulation can be feasibly administered in an intraoperative setting (38). As auditory stimulation involves thalamocortical communications (Supplementary Figure 2), which are thought to be responsible for much of intraoperative frontal alpha power (39), it is possible that auditory stimulation could promote alpha rhythms during general anesthesia.

Despite its potential benefits, neuromodulation has not been explored in the intraoperative setting. This pilot study investigates the feasibility of administering tDCS and narrow-band auditory stimulation, alone and in combination, in the perioperative setting, and their effects on frontal cortical alpha power in patients receiving general anesthesia for surgery. We hypothesized that each intervention would independently and possibly synergistically increase frontal alpha power on EEG after neuromodulation, suggestive of a more adequate state of intraoperative analgesia.

## Methods

Approval for this study was granted by the Institutional Review Board of the Columbia University Irving Medical Center (IRB No. AAAT9632). Written informed consent was obtained from each participant in the study in accordance with the Declaration of Helsinki. This exploratory study was exempt from registration at clinicaltrials.gov as a small feasibility study of a device with prior FDA Investigational Device Exception (IDE). The manuscript was written in accordance with the CONSORT guidelines for the publication of randomized clinical trial data.

## Inclusion & exclusion criteria

Adult patients receiving general anesthesia for surgeries not involving the head, neck, or spine or requiring the use of cardiopulmonary bypass were eligible for participation in this study. Before written consent was obtained, a screening questionnaire was administered to determine the safety of the tDCS intervention. After reaffirming that the patient was not receiving head, neck, or spine surgery, the questionnaire confirmed that the participant had no metal or electronic implants in the brain, skull, or chest; that the participant had no recent history of head trauma with loss of consciousness, that the participant had no severe dermatitis or eczema; that the participant had no history of epilepsy; and that, for female patients, that the participant was not pregnant. Any of the above constituted exclusion criteria for this study. Apart from receiving general anesthesia, no single protocol or technique used to provide analgesia and anesthesia to the patient was specified to the anesthesiology team for study participants. Anesthesiologists chose their anesthetic and analgesic techniques independently of patient involvement in this study.

During surgery, patient participation in the study was terminated if at any point the surgeon, anesthesiologist, or research personnel felt the neuromodulation was unsafe or interfered with the surgery itself or the anesthesiologist's ability to monitor the patient. In patients who successfully completed the study, those with burst suppression on EEG, change of anesthetic technique between the beginning and end of the study, or incomplete capture of EEG data were excluded from final analysis. Burst suppression and change in anesthetic technique were selected as exclusion criteria to better control the known confounding effect of general anesthesia on potential changes in oscillatory alpha power.

## Procedure

30 Patients receiving general anesthesia for surgery at Columbia University Irving Medical Center were recruited for participation in this double-blind, two-by-two randomized clinical trial. After enrollment, participants were randomized to one of four groups. Group TDCS/AUD received active tDCS and auditory stimulation; group TDCS/SIL received active tDCS and auditory silence; group SHAM/AUD received sham tDCS and auditory stimulation; and group SHAM/SIL received sham tDCS and auditory silence (Figure 1). These comparisons were preplanned to isolate the individual and combined effects of tDCS and auditory stimulation, based on a hypothesis that their combination would produce a synergistic effect on frontal alpha power.

After induction of general anesthesia, each participant's baseline frontal EEG was recorded for twenty minutes. After baseline tracings were obtained, twenty minutes of active or sham tDCS were administered followed by twenty minutes of auditory stimulation or silence, according to the participant's assigned group. Frontal EEG continued to be recorded during stimulation. Following both stimulation techniques, post-stimulation EEG tracings were recorded for an additional twenty minutes. All EEG data were collected before emergence from general anesthesia. After completion of the study, chart review was used to collect important covariates including patient age as well as anesthetic and analgesic medications administered.

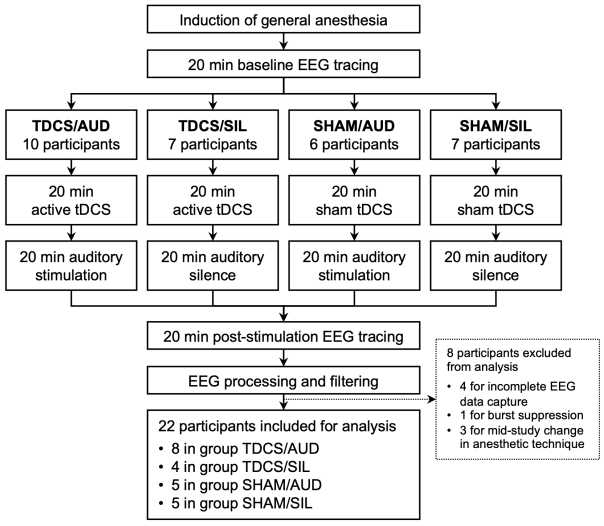


FIGURE 1
Study flow from induction of general anesthesia to completion of post-neuromodulation EEG tracing by study group, with participant counts during study and after data processing.

