Applicazioni cliniche della Brain Stimulation in Psichiatria

Dott.ssa M.C. Palazzo¹
Dott.ssa B. Benatti²

2. Università degli Studi di Milano Dipartimento di Neuroscienze, U.O. di Psichiatria, Fondazione IRCCS Ospedale Maggiore Policlinico, Milano.
Number of publications on brain stimulation (TMS, tDCS, ECT, VNS, DBS) in Pub-Med from 1994 to 2015
Different techniques, with the common feature to provide a selective electric stimulation of specific brain areas.
## Brain Stimulation Techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Convulsian</th>
<th>Con Impianto</th>
<th>Magnetic</th>
<th>Continue</th>
<th>Elettriche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimolazione Magnetica Trancranica (TMS)</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcranial Direct Current Stimulation (tDCS)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Stimolazione del Nervo Vago (VNS)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Stimolazione Cerebrale Profonda (DBS)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Terapia Elettroconvulsivante (ECT)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Magnetic Seizure Therapy (MST)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Focal Electrically Applied Seizure Therapy (FEAST)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Current pathophysiological models converge in suggesting that 2 major groups of brain regions - a "dorsal" and "ventral" network - account for the formation of the varied symptoms of affective illness.

• Within this theoretical framework, depression is hypothesized to involve concurrent hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere.

• Symptom remission may require facilitation of hypoactive dorsal brain regions and inhibition of hyperactive ventral areas.

Invasività
(tollerabilità ed effetti collaterali)

Light Therapy

TMS e tDCS

ECT

Non richiedono anestesia, sono indolori (possibili rari eventi eversi)

Richiede anestesia generale. Può dare effetti collaterali di tipo cognitivo

VNS

DBS

Richiedono intervento chirurgico d’impianto:
- Extracranico (VNS)
- Intra-parenchimale (DBS)

Neurochirurgia Funzionale
In October 2008, the FDA approved TMS Therapy for patients suffering from Major Depressive Disorder who have failed to achieve satisfactory improvement from antidepressant treatment.

To date, 3 TMS devices are currently approved in the U.S. for the treatment of Major Depressive Episodes:

NEUROSTAR---------BRAINSWAY---------MAGSTIM

Depression approvals outside the U.S.A.: Canada, Brazil, Australia, Israel, Finland, Germany, Serbia
Transcranial Magnetic Stimulation (TMS)
TMS is
‘Electrodeless’ Electrical Stimulation

1) Electrical Energy in Coil Induces
2) Magnetic Field (right hand Rule, Maxwell’s Equations)
3) Passes unimpeded through the Skull
4) Induces an electrical current in The brain

From TMS Review in Science, June 18, 2001
Repetitive TMS and stimulation parameters

- **Intensity**: 80% - 120% of Individual Motor Threshold
- **Frequency**: Slow \( \leq 1 \text{ Hz} \)  Fast \( > 1 \text{ Hz} - 30 \text{ Hz} \)
- **Length**: seconds - minutes
- **Intertrain Interval**: absent - present (30-60 sec)
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)


*Corresponding author. Tel.: +39 0577 585401; fax: +39 0577 270260.
Table 2. Summary of Neurostimulation Treatment Recommendations for Major Depressive Disorder.

<table>
<thead>
<tr>
<th>Neurostimulation</th>
<th>Overall Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>First line (for patients who have failed at least 1 antidepressant)</td>
</tr>
<tr>
<td>ECT</td>
<td>Second line</td>
</tr>
<tr>
<td>tDCS</td>
<td>Third line</td>
</tr>
<tr>
<td>VNS</td>
<td>Investigational</td>
</tr>
<tr>
<td>DBS</td>
<td>Investigational</td>
</tr>
<tr>
<td>MST</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurostimulation</th>
<th>Acute Efficacy</th>
<th>Maintenance Efficacy</th>
<th>Safety and Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>Level 1</td>
<td>Level 3</td>
<td>Level 1</td>
</tr>
<tr>
<td>ECT</td>
<td>Level 1</td>
<td>Level 1</td>
<td>Level 1</td>
</tr>
<tr>
<td>tDCS</td>
<td>Level 2</td>
<td>Level 3</td>
<td>Level 2</td>
</tr>
<tr>
<td>VNS</td>
<td>Level 2</td>
<td>Level 3</td>
<td>Level 2</td>
</tr>
<tr>
<td>DBS</td>
<td>Level 3</td>
<td>Level 3</td>
<td>Level 3</td>
</tr>
<tr>
<td>MST</td>
<td>Level 3</td>
<td>Not known</td>
<td>Level 3</td>
</tr>
</tbody>
</table>

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

Table 3. Summary of Treatment Parameters for Repetitive Transcranial Magnetic Stimulation (rTMS).

Intensity, frequency, and site
- Stimulate at 110%-120% of resting motor threshold (70%-80% for theta-burst stimulation) (Level 1)
- Select stimulation frequency and site (Table 4)

Treatment course
- Perform stimulation 5 times weekly (Level 1)
- Deliver initial course until symptom remission is achieved, up to 20 sessions (4 weeks) (Level 1)
- Extend course to 30 sessions (6 weeks) in responders who have not achieved symptom remission (Level 3)

Maintenance course
- Use rTMS as needed to maintain response (Level 3)

Table 4. Recommendation for rTMS Stimulation Protocols.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
</tr>
<tr>
<td>High-frequency rTMS to left DLPFC</td>
<td>Level 1</td>
</tr>
<tr>
<td>Low-frequency rTMS to right DLPFC</td>
<td>Level 1</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
</tr>
<tr>
<td>Bilateral rTMS to DLPFC (left high-frequency and right low-frequency)</td>
<td>Level 1</td>
</tr>
<tr>
<td>Low-frequency rTMS to right DLPFC (in nonresponders to high-frequency left DLPFC-rTMS or high-frequency rTMS to left DLPFC in nonresponders to low-frequency right DLPFC-rTMS)</td>
<td>Level 3</td>
</tr>
<tr>
<td>TBS protocols</td>
<td>Level 3</td>
</tr>
<tr>
<td>Intermittent TBS to left DLPFC</td>
<td></td>
</tr>
<tr>
<td>Left intermittent and right continuous TBS to DLPFC</td>
<td></td>
</tr>
<tr>
<td>Intermittent TBS to bilateral DMPFC</td>
<td></td>
</tr>
<tr>
<td><strong>Third line</strong></td>
<td></td>
</tr>
<tr>
<td>High-frequency rTMS to bilateral DMPFC</td>
<td>Level 3</td>
</tr>
</tbody>
</table>

DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation.

