Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Across Mental Disorders
A Systematic Review and Dose-Response Meta-Analysis

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Abstract

IMPORTANCE Noninvasive brain stimulation (NIBS) interventions have been shown to be efficacious in several mental disorders, but the optimal dose stimulation parameters for each disorder are unknown.

OBJECTIVE To define NIBS dose stimulation parameters associated with the greatest efficacy in symptom improvement across mental disorders.

DATA SOURCES Studies were drawn from an updated (to April 30, 2023) previous systematic review based on a search of PubMed, OVID, and Web of Knowledge.

STUDY SELECTION Randomized clinical trials were selected that tested transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) for any mental disorder in adults aged 18 years or older.

DATA EXTRACTION AND SYNTHESIS Two authors independently extracted the data. A 1-stage dose-response meta-analysis using a random-effects model was performed. Sensitivity analyses were conducted to test robustness of the findings. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

MAIN OUTCOMES AND MEASURES The main outcome was the near-maximal effective doses of total pulses received for TMS and total current dose in coulombs for tDCS.

RESULTS A total of 110 studies with 4820 participants (2659 men [61.4%]; mean [SD] age, 42.3 [8.8] years) were included. The following significant dose-response associations emerged with bell-shaped curves: (1) in schizophrenia, high-frequency (HF) TMS on the left dorsolateral prefrontal cortex (LDLPFC) for negative symptoms ($\chi^2 = 9.35; df = 2; P = .009$) and TMS on the left temporoparietal junction for resistant hallucinations ($\chi^2 = 36.52; df = 2; P < .001$); (2) in depression, HF-DLPPFC TMS ($\chi^2 = 14.49; df = 2; P < .001$); (3) in treatment-resistant depression, LDLPFC tDCS ($\chi^2 = 14.56; df = 2; P < .001$); and (4) in substance use disorder, LDLPFC tDCS ($\chi^2 = 33.63; df = 2; P < .001$). The following significant dose-response associations emerged with plateaued or ascending curves: (1) in depression, low-frequency (LF) TMS on the right DLPPFC (RDLPPFC) with ascending curve ($\chi^2 = 25.67; df = 2; P < .001$); (2) for treatment-resistant depression, LF TMS on the bilateral DLPPFC with ascending curve ($\chi^2 = 5.86; df = 2; P = .004$); (3) in obsessive-compulsive disorder, LF-RDLPPFC TMS with ascending curve ($\chi^2 = 20.65; df = 2; P < .001$) and LF TMS on the orbitofrontal cortex with a plateaued curve ($\chi^2 = 15.19; df = 2; P < .001$); and (4) in posttraumatic stress disorder, LF-RDLPPFC TMS with plateaued curve ($\chi^2 = 14.49; df = 2; P < .001$). Sensitivity analyses confirmed the robustness of these findings.

Key Points

Question What is the association between dose of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) interventions and response with core symptom severity across mental disorders?

Findings This systematic review and dose-response meta-analysis of 110 studies in 4820 participants found that significant dose-response associations were observed for schizophrenia, depression, obsessive-compulsive disorder, and substance use disorders, with distinct curve shapes. Most of these curves exhibited a bell-shaped pattern, indicating that TMS and tDCS may have distinct near-maximal effective doses for each disorder and stimulation site.

Meaning These findings offer guidance for clinicians and researchers, emphasizing the need for further refinement of dose-response models in TMS and tDCS to enhance comprehension of their outcomes for symptom reduction in specific mental disorders.

Supplemental content

Author affiliations and article information are listed at the end of this article.
TMS with ascending curve ($\chi^2 = 54.15; df = 2; P < .001$). Sensitivity analyses confirmed the main findings.

CONCLUSIONS AND RELEVANCE The study findings suggest that NIBS yields specific outcomes based on dose parameters across various mental disorders and brain regions. Clinicians should consider these dose parameters when prescribing NIBS. Additional research is needed to prospectively validate the findings in randomized, sham-controlled trials and explore how other parameters contribute to the observed dose-response association.


Introduction

Evidence providing support for the efficacy of noninvasive brain stimulation (NIBS) techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), in the treatment of mental disorders, such as major depression, schizophrenia, and obsessive-compulsive disorder (OCD), has accumulated steadily. Currently, there are different TMS and tDCS protocols and devices that have been approved by the US Food and Drug Administration for clinical practice across several disorders.1,2

A previous umbrella review summarizing the body of research on NIBS in mental health mapped meta-analytic evidence in support of both TMS and tDCS across mental disorders.3 The results showed that high-frequency (HF) TMS to the left dorsolateral prefrontal cortex (DLPFC) and tDCS had the highest quality of evidence in terms of response, remission, and continuous antidepressant outcomes compared with sham.