## Neuromodulation methods

Standard-definition transcranial direct current stimulation over the dorsolateral prefrontal cortex was delivered at an amplitude of 2 mA using the 1x1 transcranial Electrical Stimulation device, an FDA-approved device by Soterix Medical to employ tDCS in clinical trials. Two 5-cm-by-7-cm foam pads produced by the manufacturer were secured to the patient's forehead with a strap after lubrication with 8 mL of 0.9% saline solution and served as noninvasive electrodes for administration of tDCS (Supplementary Figure 3). For participants receiving sham tDCS, foam pads were still secured, however a pre-designed placebo was administered by the Soterix device. Manufacturer-provided six-digit codes were used to deliver either active or sham tDCS according to the participant's assigned research group without alerting research personnel to whether the program was administering active or sham stimulation.

Narrow-band auditory stimulation was engineered at 12 Hz and was delivered through external Beats® Bluetooth headphones placed over the patient's ears (Supplementary Figure 3). Audio was administered from the research personnel's phone, with tracks de-identified and either set to play 20 minutes of either the recorded track or silence. Volume was preset for a peak stimulation intensity of 80 dB in active auditory stimulation to ensure consistency and safety.

Patient baseline and post-stimulation EEG was captured using the Masimo Sedline™ Sedation Monitor's frontal EEG sensor. This four-channel frontal EEG montage is used to guide patient sedation

under general anesthesia. The monitor provides real-time interpretation of the patient's EEG to clinicians, including raw EEG, spectrograms, and commonly analyzed parameters like the spectral edge frequency and Patient State Index™. This information was viewable to the anesthesiologist and research team during the study, and the anesthesiologist was warned that during tDCS or auditory stimulation, the neuromodulation may alter the EEG waveform artificially. The Sedline™ monitor records EEG tracings at a capture rate of 178 Hz and saves them for data extraction. These EEG tracings were collected for each study participant on a secure USB drive for analysis.

## Data and statistical analysis

After excluding data from participants with burst suppression, changes in anesthetic technique, and incomplete data capture, EEG tracings from the more central L1 and R1 electrodes (Supplementary Figure 3) were processed using a fifth-order bandpass filter between 0.5 and 30 Hz and removed of impulse artifacts to generate five minutes of artifact-free EEG during each phase of the study for each participant. These electrodes were chosen as the lateral L2 and R2 had greater artifact burden. Density spectral array (DSA) spectrograms were created for each participant during each study phase. Power spectral densities (PSDs) were generated with 95 percent confidence intervals for the power density at each frequency for each study participant before and after stimulation, then averaged among participants within each study group.

The outcome analyzed in the study was the change in oscillatory alpha power after neuromodulation for each participant. A commonly employed metric to measure alpha activity, oscillatory alpha power is calculated by measuring the increase in EEG power in the alpha band relative to the adjacent theta (3.5–7.5 Hz) and beta (20–30 Hz) bands (40). Median changes and interquartile ranges for each study group were calculated. The effects of tDCS and auditory stimulation, alone and in combination, were evaluated by comparing changes in oscillatory alpha power in groups TDCS/AUD, TDCS/SIL, and SHAM/AUD to group SHAM/SIL using Wilcoxon Rank Sum tests.

Due to the small sample size of this pilot study, statistical tests did not adjust for potential confounding effects, however several demographic covariates, medical conditions, and variables known to influence the presence alpha oscillations were compared qualitatively across study groups: age; sex; American Society of Anesthesiologists (ASA) Physical Status; presence of comorbidities; and technique of general anesthesia (volatile, total intravenous anesthesia, or mixed), and whether the patient received additional opioid or non-opioid analgesia boluses during their participation in the study. No hypothesis testing was performed on these covariates. Age and sex were obtained from the patient's chart, ASA Physical Status and comorbidities were obtained from the anesthesia preoperative evaluation, and both anesthetic technique and analgesic medication administration were obtained from the intraoperative anesthesia record.