Different stimulation frequency and patterns exert different effects. Conventionally, high-frequency rTMS (5-20 Hz) is considered excitatory, while low-frequency stimulation (1-5 Hz) is inhibitory. Conventional stimulation is delivered in 2- to 10-second trains at 10- to 60-second intervals, in 15- to 45-minute sessions. TBS protocols require only 1 to 3 minutes of stimulation and may achieve comparable or stronger effects.22 Intermittent TBS (iTBS) is considered excitatory and continuous TBS (cTBS) inhibitory.
The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder

Tarique Perera a, Mark S. George b,c,*, Geoffrey Grammer d, Philip G. Janicak e, Alvaro Pascual-Leone f, Theodore S. W irecki g,i

a Contemporary Care, Greenwich, CT, USA
b Brain Stimulation Division, Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA
c TMS NeuroHealth, McLean, VA, USA
d TMS NeuroHealth, McLean, VA, USA
e Berenson-Allen Center for Non-invasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
f Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
g TMS Center of Colorado, Denver, CO, USA

Recommendation 1: TMS therapy is recommended as an acute treatment for symptomatic relief of depression in the indicated patient population.

Recommendation 2: TMS therapy is recommended for use as a subsequent option in patients who previously benefited from an acute treatment course and are experiencing a recurrence of their illness (continuation or maintenance).

Recommendation 3: TMS therapy can be administered with or without the concomitant administration of antidepressant or other psychotropic medications.

Recommendation 4: TMS therapy can be used as a continuation or maintenance treatment for patients who benefit from an acute course.

Recommendation 5: TMS therapy can be reintroduced in patients who are relapsing into depression after initially responding to TMS treatment.
Research Acquisitions and Clinical Correlates:

i) Duration of trial
ii) High vs Low Frequency
iii) Navigated TMS
iv) Other stimulation parameters
(i) Duration of Trial
TMS Efficacy Yet to Be Established: Meta-analysis of 14 Controlled Trials

Two weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Favor Treatment</th>
<th>Favor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avery et al, 1999</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Berman et al, 2000</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Garcia-Toro et al, 200ib</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Garcia-Toro et al, 200la</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>George et al, 1997</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>George et al, 2000</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Kimbrell et al, 1999</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Loo et al, 1999</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Mosimann et al, in preparation</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>98</strong></td>
<td><strong>77</strong></td>
</tr>
</tbody>
</table>

Heterogeneity $\chi^2$, $P=0.32$

Two-week follow-up

(after 2 weeks of treatment)

<table>
<thead>
<tr>
<th>Study</th>
<th>Favor Treatment</th>
<th>Favor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avery et al, 1999</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Garcia-Toro et al, 200ib</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Garcia-Toro et al, 200la</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>31</strong></td>
</tr>
</tbody>
</table>

Heterogeneity $\chi^2$, $P=0.54$

(Martin JLR et al. *Br J Psychiatry.* 2003, 182, 480-491)
recent rTMS trials have shown larger antidepressant effects when compared with the earlier studies

recent rTMS trials used novel parameters of stimulation, such as more sessions of rTMS

(Gross et al., 2007; Acta Psychiatr Scand)
Sample: n=301 medication-free outpatients with MDD who had not benefited from prior treatment (4-6 weeks, 10 Hz, 120% MT, 3000 impulses/session, left DLPFC).

Large TMS RCTs (i)

Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial

John P. O’Reardon, H. Brent Solvason, Philip G. Janicak, Shirlene Sampson, Keith E. Isenberg, Ziad Nahas, William M. McDonald, David Avery, Paul B. Fitzgerald, Colleen Loo, Mark A. Demitrack, Mark S. George, and Harold A. Sackeim

Background: We tested whether transcranial magnetic stimulation (TMS) over the left dorsolateral prefrontal cortex (DLPFC) is effective and safe in the acute treatment of major depression.

Methods: In a double-blind, multisite study, 301 medication-free patients with major depression who had not benefited from prior treatment were randomized to active (n = 155) or sham TMS (n = 146) conditions. Sessions were conducted five times per week with TMS at 10 pulses/sec, 120% of motor threshold, 3000 pulses/session, for 4–6 weeks. Primary outcome was the symptom score change as assessed at week 4 with the Montgomery–Asberg Depression Rating Scale (MADRS). Secondary outcomes included changes on the 17- and 24-item Hamilton Depression Rating Scale (HAM-D) and response and remission rates with the MADRS and HAM-D.

Results: Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a post hoc correction for inequality in symptom severity between groups at baseline), as well as on the HAM-D17 and HAM-D24 scales at weeks 4 and 6. Response rates were significantly higher with active TMS on all three scales at weeks 4 and 6. Remission rates were approximately twofold higher with active TMS at week 6 and significant on the MADRS and HAM-D24 scales (but not the HAM-D17 scale). Active TMS was well tolerated with a low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain.

Conclusions: Transcranial magnetic stimulation was effective in treating major depression with minimal side effects reported. It offers clinicians a novel alternative for the treatment of this disorder.

(O’Reardon et al., 2007; Biol Psychiatry)
Daily left prefrontal transcranial magnetic stimulation therapy for major Depressive disorder: a sham-controlled randomized trial

Prospective, multisite, randomized, active sham-controlled study, with 3 weeks of daily TMS, followed by continued blinded treatment for up to another 3 weeks in improvers. 199 antidepressant drug-free patients with nonpsychotic MDD were treated with rTMS to the left DLPFC at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using an 8 coil. Sham rTMS used.

Results: Minimal adverse effects did not differ by treatment arm, with an 88% retention rate (90% sham and 86% active).

Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1% active rTMS and 5.1% sham: P = .02). The odds of attaining remission were 4.2 times greater with active rTMS than with sham. The NNT was 12. Most remitters had low antidepressant treatment resistance.