However, despite the increased use of NIBS interventions in clinical practice, a standard dose definition currently is not available.4,5 For instance, the dose of a TMS protocol has been investigated as the number of pulses per session, number of sessions, and frequency, while for tDCS, parameters such as current intensity, session duration, and number of sessions have been used. Moreover, results from randomized clinical trials (RCTs) and meta-analyses have been inconsistent in terms of the best dose-related parameters for NIBS.6-8 Lack of consistent terminology poses a challenge for both clinical practice and research, as trials have used different combinations of parameters, resulting in increased heterogeneity and limitations in establishing a robust evidence base for specific treatment strategies.

Dose-response meta-analyses are increasingly undertaken in evidence synthesis of psychopharmacologic treatments9,10 and allow for the estimation of doses at which 50% and 95% of the maximum treatment efficacy may be achieved. Moreover, dose-response meta-analyses allow the identification of nonefficacious doses and a maximum dose above which efficacy may not be improved or even reduced. Importantly, dose-response meta-analyses also allow for the estimation of potential treatment effects achieved by doses that have not yet been explored in RCTs, guiding future clinical research and implementation. Three different types of curves are usually found: ascending/descending curves, which suggest that higher doses are associated with further improvement or worsening of symptoms; plateau curves, which suggest the reaching of a threshold after a specific dose; and bell-shaped curves, which suggest that improvements are found up to certain doses, with a reduction of benefits at higher doses.9

Identifying and understanding the dose-response association of specific NIBS parameters is therefore key to inform clinical practice. To fill this gap, we conducted a series of dose-response meta-analyses for TMS and tDCS across several mental disorders and symptoms to investigate the size and shape of associations between changes in specific parameters and treatment response. Our primary objective was to determine the near-maximal effective doses (defined as the dose beyond which additional benefit would be unlikely to occur) of total pulses received per number of sessions...
for TMS and total coulombs for tDCS. We also explored the shape of the dose-response association obtained for each stimulation site. Therefore, we included all mental disorders with a number that we deemed sufficient RCTs (≥3) with at least 2 different doses of stimulation to produce dose-response models. The secondary objective was to explore whether other parameters may influence dose-response associations.

**Methods**

This systematic review and dose-response meta-analysis is based on an update of a previous systematic review registered with the International Prospective Register of Systematic Reviews (CRD42021250057). Considering the nature of the study design, no ethical review was needed. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guideline. 11

**Inclusion Criteria**

The inclusion criteria were similar to those in our previous systematic review12 (eFigure 1 in Supplement 1), albeit with the addition of the following crucial inclusion criterion for the present analyses: Trials using TMS (including intermittent theta-burst stimulation [iTBS]) or tDCS were required to use at least 2 different doses of stimulation for the same disorder in addition to a sham stimulation for a similar stimulation site. The total amount of pulse and of coulombs were chosen to quantify the dose of stimulation received, considering that these parameters are also closely linked to the total duration of stimulation.

**Search Strategy and Selection of Studies**

We updated to April 30, 2023, using the same search strategy, the database of a systematic review that included studies up to April 26, 2021,12 based on a search in PubMed, OVID, and Web of Knowledge with no restrictions. Search terms were a combination of keywords and Medical Subject Heading terms using (random*) and (TMS or tDCS) and a list of mental health disorders from the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition or International Classification of Diseases 11th Edition. Reference lists of retrieved articles were also screened for additional articles. Two authors (J.H. and M.Sa.) examined reports independently. All data were extracted in duplicate and independently by authors M.Sa. and J.H. Any disagreement was resolved by consensus. We report the full list of included studies and of the excluded studies after checking the full text, with reasons for exclusion, in eAppendix 2 in Supplement 1. Risk of bias was assessed with version 2 of the Cochrane risk-of-bias tool for articles that were added to the database following the update.

**Statistical Analysis**

R, version 4.2.2 statistical software (R Foundation for Statistical Computing) was used for all analyses. The standardized mean difference (Cohen d) was used as the effect size measure, and a random-effects model was used to account for between-study variability. We used the doresmeta package developed by Crippa and Orsini13 to conduct a 1-stage dose-response meta-analysis using a restricted cubic spline model (nonlinear model) with 3 knots located at the 25th, 50th, and 75th percentiles of the overall dose distribution.