# Results

Of the 30 participants enrolled in this clinical trial, 10 were in group TDCS/AUD, 7 were in TDCS/SIL, 6 were in SHAM/AUD, and 7 were in SHAM/SIL. Of these, 4 participants were excluded from analysis for incomplete EEG data capture, 1 was excluded for burst suppression during the study, and 3 were excluded due to a change in anesthetic strategy during the study period. No participants were excluded due to unsuccessful administration of neuromodulation, a need to terminate study participation from intraoperative safety concerns, or interference with the procedure or anesthetic monitoring. Of the 22 participants included for final analysis, 8 were in group TDCS/AUD, 4 were in TDCS/SIL, 5 were in SHAM/AUD, and 5 were in SHAM/SIL.

## Characteristics of participants by study group

Demographic and anesthetic comparisons among participants in different study groups are provided in Table 1. Participants were slightly younger in group SHAM/AUD, however interquartile ranges of age among the four groups were comparable. Participants in group TDCS/AUD were more likely to have a higher ASA Physical Status, though the prevalence of neuropsychiatric comorbidities was comparable across all groups. In terms of anesthetic technique, more participants in group SHAM/SIL received purely inhalational anesthesia during maintenance, and more participants in groups SHAM/AUD and SHAM/SIL received additional boluses or infusions of analgesic medication during the study.

## EEG spectra and alpha power after neuromodulation

Segments of artifact-free EEG tracings and processed spectrograms of one study participant at each phase of the study are shown in Figure 2. This participant was assigned to Group TDCS/AUD. Noise from active tDCS results in the increased activity in the delta (1–4 Hz) frequency band during that phase of the study. The PSDs with 95 percent confidence intervals before and after stimulation, averaged over participants in each group of the study are depicted in Figure 3. Across all four study groups, minimal changes were seen in the average PSDs before and after stimulation.

A boxplot of changes in oscillatory alpha power by study group is provided in Figure 4. In the control group SHAM/SIL, the median change in oscillatory alpha power was +4.7 dB (IQR 4.4, 5.8 dB). In the group receiving only auditory stimulation, SHAM/AUD, the median change was +5.5 dB (IQR 5.5, 7.0 dB; $p = 0.421$). In the group receiving only tDCS, TDCS/SIL, the median change was +2.5 dB (IQR 1.5, 8.9 dB; $p = 0.730$). In the group receiving tDCS and auditory stimulation in combination, TDCS/AUD, the median change was -6.1 dB (IQR -10.2, -2.2 dB; $p = 0.045$).

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TABLE 1 Characteristics of participants in each study group.

| | TDCS/AUD *n* = 8 | TDCS/SIL *n* = 4 | SHAM/AUD *n* = 5 | SHAM/SIL *n* = 5 |
|---|---|---|---|---|
| Median Age (IQR), years | 58 (53, 61) | 56 (45, 67) | 40 (40, 63) | 64 (40, 65) |
| Sex Male | 5 (63%) | 2 (50%) | 3 (60%) | 2 (40%) |
| ASA Physical Status | | | | |
| 1 | 0 (0%) | 1 (25%) | 1 (20%) | 0 (0%) |
| 2 | 3 (38%) | 2 (50%) | 3 (60%) | 3 (60%) |
| 3 | 5 (63%) | 1 (25%) | 1 (20%) | 2 (40%) |
| Comorbid Conditions | | | | |
| Pulmonary | 7 (88%) | 3 (75%) | 3 (60%) | 2 (40%) |
| Cardiovascular | 6 (75%) | 2 (50%) | 2 (40%) | 3 (60%) |
| Neurologic | 1 (13%) | 0 (0%) | 1 (20%) | 1 (20%) |
| Psychiatric | 2 (25%) | 2 (50%) | 0 (0%) | 2 (40%) |
| Renal | 2 (25%) | 1 (25%) | 2 (40%) | 0 (0%) |
| Gastrointestinal/Hepatic | 5 (63%) | 1 (25%) | 2 (40%) | 3 (60%) |
| Endocrine | 5 (63%) | 2 (50%) | 2 (40%) | 2 (40%) |
| Hematologic | 4 (50%) | 1 (25%) | 1 (20%) | 2 (40%) |
| Oncologic | 2 (25%) | 2 (50%) | 0 (0%) | 0 (0%) |
| Anesthetic Technique | | | | |
| Inhalational | 5 (63%) | 2 (50%) | 3 (60%) | 5 (100%) |
| TIVA | 1 (13%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Mixed | 2 (25%) | 2 (50%) | 2 (40%) | 0 (0%) |
| Analgesic Redosed | 3 (38%) | 1 (25%) | 4 (80%) | 3 (60%) |

TIVA, total intravenous anesthesia.