Almost 30% of patients remitted in the open-label follow-up.
Research clues for clinical applications of rTMS:

1) The longer (3-4 weeks) the patient stays in treatment the higher the improvement rate

2) The higher the level of treatment resistance the lower the response rate
(ii) High vs Low Frequency
Left versus right repetitive transcranial magnetic stimulation in treating major depression: A meta-analysis of randomised controlled trials

Jianjun Chen\textsuperscript{a,b,c,1}, Chuanjuan Zhou\textsuperscript{a,b,c,1}, Bo Wu\textsuperscript{a,b,c}, Ying Wang\textsuperscript{a,b,c}, Qi Li\textsuperscript{a,b,c}, Youdong Wei\textsuperscript{a,b,c}, Deyu Yang\textsuperscript{a,b,c}, Jun Mu\textsuperscript{a,b,c}, Dan Zhu\textsuperscript{a,b,c}, Dezhi Zou\textsuperscript{a,b,c}, Peng Xie\textsuperscript{a,b,c,*}

\textsuperscript{1}Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China 400016
\textsuperscript{2}Chongqing Key Laboratory of Neurobiology, Chongqing, China 400016
\textsuperscript{3}Institute of Neuroscience, Chongqing Medical University, Chongqing, China 400016

\section*{Contents}

\section*{Keywords}

MDD, rTMS, L-DLPFC, R-DLPFC

\section*{1. Introduction}

Many studies have shown the efficacy of high-frequency (HF) or low-frequency (LF) repetitive transcranial magnetic stimulation (rTMS) to the left and right DLPFC, respectively, for the treatment of major depressive disorder (MDD). The latter emerged from several clinical trials as well as several meta-analyses. However, the preferred side of the stimulation remains controversial. The present study aimed to compare the efficacy and safety of LF rTMS to the left and right DLPFC, respectively, for the treatment of MDD.

\section*{2. Methods}

\subsection*{2.1. Literature search}

We searched PubMed and PsycINFO for publications on rTMS in major depression from 2000 to 2013. The search terms included "repetitive transcranial magnetic stimulation" and "major depression." After screening and extraction of the data, 1164 patients were included in the study.

\subsection*{2.2. Outcome measures}

The primary outcome measures were response rate, remission rate, and adverse events.

\subsection*{2.3. Data extraction}

The following data were extracted: study design, sample size, treatment group, and outcome measures.

\subsection*{2.4. Statistical analysis}

A meta-analysis was conducted using the Stata software package. The odds ratio (OR) was calculated to compare the efficacy of LF rTMS applied to the left and right DLPFC, respectively, for the treatment of MDD. A p-value of less than 0.05 was considered statistically significant.

\section*{3. Results}

\subsection*{3.1. Literature search}

Eight randomised controlled trials were included in the meta-analysis. The total sample size was 249 patients, with 126 patients treated with LF rTMS to the left DLPFC and 123 patients treated with LF rTMS to the right DLPFC.

\subsection*{3.2. Response rates}

The pooled examination demonstrated that both rTMS methods were equally effective therapies for MDD, with an OR of 1.15 (95% CI: 0.65–2.03). A sensitivity analysis suggested that the OR value was 2.71 (95% CI: 0.64–12.53) for the studies that included dropout analysis based on only two studies was insufficient.

\subsection*{3.3. Remission rates}

With respect to the safety analysis, although no significant difference was found in the response rates between HFL-DLPFC and LFR-DLPFC (43.1% and 42.8%, respectively), with a p-value of 0.64. In addition, no significant difference was found in the remission rates between HFL-DLPFC and LFR-DLPFC (43.1% and 42.8%, respectively), with a p-value of 0.64.

\section*{4. Discussion}

The results of the meta-analysis suggest that LF rTMS to the left and right DLPFC, respectively, for the treatment of MDD is equally effective. However, further studies are needed to confirm these findings.

\section*{Role of funding source}

The funding for this study was provided by the National Natural Science Foundation of China (Nos. 81100662 and 81271164). The sponsors had no role in the study design, data collection, analysis, or interpretation of the data, nor in the decision to submit the paper for publication.

\section*{Acknowledgements}

We thank Dr. N.D. Melgiri for editing and proofreading the manuscript. We also thank Dr. C. G. Liu, Dr. W. F. Wang, Dr. J. Wu, and Dr. W. Y. Zhao for retrieving the studies for this review. We also thank Dr. N. D. Melgiri for editing and proofreading the manuscript.
(iii) Navigated TMS
TARGET LOCALIZATION: the ‘5 cm rule’

Herwig et al, 2001
Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials

Petro Julkunen a,⁎, Laura Säisänen a,b, Nils Danner b, Eini Niskanen a,c, Taina Hukkanen a, Esa Mervaala a,b, Mervi Könönen a,d

⁎Corresponding author.

a Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland
b Department of Clinical Neurophysiology, University of Kuopio, Kuopio, Finland
c Department of Physics, University of Kuopio, Kuopio, Finland
d Department of Clinical Radiology, Kuopio University Hospital, Kuopio, Finland

Abstract

Navigated transcranial magnetic stimulation (TMS) is an elegant technique for localizing the motor cortex and determining the motor threshold. The location of the motor cortex (MC) is determined by mapping the motor evoked potentials (MEPs) with TMS. To date, however, the spatial precision of determining the MC has not been accurately determined. This case series demonstrates that the navigated TMS can increase the spatial precision of determining the MC. Moreover, we demonstrate that the navigated TMS can increase the repeatability and accuracy of the motor threshold (MT) and MEPs with TMS. The navigated TMS can be performed in about 20 minutes, which is valuable in clinical practice. The navigated TMS also allows the motor cortex to be mapped in a few minutes, which is much faster than traditional TMS. The navigated TMS is a useful technique for determining the motor threshold and mapping the motor cortex in clinical practice.

Keywords: TMS, motor cortex mapping, motor threshold, motor evoked potentials, repeatability of location and EFs

Introduction

Navigated TMS is a technique for localizing the motor cortex and determining the motor threshold. The location of the motor cortex is determined by mapping the motor evoked potentials (MEPs) with TMS. The navigated TMS can be performed in about 20 minutes, which is valuable in clinical practice. The navigated TMS also allows the motor cortex to be mapped in a few minutes, which is much faster than traditional TMS.