Separate analyses were conducted to investigate the association between total pulses delivered (TMS) or the total coulombs received (tDCS) with symptoms change. These analyses were performed for each stimulation site and frequency (low vs high). Dose-response curves extracted from the data were examined to estimate the 95% effective dose (ED$_{95}$) and median effective dose. The ED$_{95}$ represents the near-maximal effective dose of the maximum effect compared with sham stimulation.

In the presence of a significant dose-response association, sensitivity analyses were conducted to exclude studies with a high risk of bias. Heterogeneity was assessed using a multivariable
extension of the $I^2$ statistic, the variance partition coefficient defined as the ratio of the between-study component to the total residual.13

**Results**

**Included Studies**

We included 110 studies, encompassing a total of 4820 participants.14-124 The majority of participants were male (2959 [61.4%] compared with 1861 females [38.6%]), and the mean (SD) age was 43 (8.8) years.

The details of all retained studies and the overall results for dose equivalents are reported in eTable 1 in Supplement 1 and the Table, respectively. Overall, considering the important heterogeneity found for borderline disorder and autism spectrum disorder, we included 33 studies on schizophrenia,24, 26, 31, 33, 34, 38, 39, 45, 51-53, 58, 59, 62, 65, 69, 71, 75, 76, 81, 89, 95-98, 105, 115, 117-120, 122, 123 on mood disorders,18, 20, 21, 23, 25, 27, 28, 30, 32, 35, 42-44, 47-49, 56, 57, 61, 63, 67, 70, 73, 74, 82-84, 87, 88, 90, 91, 94, 101-103, 107, 110-114, 121, 124 on OCD,17, 19, 22, 41, 50, 54, 60, 64, 68, 77-79, 86, 92, 93, 99, 100, 104 on posttraumatic stress disorder (PTSD),16, 29, 85,116 and 11 on substance use disorder (SUD).14, 15, 36, 37, 40, 46, 55, 66, 80, 108, 109 We also included 32 studies on treatment-resistant depression.18, 20, 21, 23, 25, 27, 28, 30, 32, 35, 43, 44, 47, 56, 57, 63, 83, 84, 87, 88, 90, 91, 107, 111, 112, 114, 121, 124 and 5 on persistent auditory hallucinations.24, 33, 52, 89,118

The characteristics of each study, including condition treated, stimulation type and site, and treatment strategy, are detailed in eTable 1 in Supplement 1 and briefly summarized here. Magnetic resonance imaging-guided neuronavigation was used in 6 studies on schizophrenia (17%), 6 studies in patients with a current depressive episode (12%), and 2 studies in patients with OCD (11%). For TMS studies, figure-eight coils were used in 76 (95%), and for tDCS studies, 29 used electrodes of 35 cm² (79%). Furthermore, while mixed methods were used in studies of patients with schizophrenia to determine stimulation site, the 10-20 electroencephalographic system was mostly used for tDCS studies (29 [96%]), and the 5-cm rule in TMS studies for patients with depression (61 [77%]). The treatment strategy was augmentation or mixed for most studies, albeit some studies on depression and almost all studies on SUD.

**Dose-Response Meta-Analyses**

**Schizophrenia**

Fourteen sham-controlled studies delivered HF-LDLPFC TMS for schizophrenia for 909 participants over a mean (SD) duration of 3.9 (2.0) weeks.53, 59, 71, 95-98, 105, 115, 117, 119, 120, 122, 123 A significant dose-response association with a bell-shaped dose-response curve was obtained ($\chi^2 = 9.35; df = 2; P = .009$) (Figure 1A), peaking at 21695 total pulses (95% CI, 19971-23531 total pulses), with considerable heterogeneity ($I^2 = 83\%$). Such bell-shaped curves suggest that a higher amount of total pulse stimulation is associated with less improvement of negative symptoms in the short term.

We conducted a safety analysis regarding outcomes associated with positive symptoms (Figure 1B). A flat curve was obtained, suggesting the absence of an effect on positive symptoms ($\chi^2 = 0.05; df = 2; P = .98; I^2 = 75\%$). For all analyses, the exploration of heterogeneity is reported in eTable 2 in Supplement 1.