## Discussion

Given that every enrolled participant was able to successfully complete the protocol without safety concerns from the surgical team, anesthesiology team, or research team, this study demonstrates that tDCS and narrow-band auditory stimulation can be administered safely to patients receiving general anesthesia during surgery. That said, as patients were not followed postoperatively, no guarantee against complications can be given based on these data. That complications are known and minimal after administration of tDCS and auditory stimulation in awake patients suggests similar rates after receiving these interventions intraoperatively, however this study cannot address that question.

Analysis of EEG spectra showed that active tDCS and auditory stimulation, alone and in combination, did not visibly increase oscillatory alpha power in this study. Although the combination of tDCS and auditory stimulation produced a lower change in oscillatory alpha power than no neuromodulation at all, the fact that this result was seen without any observable decrease in alpha power after either form of neuromodulation alone suggests that the observed decrease may be due to unmeasured confounding.

Given that each of these techniques achieves neuromodulation in awake and sleeping patients (17–22, 34–37), it is reasonable to conclude that their effects in patients under general anesthesia for surgery may be modest when compared to the influence of age, comorbidities, noxious stimulation during surgery, and pharmacologic strategy. While alpha power is a putative mechanism of action which is very much linked to pain, other factors might be at play, such as changes in excitability, connectivity, or blood flow. The stimulation threshold may be higher in patients under general anesthesia, as the pharmacologic agents themselves are profound neuromodulators. In this study, auditory stimulation was administered at close to the upper threshold of what is accepted as a safe decibel level, but tDCS intensities can vary greatly. While this study employed tDCS at 2 mA, a common selection, higher intensities may be necessary to induce the desired neuromodulation in patients under anesthesia.

The small sample size, broad inclusion criteria, and inherent design in this pilot study limit the ability to control for potential confounding effects. Furthermore, the randomization protocol in this study did not result in equal group sizes. While age ranges were similar among study groups (Table 1), median age was lower in the

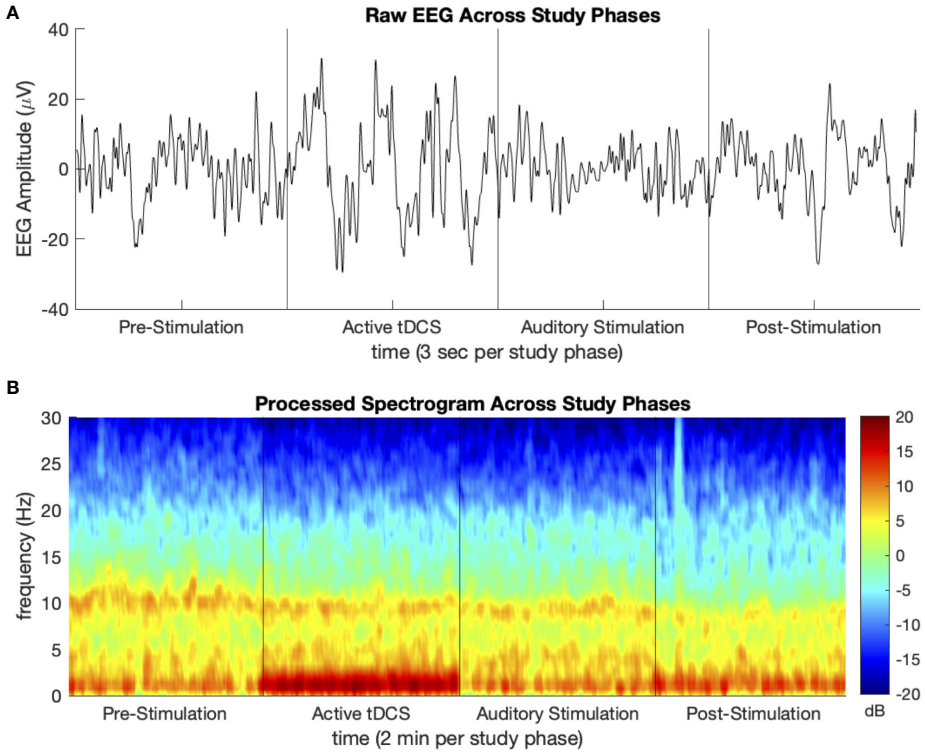


FIGURE 2
Sample **(A)** processed EEG tracing and **(B)** density spectral array (spectrogram) for one study participant at each phase of the study. Participant group TDCS/AUD.