Materials and Methods

The present study recruited eight participants (mean±SD age 21±4 years, six men) with no history of neurological or psychiatric disorders. The participants were seated in a comfortable chair, with the arms resting on the table and the hand relaxed. The TMS coil was placed over the hand knob of the participant, and the target for stimulation was located in the hand area of the motor cortex. The TMS coil was orientated 45 degrees to the axial plane of the motor cortex, and the coil was moved in 10-degree increments along the axis of the motor cortex. The duration of each stimulation was 100 ms, and the intensity was 1.5×the motor threshold. The intensity was kept constant throughout the experiment.

Results

The MTs were similar when determined in the second session at 24±4 mV and 23±4 mV, respectively, using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Differences between the hemispheres, navigation and hemisphere were tested using Wilcoxon signed ranks test.

Conclusion

The navigated TMS can increase the spatial precision of determining the MC in clinical practice. The navigated TMS also allows the motor cortex to be mapped in a few minutes, which is much faster than traditional TMS.
(iv) Other Stimulation Parameters
Coil Shape and Field Distribution

Jalinous, 1995
Depth of penetration
~2 cm, at junction between grey and white matter
Review

Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: An exploratory systematic review and meta-analysis

Karina Karolina Kedzior a,*, Helena Marie Gellersen b, Anna Katharina Brachetti b, Marcelo T. Berlim c

a Institute of Psychology and Transfer, University of Bremen, Grazer Straße 2c, 28359 Bremen, Germany
b School of Engineering and Science, Jacobs University Bremen, Bremen, Germany
c Department of Psychiatry, McGill University, and Neuromodulation Research Clinic, Douglas Institute, Montreal, Canada

In January 2013, the FDA approved Deep TMS for the treatment of depressive episodes in adult patients suffering from MDD, who failed to achieve satisfactory improvement from 1-4 previous antidepressant treatments in the current episode.

9 studies selected: HF-DTMS appears to have acute antidepressant effects after 20 sessions in mostly unipolar and treatment-resistant patients. Concurrent treatment with antidepressants might enhance the efficacy of DTMS. Results are based on data from a low number of open-label studies.
Coil design considerations for deep transcranial magnetic stimulation

Zhi-De Deng a, Sarah H. Lisanby a,b, Angel V. Peterchev a,c,d,*

aDepartment of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA
bDepartment of Psychology and Neuroscience, Duke University, Durham, NC, USA
cDepartment of Biomedical Engineering, Duke University, Durham, NC, USA
dDepartment of Electrical and Computer Engineering, Duke University, Durham, NC, USA

Methods: The focality advantage of smaller TMS coils over larger coils diminishes with increasing target depth.

Conclusions: The electric field magnitude is normalized to the peak voltage, which is adjusted to produce the desired electric field strength that exceeds the upper limit in current safety guidelines.

Direct TMS of targets at depths of ~4 cm or more results in superficial stimulation strength that is certainly unsafe considering the excessive superficial stimulation strength and activated brain volume.

Approaching depths of ~6 cm is almost certainly unsafe.

Fig. 2. Simulation models of seven TMS coil configurations and the corresponding electric field distribution in the brain: (a) Magstim 90 mm circular coil, (b) Brainsway H1 coil, (c) crown coil (x = 65°, β = 40°; Fig. 1(a)), (d) Magstim 70 mm figure-8 coil, (e) Neuronetics iron core figure-8 coil, (f) Magstim double cone coil, (g) stretched C-core coil. A quarter of the brain sphere is removed to visualize the electric field in depth. The electric field magnitude is normalized to the peak rate of change of the magnetic field (max(|Ez, s|)) due to increased magnetic reluctance and pulse duration. Direct rTMS of targets at depths of >4 cm or more is likely unsafe as it results in superficial stimulation strength that exceeds the upper limit in current safety guidelines.
Clinical indications and future perspectives
## Use of rTMS beyond MDD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Level of Evidence</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Possible Efficacy (auditory hallucinations)</td>
<td>- Left LF Temporoparietal Cortex - DLPFC</td>
</tr>
<tr>
<td></td>
<td>Probable Efficacy (negative symptoms)</td>
<td></td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>Insufficient</td>
<td>- Left HF DLPFC (Depr.)</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>Insufficient</td>
<td>- Left HF DLPFC</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>Insufficient</td>
<td>- Left HF DLPFC</td>
</tr>
<tr>
<td>Post-traumatic Stress Disorder</td>
<td>Possible Efficacy</td>
<td>- Left and right DLPFC</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>Mixed (different targets)</td>
<td>- SMA, OFC, DLPFC</td>
</tr>
<tr>
<td>Cigarette craving and consumption</td>
<td>Possible Efficacy</td>
<td>- HF DLPFC</td>
</tr>
</tbody>
</table>

(Dell’Osso et al, 2016)
Review Articles

Review of the Effectiveness of Transcranial Magnetic Stimulation for Post-traumatic Stress Disorder

Ethan F. Karsen a,*, Bradley V. Watts a,*, Paul E. Holtzheimer a,c

a Department of Psychiatry, Geisel School of Medicine at Dartmouth, One Medical Center Drive, Lebanon, New Hampshire, USA
b Department of Psychiatry, Veterans Affairs National Center for Patient Safety, White River Junction, Vermont, USA
c Department of Surgery, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire, USA

ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is a psychiatric condition with significant morbidity and limited treatment options. Transcranial magnetic stimulation (TMS) has been shown to be an effective treatment for mental illnesses including major depressive disorder.

Objective: Review effectiveness of TMS for PTSD.

Methods: Literature review with descriptions of primary studies as well as meta-analysis of studies.

Results: Of the 13 studies reviewed, 10 studies met criteria to be included in the meta-analysis.

Conclusions: TMS is an effective treatment for mental illnesses including PTSD.

Keywords: PTSD, TMS, Meta-analysis, Depression, Anxiety.

Table 3

Table 3 Forest plot showing effect size calculated as Hedges g for TMS on PTSD symptom scales.

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size</th>
<th>CI lower</th>
<th>CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen (low)</td>
<td>0.73</td>
<td>-0.36</td>
<td>1.82</td>
</tr>
<tr>
<td>Cohen (high)</td>
<td>1.84</td>
<td>0.64</td>
<td>3.04</td>
</tr>
<tr>
<td>Boggio (right)</td>
<td>3.78</td>
<td>2.32</td>
<td>5.25</td>
</tr>
<tr>
<td>Boggio (left)</td>
<td>2.68</td>
<td>1.47</td>
<td>3.88</td>
</tr>
<tr>
<td>Watts</td>
<td>1.99</td>
<td>0.92</td>
<td>3.06</td>
</tr>
<tr>
<td>Pooled</td>
<td>2.67</td>
<td>1.11</td>
<td>4.23</td>
</tr>
</tbody>
</table>

Cl = confidence interval.