Nonsignificant associations were found for 2 studies of BLDLPFC TMS for both positive and negative symptoms26,38 (eAppendix 1, eFigures 2 and 3 in Supplement 1). Nonsignificant associations were also found for LDLPFC tDCS for negative symptoms (eAppendix 1, eFigure 5 in Supplement 1).

We included 5 sham-controlled studies delivering low-frequency (LF) left temporoparietal junction (LTPJ) TMS for 159 participants over a mean (SD) duration of 1.7 (0.5) weeks.24, 33, 52, 89,118 A significant dose-response association was found with a bell-shaped curve ($\chi^2 = 36.52; df = 2; P < .001$) (Figure 1C) in the presence of considerable heterogeneity ($I^2 = 95\%$). The ED₉₅ was reached at 5000 pulses. Nonsignificant associations were found for 7 studies of LDLPFC tDCS for treatment-resistant hallucinations31, 33, 45, 65, 69, 75,81 (eAppendix 1, eFigure 5 in Supplement 1).
<table>
<thead>
<tr>
<th>Table. Dose Equivalents for TMS and tDCS With Consideration of Near-Maximal Total Pulses or Total Coulombs Received</th>
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<tr>
<td><strong>Stimulation site</strong></td>
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<tr>
<td>TMS for patients with schizophrenia</td>
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<tr>
<td><strong>TMS negative symptoms</strong></td>
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<tr>
<td>HF-LDLPFC</td>
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<td>BL DL PFC</td>
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<td><strong>TMS positive symptoms</strong></td>
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<td><strong>TMS-resistant hallucinations</strong></td>
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<td><strong>TDCS negative symptoms</strong></td>
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<td>LDL PFC</td>
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<td>LDL PFC</td>
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<td>TMS for patients with treatment-resistant depression</td>
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<td>BL DL PFC</td>
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<td>LF-RDL PFC</td>
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<th>No. of patients</th>
<th>Mean (SD)</th>
<th>Duration of trials, wk</th>
<th>Frequency among all studies</th>
<th>Mean total pulses or coulombs delivered among included studies (range)</th>
<th>Total pulses or coulombs corresponding to the ED&lt;sub&gt;50&lt;/sub&gt;</th>
<th>Total pulses or coulombs corresponding to the ED&lt;sub&gt;95&lt;/sub&gt; after exclusion of high-risk studies (P value)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Heterogeneity, %&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>LDLPFC</td>
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<td>43.5</td>
<td>12</td>
<td>3.14</td>
<td>1.9 mA</td>
<td>82.4 C (50.4-192.1 C)</td>
<td>31.2 C</td>
<td>48.2 C (&lt;.001); 49.2 C (&lt;.001)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>42</td>
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<td>20 Hz</td>
<td>2300 (1600-3000)</td>
<td>2338</td>
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<td>2.25 mA</td>
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<td>138</td>
<td>30.5</td>
<td>11.6</td>
<td>9.6</td>
<td>1 Hz</td>
<td>13 560 (7200-20000)</td>
<td>9429</td>
<td>18 923 (&lt;.001)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>LF-OFC</td>
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<td>85</td>
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<td>2</td>
<td>1 Hz</td>
<td>12 000 (9000-15 000)</td>
<td>5001</td>
<td>13 679 (&lt;.001)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>8</td>
<td>8</td>
<td>10 Hz</td>
<td>40 000 (20 000-60 000)</td>
<td>7854</td>
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<td>17</td>
<td>3.25</td>
<td>1 Hz</td>
<td>39 900 (12 000-90 000)</td>
<td>4262</td>
<td>10 766 (.50)</td>
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<td>12.5</td>
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<td>17.5 Hz</td>
<td>7525 (7500-7600)</td>
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<td>LF-RDLPFC</td>
<td>39, 85, 116</td>
<td>49</td>
<td>45.5</td>
<td>11.6</td>
<td>2.3</td>
<td>1 Hz</td>
<td>15 333 (12 000-18 000)</td>
<td>12 811</td>
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<td>HF-RDLPFC</td>
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<td>20 Hz</td>
<td>20 000 (16 000-24 000)</td>
<td>4484</td>
<td>11 234 (.12)</td>
<td>95</td>
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<td>LDLPFC (CUD and MUD)</td>
<td>714, 15, 40, 46, 55, 66, 80</td>
<td>242</td>
<td>35.8</td>
<td>7.3</td>
<td>2.7</td>
<td>1.87 mA</td>
<td>17.4 C (2.4-36.0 C)</td>
<td>3.4 C</td>
<td>9.6 C (&lt;.001); 9.8 C (&lt;.001)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>ITBS for SUD</td>
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<td>LDLPFC</td>
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<td>32.9</td>
<td>17.5</td>
<td>3.5</td>
<td>50 Hz</td>
<td>15 725 (9000-18 000)</td>
<td>3592</td>
<td>9724 (&lt;.001)</td>
<td>70</td>
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Abbreviations: BL-DLPFC, bilateral dorsolateral prefrontal cortex; CUD, cocaine use disorder; ED<sub>50</sub>, median effective dose; ED<sub>95</sub>, 95% effective dose (or near-maximal effective dose); HF, high frequency; ITBS, intermittent theta-burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; LF, low frequency; LTPJ, left temporoparietal junction; MUD, methamphetamine use disorder; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PTSD, posttraumatic stress disorder; RDLPFC, right dorsolateral prefrontal cortex; SMA, supplementary motor area; SUD, substance use disorder; TDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