SHAM/AUD group, and the TDCS/AUD group had a greater prevalence of comorbid disease, as evidenced by the substantially higher rates of ASA 3 Physical Status (Table 1). As age has a known correlation with alpha power (41), and comorbidities can influence the physiologic response to any intervention, future larger and more balanced studies investigating benefits of intraoperative neuromodulation will need to control for these potential confounding effects.

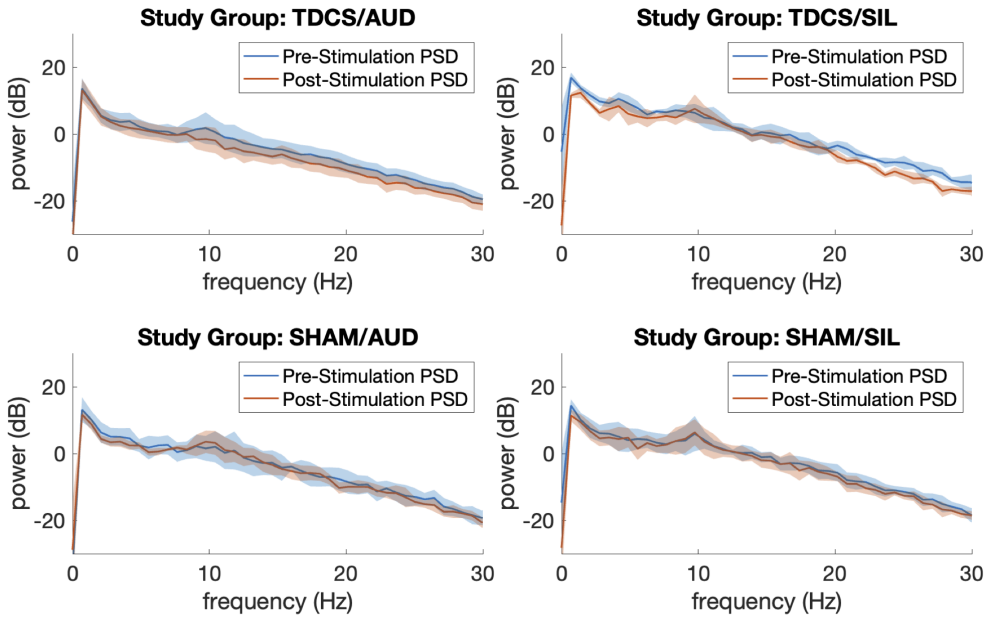


FIGURE 3
Average power spectral densities by study group before and after neuromodulation with 95% confidence intervals.

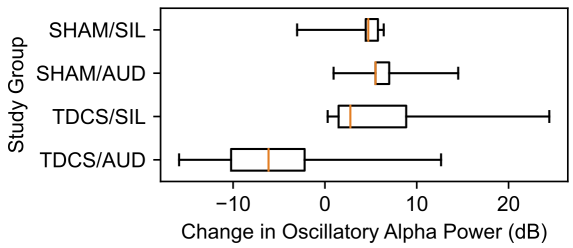


FIGURE 4
Change in oscillatory alpha power, in decibels, after neuromodulation by study group.

Additionally, noxious stimulation is known to have a potent influence on alpha power (11, 13). Without controlling for the precise type of surgery, it is difficult to account for this effect. Moreover, pre-stimulation baseline tracings were often recorded between induction of general anesthesia and first surgical incision, whereas post-stimulation tracings were recorded mid-procedure. This profound difference in degree of stimulation, even though it was present across all four study groups, may have masked any observable effect of tDCS and auditory stimulation on alpha activity, decreasing study power.

Along with noxious stimulation, administration of analgesic medication improves alpha power (11). The protocol for how to dose analgesic medication is not standardized in anesthesia (42), nor was it specified to anesthesiologists during this study. As is seen in Table 1, participants who received sham tDCS were more likely to have received a bolus of analgesia than participants who received active tDCS. Although the small sample size in this study precluded the investigation of any potential confounder via a statistical model, it can be noted that such a difference may specifically mask the beneficial effect of tDCS.