Fig. 1. Study met criteria to be included in the meta-analysis.

Watts 1.1 0.15 2.05
Boggio (right) 2.04 2.19 5.04
Boggio (left) 2.14 2.45 4.23
Cohen (low) 0.73 0.36 1.82
Cohen (high) 1.84 0.64 3.04
Boggio (right) 3.78 2.32 5.25
Boggio (left) 2.68 1.47 3.88
Watts 1.99 0.92 3.06
Pooled 2.67 1.11 4.23

Hedges’s g and 95% CI

Pre-post Y-BOCS scores.
Patterned rTMS

The standard theta burst pattern consists of three bursts of pulses given at 50Hz and repeated every 200 ms.
Clinical Trials at Policlinico IRCCS of Milan
Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression


Objectives: The efficacy of transcranial magnetic stimulation (TMS) has been poorly investigated in bipolar depression. The present study aimed to assess the efficacy of low-frequency repetitive TMS (rTMS) of the right dorsolateral prefrontal cortex (DLPFC) combined with brain navigation in a sample of bipolar depressed subjects.

Methods: Eleven subjects with bipolar I or bipolar II disorder and major depressive episode who did not respond to previous pharmacological treatment were treated with three weeks of open-label rTMS at 1 Hz, 110% of motor threshold, 300 stimuli/day.

Results: All subjects completed the trial showing a statistically significant improvement in the 21-item Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale, and Clinical Global Impression severity of illness scale (ANOVA with repeated measures: $F = 22.36, p < 0.0001$; $F = 12.66, p < 0.0001$; and $F = 10.41, p < 0.0001$, respectively). In addition, stimulation response, defined as an endpoint HAM-D score reduction of ≥50% compared to baseline, was achieved by 6 out of 11 subjects, 4 of whom were considered remitters (HAM-D endpoint score ≤8). Partial response (endpoint HAM-D score reduction between 25% and 50%) was obtained by 3/11 patients. No manic/hypomanic activation was detected during the treatment according to Young Mania Rating Scale scores (ANOVA with repeated measures: $F = 0.62, p = 0.61$). Side effects were slight and were limited to the first days of treatment.

Conclusions: Augmentative low-frequency rTMS of the right DLPFC combined with brain navigation was effective and well tolerated in a small sample of drug-resistant bipolar depressive patients, even though the lack of a sham controlled group limits confidence in the results.

Key words: bipolar depression; brain navigation; DLPFC - dorsolateral prefrontal cortex; TMS - transcranial magnetic stimulation

Received 5 October 2007, revised and accepted for publication 11 April 2008

Corresponding author: Bernardo Dell'Oso, M.D., Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Department of Clinical Sciences, L. Sacco, University of Milan, Milano, Italy

e-mail: bernardo.delloso@policlinico.mi.it
After the completion of an acute trial with augmentative, low-frequency, navigated rTMS, 11 drug-resistant depressed bipolar subjects (DSM-IV-TR criteria) entered a naturalistic follow-up with monthly evaluations through the HDRS and the YMRS.

**RESULTS:** After 1 year of follow-up, results showed that the achievement of remission after acute rTMS was predictive of maintenance of response at 1 year. On the other hand, the absence of acute rTMS response predicted the absence of subsequent response in the long-term.
Augmentative repetitive Transcranial Magnetic Stimulation (rTMS) in the acute treatment of poor responder depressed patients: A comparison study between high and low frequency stimulation

B. Dell’Osso a,⁎, b, L. Oldani a, G. Camuri a, C. Dobrea a, L. Cremaschi a, B. Benatti a, C. Arici a, B. Grancini a, A. Carlo Altamura a

⁎Department of Psychiatry, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milano, Italy

aBipolar Disorders Clinic, Stanford Medical School, Stanford University, CA, USA

Fig. 1. Total sample's primary outcome measures at different timepoints. HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; CGI: Clinical Global Impression. □ T0–T1 (t = 8.3; P < 0.001); □□ T1–T2 (t = 2.7; P = 0.01); □□□ T0–T4 (t = 8.6; P < 0.001). * T0–T1 (t = 6.2; P < 0.001); T1–T2 (t = 3.9; P = 0.001); *** T0–T4 (t = 8.1; P < 0.001). ▽ T1–T2 (t = 2.4; P = 0.02). ▼▼ T0–T4 (t = 4.6; P < 0.001).
Focus su Transcranial Direct Current Stimulation (tDCS)
Transcranial stimulation (TMS and tDCS): a common rational for use in MD

Ultimately, transcranial neuromodulatory techniques, like TMS and tDCS, though with different mechanisms of action, are supposed to restore the functional balance between the 2 hemispheres.

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments

Roumen V. Milev, MD, PhD¹, Peter Giacobbe, MD, MSc², Sidney H. Kennedy, MD², Daniel M. Blumberger, MD, MSc², Zafiris J. Daskalakis, MD, PhD², Jonathan Downar, MD, PhD², Mandana Modirrousta, MD, PhD³, Simon Patry, MD⁴, Fidel Vila-Rodriguez, MD, MSc⁵, Raymond W. Lam, MD⁵, Glenda M. MacQueen, MD, PhD⁶, Sagar V. Parikh, MD²,⁷, Arun V. Ravindran, MB, PhD², and the CANMAT Depression Work Group⁸

Emmanuel Poulet e,s, Alberto Priori f,g,t, Simone Rossi u, Martin Schecklmann k, Sven Vanneste v,w, Ulf Ziemann x, Luis Garcia-Larrea y, Walter Paulus c,1
- Consiste nell’applicazione di deboli correnti elettriche (1-2 mA) che modulano l’attività dei neuroni cerebrali.
- 2 elettrodi - un anodo e un catodo – sono posizionati sullo scalpo permettendo alla corrente di passare da un polo all’altro e dando luogo ad un’ampia polarizzazione neuronale a livello della corteccia.
- L’apparecchiatura per l’utilizzo della tDCS ha costi limitati ed è di facile utilizzo.
Transcranial direct current stimulation

- Perhaps the simplest way of focally stimulating the brain.