<sup>a</sup> Sensitivity analyses were conducted for these statistically significant results.

<sup>b</sup> eFigure 9 in Supplement 1.
Twenty-six sham-controlled studies delivered HF-LDLPFC TMS for 1096 participants with treatment-resistant depression. The mean (SD) duration of trials was 2.8 (1.0) weeks. A significant dose-response association was found ($\chi^2 = 14.49; df = 2; P < .001$), with a bell-shaped curve suggesting that a higher dose than the ED$_{95}$ is associated with less improvement of depressive symptoms (Figure 2A). The ED$_{95}$ was reached at 12,374 total pulses (95% CI, 11,185-12,026 total pulses) in the presence of considerable heterogeneity ($I^2 = 90\%$).

Four studies delivered LF-BLDLPFC TMS for 178 patients with treatment-resistant depression. The mean (SD) duration of trials was 2.8 (0.5) weeks. A significant dose-response association was found ($\chi^2 = 5.86; df = 2; P = .004$) with an ascending curve (Figure 2B) and considerable heterogeneity ($I^2 = 95\%$). The ED$_{95}$ was reached at 34,773 total pulses (95% CI, 32,256-36,521 total pulses). Nonsignificant associations were found in 4 studies of LF-RDLPFC TMS for treatment-resistant depression ($\chi^2 = 0.05; df = 2; P = .98; I^2 = 75\%$).

Five studies delivered HF-LDLPFC TMS for 209 participants with depression over a mean (SD) duration of 2.5 (0.5) weeks. A bell-shaped curve was obtained, with coherent results. However, since the curve passes through the abscissa line, the dose-response association was not statistically significant (Figure 3A). The ED$_{95}$ was reached at 14,054 total pulses (95% CI, 9,522-19,235 total pulses).
The dose-response curves represent the standardized mean difference reduction of symptoms for the treatment arm compared with the sham arm. Circles represent the number of individuals per dose included. The dotted lines are 95% CIs. Knot locations are at the 25th, 50th, and 75th percentiles to anchor the curves. A. Although with a moderate effect size, the maximum reduction of negative symptoms (95% effective dose) was reached at 12,374 total pulses (95% CI, 11,185-15,026 total pulses; mean [SD] duration, 2.8 [1.0] weeks; 26 studies18,20,21,23,25,27,28,30,32,35,43,44,47,56,83,84,87,88,90,91,107,111,112,114,121,124; 1,166 participants; $\chi^2 = 14.49; df = 2; P < .001; I^2 = 90%$). B. The maximum reduction of depressive symptoms (95% effective dose) was reached at 34,773 total pulses (95% CI, 32,256-36,521 total pulses; mean [SD] duration, 2.8 [0.5] weeks; 4 studies28,44,83,94; 178 participants; $r = 5.86; df = 2; P = .004; I^2 = 95%$).