The effects of intraoperative pharmacologic decision-making must also be considered. Different anesthetic strategies, as well as different doses of each individual hypnotic or analgesic drug, can influence alpha power (14, 16). Such variability can significantly influence this study's observed result. In several cases, the anesthesia team prepared for emergence by switching from maintenance with a volatile anesthetic to a propofol infusion before this study's EEG recording was completed. Additionally, one patient received an excessive dose of sedative-hypnotic agent, and burst suppression was witnessed. Apart from excluding these specific cases from analysis, this study had limited control for differing anesthetic techniques. Future research into the effects of nonpharmacologic neuromodulation will have to standardize anesthetic technique, both in managing level of sedation and analgesia. Indeed, given that different anesthetic and analgesic agents produce different neuromodulation according to their pharmacologic mechanisms of action—opioid receptor agonism by opioids; GABA agonism by propofol, etomidate, volatiles, or benzodiazepines; NMDA antagonism by ketamine; alpha$_2$ agonism by dexmedetomidine—future research may well find that these nonpharmacologic neuromodulation techniques are more effective when combined with a particular anesthetic, producing more synergistic neuromodulation.

Perhaps a final limiting feature of the study's ability to detect the benefit of tDCS was the nature in which the neuromodulation was administered. This study employed standard-definition tDCS, which utilizes large 5-cm-by-7-cm moistened foam electrodes on either side of the forehead (Supplementary Figure 3). High-definition tDCS (HD-tDCS) is a technique using much smaller gel-based electrodes at precisely chosen sites, which if applied correctly, have the potential to target brain structures of interest much more specifically (43). Similarly, transcranial alternating current stimulation (tACS), which delivers alternating current at a specified frequency, may also offer a route to entrain specific EEG frequencies. Intraoperatively, alpha frequencies may be entrained, while postoperatively, higher frequency beta and gamma (30- to 40-Hz) waves may be augmented to potentially enhance recovery. These two variants of the tDCS technique explored in this study may also prove to be valuable techniques of nonpharmacologic neuromodulation in the intraoperative setting.

## Conclusions

In this pilot study, transcranial direct current stimulation and narrow-band auditory stimulation were safe and feasible to administer in the intraoperative setting. Their benefits on frontal alpha power are more difficult to elicit under a state of general anesthesia than in an awake state. Further research investigating the potential utility of these interventions in patients receiving general anesthesia will need larger sample sizes, better control for pharmacologic technique and noxious stimulation, and an investigation of different intensities of neuromodulation.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Columbia University Irving Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

OI: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software,

Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MK: Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Project administration, Resources, Software, Supervision, Validation. AD: Conceptualization, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. PG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

MK and PG are named as inventors for a patent recently filed on a method for intraoperative EEG monitoring that accounts for spectral and entropic features of age System, method and computer-accessible medium which takes into consideration the changes of spectral and entropic features age in the electroencephalogram in patients under sevoflurane anesthesia; U.S. Provisional Patent Application No. 62/914,183 filed on October 11, 2019. MK and PG are named as inventors for a patent recently filed on a novel method for intraoperative EEG monitoring System, method and computer-accessible medium for anesthesia monitoring using electroencephalographic monitoring; U.S. Patent Application Serial No. 62/960,947; filed on January 14, 2020.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1362749/full#supplementary-material

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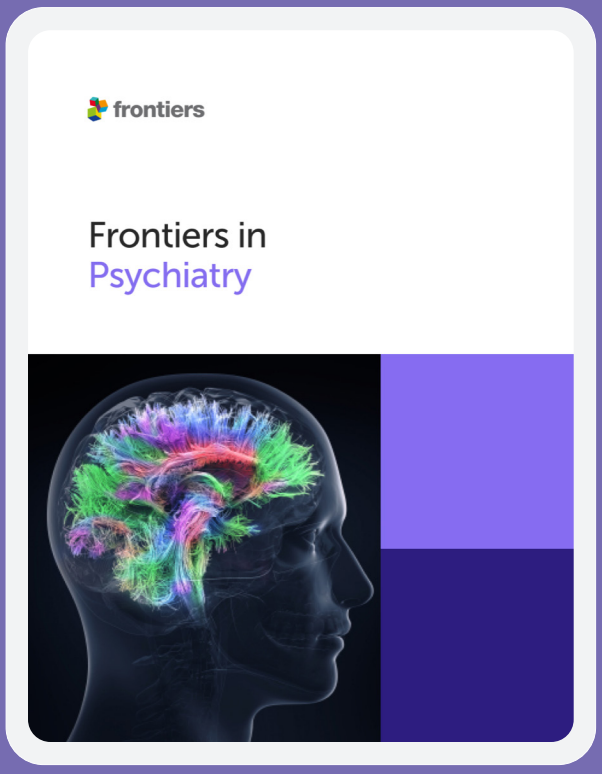


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