- Involves passing a weak direct current through the brain between two electrodes. The current enters the brain from the anode, travels through the tissue and exits out the cathode.

- Is referred as either anodal or cathodal tDCS depending on which electrode is placed over the region that is being modified.

- In most studies, the area under the anode is more active (or excited) and the area under the cathode is more inhibited.

(George and Higgins, 2009: transcranial direct current stimulation in: “Brain Stimulation Therapies for Clinicians”; APPI)
tDCS vs ECT

- In tDCS, small currents are used over 20-30 minutes. It is constant and the brain has time to accommodate to the gentle current.

- By contrast, ECT uses a short, powerful, bidirectional current, which typically has a waveform that makes it resemble an alternating current. The brain cannot adapt to the ECT stimulus and a seizure is induced.

- However, the total amount of electricity used in a session of ECT compared with a session of tDCS is not that different.

(George and Higgins, 2009: transcranial direct current stimulation in: “Brain Stimulation Therapies for Clinicians”; APPI)
RCTs with tDCS

- 5 double-blind sham controlled trials conducted with tDCS in major depression to date (Dell’Osso et al, Biol Psychiatry 2012)

The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial.

To assess the combined safety and efficacy of tDCS vs sertraline 50 mg/d in a double-blind, controlled trial. 120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD, treated for 6 weeks with 2-mA anodal left/cathodal right prefrontal tDCS (12 sessions, 30-minute each: 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week) and sertraline (50 mg/d).

RESULTS: Significant difference in MADRS scores when comparing the combined treatment group (sertraline/active tDCS) vs sertraline only (mean difference, 8.5 points), tDCS only (mean difference, 5.9 points), and placebo/sham tDCS (mean difference, 11.5 points). Analysis of tDCS only vs sertraline only presented comparable efficacies (mean difference, 2.6 points). Use of tDCS only (but not sertraline only) was superior to placebo/sham tDCS. Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS. There were 7 episodes of treatment-emergent mania or hypomania, 5 occurring in the combined treatment group.

CONCLUSIONS: In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety of tDCS and sertraline did not differ.
tDCS: stato attuale e prospettive cliniche

- **Stato Attuale**: In fase iniziale, pochi studi clinici controllati. Buono il profilo di tollerabilità. L’utilizzo in Italia nella Depressione Resitente/con scarsa risposta alle terapie è da ritenersi sperimentale.

Efficacy and Safety of Transcranial Direct Current Stimulation in Major Depression

To the Editor:

Over the last years, a novel neuromodulation technique—transcranial direct current stimulation (tDCS)—has been investigated for noninvasive and painless modulation of human brain activity through the scalp, particularly of the dorsolateralprefrontal cortex (DLPFC). Transcranial direct current stimulation delivers weak direct currents (1–2 mA) through sponge electrodes on the scalp (1), differently from transcranial magnetic stimulation (TMS), which involves magnetic fields to induce electri
cal stimulations currents into the cortex. Part of the delivered current enters the skull, modulating the activity of cortical neurons and leading to polarity-dependent changes in cortical excitability. Two electrodes—an anode and a cathode—are generally placed on the scalp, allowing current to flow throughout the brain between the two sites and polarization to occur over a relatively wide cortical area. Even though focality of stimulation is lower with tDCS than TMS, potential advantages of tDCS include its portability, safety, and reduced costs. In addition, both cathodal and anodal tDCS—the two modalities of action of the technique—cannot be discriminated by the patient from each other and versus sham stimulation, which might be of interest for planning sham-controlled trials.

In terms of mechanisms of action, electrophysiological data suggest that tDCS might strengthen synaptic connections through a neurotransmitter system, and promote brain-derived neurotrophic factor–dependent synaptic plasticity (1,2). In addition, changes in spontaneous neuronal firing rates, cerebral blood flow, and metabolism have been reported (1–3). Given that the modulatory effects of tDCS over the cortex can be long-lasting, its action on cognitive and emotional functions has started to be investigated in healthy subjects and neuropsychiatric disorders (e.g., stroke rehabilitation) and psychiatric disorders (i.e., major depression [MDD]) (4). Despite preliminary encouraging results in the field of depressive disorders, it needs to be stressed that tDCS is currently an investigational therapy and lacks formal approval for the treatment of these conditions by the US Food and Drug Administration (FDA) (5). On the basis of these findings, there is no sufficient evidence to support tDCS as a recommended therapeutic modality for depression. However, a growing body of evidence with double-blind, sham-controlled trials, in particular, represent a first specific step in this direction and encourage further studies in this area. As for TMS, additional investigation is required to clarify optimal parameters of stimulation (e.g., duration of treatment, electrode placement), clinical target (i.e., MDD or TRD), treatment modality (i.e., monotherapy or augmentation), duration of benefit, and patient characteristics that might condition response to tDCS. Nevertheless, the implementation of novel neuromodulatory techniques with minimal levels of invasiveness and minor side effects in the field of psychiatric treatments provides further confirmation of the pathophysiological acquisitions in this area as well as the presence of a “third way” of treatments besides psychotropic drugs and psychotherapy.

Bernardo Dell’Osso* Alberto Priori† A. Carlo Altamura§

*Bureau of Psychiatry, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico; †Center for Neurostimulation, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, University of Milan, Italy

*Corresponding author E-mail: bernardo.delloso@unimi.it

Dr. Alberto Priori is president and a shareholder of the company Neuronsa s.r.l., Milan, and reports his patents pending “Process for Reducing Neuromuscular Fatigue Caused by Exercise,” patent number WO2008155114 (A1). All other authors report no biomedical financial interests or potential conflicts of interest.

Transcranial direct current stimulation in the treatment of major depression: a meta-analysis

U. G. Kalu, C. E. Sexton, C. K. Loo and K. P. Ebmeier

Department of Psychiatry, University of Oxford, Oxford, UK

Background. So far, no comprehensive answer has emerged to the question of whether transcranial direct current stimulation (tDCS) can make a clinically useful contribution to the treatment of major depression. We aim to present a systematic review and meta-analysis of tDCS in the treatment of depression.