The dose-response curves represent the standardized mean difference reduction of symptoms for the treatment arm compared with the sham arm. Circles represent the number of individuals per dose included. The dotted lines are 95% CIs. Knot locations are at the 25th, 50th, and 75th percentiles to anchor the curves. A. The maximum improvement of depressive symptoms (95% effective dose [ED$_{95}$]) was reached at 14,054 total pulses (95% CI, 9,522-19,235 total pulses; mean [SD] duration, 2.8 [0.5] weeks; 5 studies42,57,70,110,113; 209 participants; $r = 1.46; df = 2; P = .48; I^2 = 85%$). B. The maximum improvement of depressive symptoms (ED$_{95}$) was reached at 1835 total pulses (95% CI, 1,721-1,919 total pulses; mean [SD] duration, 2.8 [1.0] weeks; 2 studies61,67; 97 participants; $r = 25.67; df = 2; P = .001; I^2 = 95%$). C. The maximum improvement of depressive symptoms (ED$_{95}$) was reached for a total of 48.2 coulombs (C) (95% CI, 35.55 C; mean [SD] duration, 3.1 [0.9] weeks; 6 studies28,73,74,82,101,102; 265 participants; $r = 14.56; df = 2; P < .001; I^2 = 96%$).
Two studies delivered LF-RDLPFC TMS for 97 participants with depression. The mean (SD) duration of trials was 2.8 (1.0) weeks. The dose-response association was statistically significant ($\chi^2 = 25.67; df = 2; P = .001$), with a straight ascending curve. Such curves suggest that the higher total amount of pulse was associated with a further decrease of symptoms (Figure 3B). The ED$_{95}$ was reached for 1835 total pulses (95% CI, 1721-1919 total pulses) in the presence of considerable heterogeneity ($I^2 = 95\%$).

Six studies delivered LDLPFC tDCS for 351 participants with treatment-resistant depression. The mean (SD) trial duration was 3.1 (0.9) weeks. A significant association was found with a bell-shaped dose-response curve ($\chi^2 = 14.56; df = 2; P < .001$) (Figure 3C), with considerable heterogeneity ($I^2 = 96\%$). suggesting that the ED$_{95}$ was reached for a total of 48 coulombs (C) (95% CI, 35-55 C).

Nonsignificant results were found for 2 studies that delivered HF-LDLPFC TMS for bipolar depression (eAppendix 1, eFigure 7 in Supplement 1). Nonsignificant results also were found for 2 studies that delivered LDLPFC tDCS for bipolar depression (eAppendix 1, eFigure 8 in Supplement 1).

**Obsessive-Compulsive Disorder**

Five studies delivered LF-RDLPFC TMS for 138 participants with OCD, with a mean (SD) duration of 9.6 (1.8) weeks. A significant dose-response association ($\chi^2 = 20.65; df = 2; P < .001$) with an ascending curve was obtained (Figure 4A) in the presence of moderate heterogeneity ($I^2 = 60\%$). The ED$_{95}$ was reached for 1917 total pulses (95% CI, 7837-19543 total pulses).

Three studies delivered LF tMS of the orbitofrontal cortex for 85 participants with OCD, with a mean (SD) duration of 2.0 (1.0) weeks. A significant dose-response association ($\chi^2 = 15.19; df = 2; P < .001$) with an ascending dose-response curve was obtained in the presence of moderate heterogeneity ($I^2 = 60\%$) (Figure 4B). The ED$_{95}$ was reached at 13 679 total pulses (95% CI, 7117-14 734 total pulses).

Nonsignificant associations were found for 2 studies that delivered HF-RDLPFC TMS (eAppendix 1, eFigure 9 in Supplement 1) and 2 studies that delivered HF-LDLPFC TMS (eAppendix 1, eFigure 10 in Supplement 1) for OCD. Nonsignificant associations also were found for 4 studies that delivered LF supplementary motor area stimulation for OCD (eAppendix 1, eFigure 11 in Supplement 1).

**Posttraumatic Stress Disorder**

Three studies delivered LF-RDLPFC TMS for 49 participants with PTSD, with a mean (SD) duration of 2.3 (1.3) weeks. A significant dose-response association was found ($\chi^2 = 54.15; df = 2; P < .001$), with an ascending curve (Figure 4C). The ED$_{95}$ was reached at 17 495 total pulses (95% CI, 16 596-18 523 total pulses) in the presence of moderate heterogeneity ($I^2 = 45\%$). Nonsignificant associations were found in 2 studies that delivered HF-RDLPFC TMS for PTSD (eAppendix 1, eFigure 12 in Supplement 1).

**Substance Use Disorder**

Seven studies delivered LDLPFC tDCS for 151 participants with methamphetamine use disorder, with a mean (SD) duration of 2.7 (1.0) weeks. A bell-shaped curve showed a significant dose-response association ($\chi^2 = 33.63; df = 2; P < .001$) (Figure 4D). The ED$_{95}$ was reached at 9.6 C (95% CI, 8.9-13.2 C) in the presence of moderate heterogeneity ($I^2 = 60\%$).