Method. Medline and Embase were searched for open-label and randomized controlled trials of tDCS in depression using the expressions (‘transcranial direct current stimulation’ or ‘tDCS’) and (‘depression’ or ‘depressed’). Study data were extracted with a standardized data sheet. For randomized controlled trials, effect size (Hedges’ g) was calculated and the relationships between study variables and effect size explored using meta-regression.

Results. A total of 108 citations were screened and 10 studies included in the systematic review. Six randomized controlled trials were included in the meta-analysis, with a cumulative sample of 96 active and 80 sham tDCS courses. Active tDCS was found to be more effective than sham tDCS for the reduction of depression severity (Hedges’ g = 0.743, 95% confidence interval 0.21–1.27), although study results differed more than expected by chance (Q = 15.52, df = 6, p = 0.017, F = 61.35). Meta-regression did not reveal any significant correlations.

Conclusions. Our study was limited by the small number of studies included, which often had small sample size. Future studies should use larger, if possible representative, health service patient samples, and optimized protocols to evaluate the efficacy of tDCS in the treatment of depression further.

Received 23 November 2010; Revised 9 December 2011; Accepted 15 December 2011; First published online 12 January 2012

Key words: Depression, meta-analysis, review, transcranial direct current stimulation.

- 6 RCTs included, with a sample of 96 active and 80 sham tDCS courses.
- Active tDCS was found to be more effective than sham tDCS for the reduction of depression severity, although study results differed more than expected by chance.
- Meta-regression did not reveal any significant correlations with specific variables.

(Kalu et al. Psychol Med, 2012)
Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials

Marcelo T. Berlim a,b,c, Freiderique Van den Eynde a,b, Z. Jeff Daskalakis d,e

aNeuromodulation Research Clinic, Douglas Mental Health University Institute, Montréal, Québec, Canada
bMcGill University, Montréal, Québec, Canada
cDepressive Disorders Program, Douglas Mental Health University Institute, Montréal, Québec, Canada
dBrain Stimulation Treatment and Research Program, Centre for Addiction and Mental Health, Ontario, Canada
eUniversity of Toronto, Ontario, Canada

Objective:

We searched the literature for English language randomized, double-blind and sham-controlled RCTs that compared active and sham tDCS in the treatment of major depression (MD). Our main results clearly contrast with those previously reported in favor of active tDCS.

Methodology:

We included 21 RCTs and 1 RCT with a crossover design (a total of 200 subjects). The meta-analysis conducted in this study included data from 6 RCTs. Data were pooled into 4 main categories (response vs. sham tDCS, remaining factors were absent). No differences were observed between active and sham tDCS groups. Therefore, the clinical utility of tDCS as a monotherapy for MD remains unclear when clinically relevant comparing the difference in response rates between active and sham tDCS (23.3% vs. 12.4%).

Conclusion:


Review

Data obtained from 6 RCTs including a total of 200 subjects with MD.

After an average of 10.8 ± 3.76 tDCS sessions, no significant difference was found between active and sham tDCS in terms of response (23.3% vs. 12.4%) and remission (12.2% vs. 5.4%).

However, tDCS used as monotherapy was associated with higher response rates when compared to sham tDCS (p = 0.04).
To assess the combined safety and efficacy of tDCS vs sertraline 50 mg/d in a double-blind, controlled trial. 120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD, treated for 6 weeks with 2-mA anodal left/cathodal right prefrontal tDCS (12 sessions, 30-minute each: 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week) and sertraline (50 mg/d).

RESULTS:
- Significant difference observed in MADRS scores when comparing the combined treatment group (sertraline/active tDCS) vs sertraline only (mean difference, 8.5 points), tDCS only (mean difference, 5.9 points), and placebo/sham tDCS (mean difference, 11.5 points).
- Analysis of tDCS only vs sertraline only presented comparable efficacies (mean difference, 2.6 points).
- Use of tDCS only (but not sertraline only) was superior to placebo/sham tDCS.
- Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS.
- There were 7 episodes of treatment-emergent mania or hypomania, 5 occurring in the combined treatment group.

CONCLUSIONS: In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety of tDCS and sertraline did not differ.
**Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis**

Pedro Shiozawa1,2, Felipe Fregni3, Isabela M. Benseñor4, Paulo A. Lotufo5, Marcelo T. Berlim4, Jeff Z. Daskalakis6, Quirino Cordeiro4 and André. R. Brunoni1,8

1 Interdisciplinary Centre for Applied Neuromodulation – University Hospital, University of São Paulo, Brazil
2 Laboratory of Neuromodulation, Santa Casa Medical School – São Paulo, Brazil
3 Neuromodulation Laboratory, Spaulding Rehabilitation Center – Harvard Medical School, Boston, MA, USA
4 Department of Psychiatry, McGill University, Montréal, Canada
5 Centre for Addiction and Mental Health (CAMH) Collaborative Program in Neuroscience, University of Toronto, Canada
6 Service of Interdisciplinary Neurosciences (Lino-27), Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil

---

**Table 2.**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumberger (2012)</td>
<td>-0.13 (-0.94, 0.67)</td>
<td>11.58</td>
</tr>
<tr>
<td>Boggio (2008)</td>
<td>0.88 (0.09, 1.67)</td>
<td>11.89</td>
</tr>
<tr>
<td>Brunoni (2013)</td>
<td>0.52 (0.01, 1.04)</td>
<td>19.51</td>
</tr>
<tr>
<td>Fregni (2006)</td>
<td>1.19 (0.16, 2.21)</td>
<td>8.12</td>
</tr>
<tr>
<td>Loo (2010)</td>
<td>-0.25 (-0.87, 0.37)</td>
<td>16.00</td>
</tr>
<tr>
<td>Loo2 (2012)</td>
<td>0.56 (0.06, 1.06)</td>
<td>20.06</td>
</tr>
<tr>
<td>Palm1 (2012)</td>
<td>0.13 (-1.11, 1.38)</td>
<td>5.92</td>
</tr>
<tr>
<td>Palm2 (2012)</td>
<td>-0.01 (-1.14, 1.12)</td>
<td>6.91</td>
</tr>
<tr>
<td>Overall (I-squared = 35.3%, p = 0.147)</td>
<td>0.37 (0.04, 0.70)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