Four studies delivered LDLPFC iTBS for 186 participants with methamphetamine use disorder, with a mean (SD) duration of 3.5 (1.0) weeks. A significant dose-response association was found ($\chi^2 = 92.82; df = 2; P < .001$), with a curve that plateaued (Figure 4E). Such a curve suggests that the optimal reduction of craving score was reached, with an ED$_{95}$ of 9724 total pulses.
Figure 4. Dose-Response Curves for Transcranial Magnetic Stimulation (TMS) for Treating Obsessive-Compulsive Disorder (OCD) and Posttraumatic Stress Disorder (PTSD), Transcranial Direct Current Stimulation (tDCS) for Treating Methamphetamine Disorder (MUD) and Cocaine Use Disorder (CUD), and Intermittent Theta-Burst Stimulation (iTBS) for Treating MUD.

The dose-response curves represent the standardized mean difference reduction of symptoms for the treatment arm compared with the sham arm. Circles represent the number of individuals per dose included. The dotted lines are 95% CIs. Knot locations are at the 25th, 50th, and 75th percentiles to anchor the curves. A. The maximum improvement of OCD symptoms (95% effective dose [ED_{95}]) was reached at 18,923 total pulses (95% CI, 7,837-19,543 total pulses; mean [SD] duration, 9.6 [1.8] weeks; 5 studies\cite{17,41,64,68,93}; 138 participants; \chi^2 = 20.65; df = 21; P < .001; I^2 = 60%). B. The maximum improvement in Yale-Brown Obsessive-Compulsive Scale (Y-BCOS) scores (ED_{95}) was reached at 13,679 total pulses (95% CI, 7,117-14,734 total pulses; mean [SD] duration, 2.0 [1.0] weeks; 3 studies\cite{68,86,99}; 85 participants; \chi^2 = 15.19; df = 2; P < .001; I^2 = 60%). C. The maximum improvement in Desires for Drug Questionnaire (DDQ) scores (ED_{95}) was reached at 17,495 total pulses (95% CI, 16,596-18,523 total pulses; mean [SD] duration, 2.3 [1.3] weeks; 3 studies\cite{29,85,116}; 49 participants; \chi^2 = 54.15; df = 2; P < .001; I^2 = 45%). D. The maximum improvement in DDQ scores (ED_{95}) was reached for a total of 9.61 coulombs (C) (95% CI; 8.9-13.2 C; mean [SD] duration, 4.0 [2.1] weeks; 3 studies for MUD\cite{14,15,40}; 151 participants), 3 studies for CUD\cite{46,66,80}; 50 participants), and 1 study for alcohol use disorder\cite{55}; 21 participants; \chi^2 = 33.63; df = 2; P < .001; I^2 = 60%). E. The maximum improvement DDQ scores (ED_{95}) was reached at 9,724 total pulses (95% CI, 7,464-17,423 total pulses; mean [SD] duration, 3.5 [1.0] weeks; 4 studies\cite{36,37,108,109}; 186 participants; \chi^2 = 92.82; df = 2; P < .001; I^2 = 70%).
Discussion

To our knowledge, this series of dose-response meta-analyses is the first to investigate the association of treatment using different doses (total pulses or coulombs) of TMS and tDCS, compared with sham, with core symptoms within a broad range of mental disorders. We discuss here the significant dose-response associations of TMS and tDCS protocols by disorder and, where possible, compare them with associations observed for pharmacologic treatments.

For TMS protocols targeting symptoms of schizophrenia, we observed bell-shaped curves for HF-LDLPFC TMS targeting negative symptoms and for LF-LTPJ TMS targeting treatment-resistant hallucinations. The findings suggest that beyond a certain threshold, further stimulation was associated with diminished symptom reduction. Notably, these observed dose-response associations were similar to those found in a recent series of dose-response meta-analyses for antipsychotic medications targeting schizophrenia symptoms.9

For protocols targeting symptoms of depression in patients with treatment-resistant depression, we observed bell-shaped curves for HF-LDLPFC TMS and LDLPFC tDCS, suggesting that beyond a certain threshold, further stimulation was associated with diminished symptom reduction. These curves were similar to those recently observed in a series of dose-response meta-analyses for selective serotonin reuptake inhibitors for depressive symptoms. 125 By contrast, we observed ascending curves for BLDDLPC TMS and LF-RDLPFC TMS protocols for patients with treatment-resistant depression and patients with depression, respectively, with protocols delivering a greater number of total pulses associated with an increased reduction of depressive symptoms. We also observed an ascending curve for LF-RDLPFC TMS targeting symptoms of PTSD. Future studies could therefore explore the feasibility and efficacy of TMS protocols for these mental disorders with a greater number of total pulses than were included in the current analysis. Nevertheless, a recent study in 7215 patients with depression observed that in clinical practice, patients with longer than standard courses typically show less initial improvement and a more gradual trajectory and that meaningful benefit accrues with treatment beyond 36 sessions.126

For protocols targeting symptoms of OCD, we observed curves starting to plateau for LF-RDLPFC TMS and LF-OFC TMS. These curves suggest that beyond a certain threshold, further stimulation may not lead to an improved reduction in symptoms. This finding is different from the dose-response association found in a previous meta-analysis investigating selective serotonin reuptake inhibitors for OCD symptoms, which reported an ascending curve, albeit with higher doses associated with an increased side effect burden.127

Finally, for protocols targeting craving symptoms in methamphetamine use disorder, we observed a bell-shaped curve for LDLPFC tDCS, with stimulation beyond a certain threshold resulting in diminished symptom reduction. For LDLPFC iTBS, we observed a plateauing curve, indicating that beyond a certain threshold, further stimulation may not lead to more reductions in cravings.

While the exact mechanisms of NIBS are still unknown, recent research has suggested that increasing the number of TMS pulses beyond a certain point may saturate structural network reorganization,128 which may provide some explanation for the bell-shaped and plateauing dose-response associations we observed in some TMS protocols. However, TMS protocols that deliver
stimulation in intermittent patterns (e.g., iTBS) may still show additive outcomes for symptom reduction when delivering a high number of pulses. Thus, more studies are needed to understand the treatment mechanisms of NIBS and how they might explain dose-response associations.

**Limitations**
This study has several limitations. First, some analyses had a limited participant pool, resulting in nonsignificant dose-response curves for specific protocols, such as LF-LTPJ TMS for treatment-resistant hallucinations or LF-RDLPFC TMS for major depressive disorder. This limitation stemmed from a restricted number of enrolled participants. Our analysis suggests a minimum of 150 participants is necessary to establish reliable dose-response models for each stimulation type. While we included a substantial number of trials and participants for treatment-resistant depression and schizophrenia, particularly in TMS studies (2075 participants), robust dose-response models for other mental disorders necessitate additional trials.

Another limitation is the omission of various NIBS parameters in the included trials (e.g., trial duration, stimulation intensity, initial symptom severity). Participant-specific factors such as age, sex, duration of episode, or previous response to electroconvulsive therapy may also be associated with treatment response. Specific symptoms, such as cognitive symptoms of schizophrenia, were also not analyzed. Indeed, due to the recommendation of having a minimum of 10 studies per regressor in meta-regression analyses and considering the inconsistent reporting of data on potential regressors across studies, we were unable to investigate the intended regressors. Furthermore, selective participant enrollment was lacking in most trials, as exemplified by only 2 studies focusing on negative symptoms of schizophrenia that selected participants with predominantly negative symptoms.

Inconsistencies in reporting inclusion criteria and definitions of treatment resistance further contribute to the limitations, except for trials involving patients with treatment-resistant hallucinations. The absence of magnetic resonance imaging-based neuronavigation, used in only a few trials with conflicting results, is another limitation. Additionally, the lack of available data in the retrieved studies prevented the establishment of a dose-response association for adverse effects. Finally, while there is preliminary evidence on the outcomes of NIBS in autism spectrum disorder, borderline personality, attention-deficit/hyperactivity disorder, insomnia, and specific SUDs, the limited number of retrieved publications and the important heterogeneity within protocols limited us in approaching optimal efficacy for symptom improvement. Future RCTs exploring multiple doses of neurostimulation will be needed to address these gaps and expand our understanding across disorders.

**Conclusions**

The findings of this systematic review and dose-response meta-analysis contribute to the understanding of optimal stimulation parameters across disorders and brain areas in the field of neuromodulation. Future research should address the identified limitations and further explore the optimal dose and potential adverse effects in longer-term trials.
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SUPPLEMENT 1.

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eTable 2. Heterogeneity Assessments With the Variance-Partition-Coefficient (VPC) for the Primary Outcome

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SUPPLEMENT 2.

Data Sharing Statement