---

**Table 2 (continued).**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumberger (2012)</td>
<td>-0.13 (-0.94, 0.67)</td>
<td>11.14</td>
</tr>
<tr>
<td>Boggio (2008)</td>
<td>0.88 (0.09, 1.67)</td>
<td>11.42</td>
</tr>
<tr>
<td>Brunoni (2013)</td>
<td>0.64 (0.28, 1.01)</td>
<td>23.17</td>
</tr>
<tr>
<td>Fregni (2006)</td>
<td>1.19 (0.16, 2.21)</td>
<td>7.92</td>
</tr>
<tr>
<td>Loo (2010)</td>
<td>-0.25 (-0.87, 0.37)</td>
<td>15.11</td>
</tr>
<tr>
<td>Loo2 (2012)</td>
<td>0.56 (0.06, 1.06)</td>
<td>18.63</td>
</tr>
<tr>
<td>Palm1 (2012)</td>
<td>0.13 (-1.11, 1.38)</td>
<td>5.83</td>
</tr>
<tr>
<td>Palm2 (2012)</td>
<td>-0.01 (-1.14, 1.12)</td>
<td>6.77</td>
</tr>
<tr>
<td>Overall (I-squared = 42.4%, p = 0.096)</td>
<td>0.40 (0.07, 0.73)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

---

7 RCTs (n = 259) included, most with small sample sizes, assessing tDCS as either mono or add-on therapy.

- **Active vs. sham tDCS was significantly superior for all outcomes.**
- Risk of publication bias was low.
- No predictors of response were identified, possibly owing to low statistical power.

**Conclusions:** Active tDCS was statistically superior to sham tDCS for the acute depression treatment, although its role as a clinical intervention is still unclear owing to the mixed findings and heterogeneity of the reviewed studies.

Review

Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability

Daniel Meron a,b, Nicholas Hedger c, Matthew Garner a,c, David S. Baldwin a,d,*

a Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, University Department of Psychiatry, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DY, United Kingdom
b Avon & Wiltshire Partnership NHS Trust, Jenner House, Langley Park, Chippenham SN15 1GG, Wiltshire, United Kingdom
c Psychology, Faculty of Social, Human and Mathematical Sciences, University of Southampton, Southampton, United Kingdom
d University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability

Daniel Meron a,b, Nicholas Hedger c, Matthew Garner a,c, David S. Baldwin a,d,*

a Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, University Department of Psychiatry, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DY, United Kingdom
b Avon & Wiltshire Partnership NHS Trust, Jenner House, Langley Park, Chippenham SN15 1GG, Wiltshire, United Kingdom
c Psychology, Faculty of Social, Human and Mathematical Sciences, University of Southampton, Southampton, United Kingdom
d University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

-10 RCTs included.
- tDCS was superior to sham tDCS.
- Adjunctive antidepressant and cognitive control training negatively impacted on the treatment effect.
- The pooled log odds ratios for response and remission were positive, but statistically non-significant.

-Conclusions: tDCS may be efficacious for treatment of MDE. The data do not support the use of tDCS in treatment-resistant depression, or as an add-on augmentation treatment.

(Meron et al. Neurosci Biobehav Rev, 2015)
Esperienza del Policlinico IRCCS di Milano
Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients

B. Dell’Osso a,+, S. Zanoni a, R. Ferrucci b,c, M. Vergari b,c, F. Castellano a, N. D’Urso a, C. Dobra a, B. Benatti a, C. Arici a, A. Priori b,c, A.C. Altamura a

a Dipartimento di Neuroscienze, Università degli Studi di Milano, Dipartimento di Salute Mentale Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milano, Italy
b Centro Clinico per le Neuronanotecnologie e la Neurostimolazione, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milano, Italy
c U.O. Neurofisiopatologia, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milano, Italy

23 depressed patients, with MDD or BD treated with augmentative tDCS for 5 days, 2 sessions per day in a blind-rater trial.

All patients completed the trial without relevant side-effects.

A significant reduction of HAM-D and MADRS total scores was observed during the study (P<0.0001).

Treatment response (endpoint HAM-D reduction ≥50%) was obtained by 17.4% of patients at T1 and by 30.4% at T2 and remission by 13.0% of patients at T1 and by 17.4% at T2.
Augmentative transcranial direct current stimulation (tDCS) in poor responder depressed patients: a follow-up study

Bernardo Dell’Osso,1* Cristina Dobrea,1 Chiara Arici,1 Beatrice Benatti,1 Roberta Ferrucci,2 Maurizio Vergari,2 Alberto Priori,2 and A. Carlo Altamura1

1 Department of Psychiatry, University of Milan, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy
2 Center of Neurostimulation, University of Milan, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy

Even though a progressive reduction of follow-up completers was observed from T2 to T4 (95.6% at T2, 65.2% at T3, and 47.8% at T4), the antidepressant effects of acute tDCS persisted over 3 months in almost half of the sample.

Of note, no post-acute side effects emerged during the follow-up observation.

The most frequent causes of drop-out from this study included major modifications in therapeutic regimen (30%) and poor adherence to follow-up visits (17%).

With respect to YMRS scores, no significant increase was observed over the follow-up period (T1–T2, p = 0.329; T2–T3, p = 0.334; T3–T4, p = 1.000).

Figure 1. Outcome measures (mean scores) of the study completers at the different time-points. T1 = assessment at the end of the treatment, T2 = assessment at 1 week after the end of the treatment, T3 = assessment at 1 month after the end of the treatment, T4 = assessment at 3 months after the end of the treatment. For definition of HAM-D melancholic items, see the text.
Conclusioni

• Considerato l’alto tasso di resistenza e risposta parziale ai trattamenti standard di alcuni disturbi psichiatrici quali la Depressione Maggiore, vi è sempre maggior interesse nei confronti di nuove strategie terapeutiche.

• Gli Interventi di Stimolazione Cerebrale potrebbero costituire una terza via di trattamento accanto agli interventi psicofarmacologici e psicoterapici in alcuni di questi Disturbi Psichiatrici.

• Gli Interventi di Stimolazione Cerebrale sono caratterizzati da una maggior selettività e specificità rispetto all’ECT e alla maggior parte dei trattamenti farmacologici disponibili.

• Sono inoltre caratterizzati da una buona tollerabilità e da buone percentuali di efficacia e alcune tecniche hanno già ottenuto l’approvazione dalla FDA (VNS, DBS e TMS) e dall’EMEA (VNS) per il trattamento della DM resistente e per altre tecniche l’approvazione potrebbe arrivare a breve.