Transcranial magnetic stimulation for the treatment of major depressive disorder: effectiveness of bilateral stimulation when patients are not responding to unilateral stimulation

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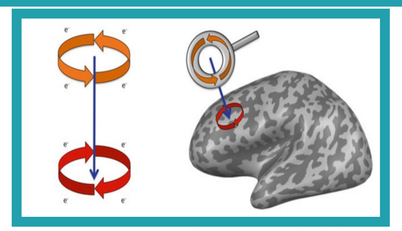
BACKGROUND

Transcranial magnetic stimulation (TMS) is a method of noninvasive neuromodulation that is widely used in research and clinical contexts. Among its clinical applications, TMS is FDA approved to treat major depressive disorder (MDD).[1] TMS treatment parameters for MDD include stimulation administered to the left or right dorsolateral prefrontal cortex (left or right DLPFC), repeated daily for 4-6 weeks, followed by a tapering period of 2-3 weeks.[2]

While the overall efficacy of TMS for treatment of MDD is well-established, there is limited investigation into the effectiveness of adjustments made to TMS parameters when patients are not adequately responding to treatment. One such minimally-researched treatment adjustment is a change from unilateral TMS, where one hemisphere of the DLPFC is stimulated, to bilateral TMS, where TMS is sequentially administered to both hemispheres of the DLPFC. Although implemented in clinical practice, there is little investigation into whether this parameter adjustment increases overall efficacy of and response to TMS treatment.



Camprodon, J. (2016).

Biophysical mechanisms of TMS. "The primary electrical field in the coil (orange) generates a magnetic field (blue) that travels unimpeded until it finds an electrically conductive material- in this case, cortical neurons, which act as a pickup coil where a secondary electrical field (red) is generated. The primary and secondary electrical fields are in the same plane, but opposite direction." [1]

METHODS

Participants: In this retrospective study, we analyzed clinical data from 39 patients who received at least one full course of TMS treatment (≥ 36 sessions) for MDD at the MGH TMS Clinical Service. During these patients' courses, TMS parameters were adjusted from unilateral to bilateral TMS due to lack of treatment response, as determined by clinical assessments, patient self-report questionnaires, and subjective patient reports.

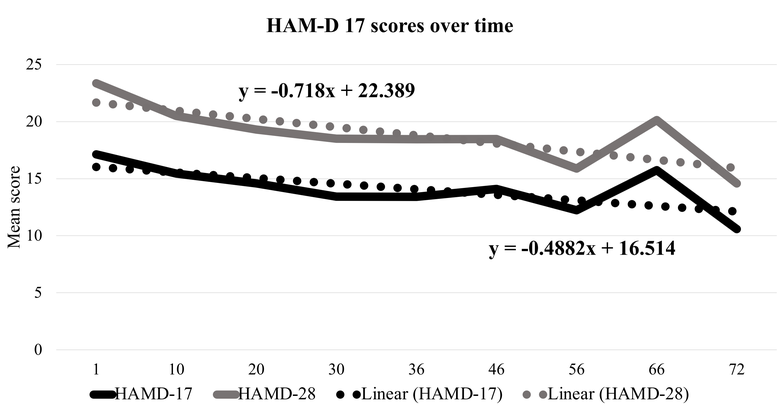
Endpoints: Changes in depression symptoms were measured using the Hamilton Depression Rating Scale- 17 item questionnaire (HAM-D 17). This questionnaire was administered at sessions 1, 10, 20, 30, 36, 46, 56, 66, and 72. Criteria for "response" was defined as ≥ 50% reduction in HAM-D 17 scores. "Partial response" was defined as a 30% ≤ x < 50% reduction in HAM-D scores.. Patients who met response criteria remained classified as responders if their HAM-D scores did not increase more than 25.0% after meeting response criteria.

Analysis: We first used simple linear regression to assess the general relationship between number of TMS sessions received and change in HAM-D 17 scores over time. We then looked at treatment outcomes and clinical characteristics of patients who responded to unilateral or bilateral TMS, and those who failed to respond. Finally, we investigated potential differences in treatment outcomes between patients who began their TMS treatment course with stimulation to the left DLPFC (unilateral left DLPFC TMS), and patients initially received treatment to the right DLPFC (unilateral right DLPFC TMS). In our assessment of response to bilateral TMS, the baseline HAM-D score used was the last HAM-D score collected while the patient was receiving unilateral treatment.

RESULTS

Patient demographics

Number of patients:	**n = 39**
Gender:	24 women; 11 men; 1 did not disclose
Age (mean ± std. dev):	40.97 ± 19.89 years
Baseline HAM-D 17 score (mean ± std. dev):	17.13 ± 7.37



Linear regression: HAM-D 17 scores over time

Simple linear regression analysis showed an **increased improvement in depression symptoms as a function of number of TMS sessions** (F-statistic: 10.09 on 1 and 260 DF, p-value 0.001668)

RESULTS (continued)

Clinical characteristics of patient cohort

	Count. (%)	Age (mean ± std. dev.)	Gender	Baseline HAM-D (mean ± std. dev.)	Unilateral sessions (mean ± std. dev.)	Bilateral Sessions (mean ± std. dev.)	Total number of sessions
Partial responders: unilateral	4 (10.3%)	33.75 ± 9.11	2 F /2 M	15.71 ± 5.38	27.6 ± 13.59	32.75 ± 18.69	63.00 ± 19.71
Partial responders: bilateral	3 (7.9%)	51.49 ± 16.24	31 F	9.33 ± 4.04	22.0 ± 4.36	26 ± 16.46	48.0 ± 20.78
Responders: unilateral	1 (2.6%)	61.00	1 F	6.00	27.00	45.00	72.00
Responders: bilateral	9 (23.08%)	46.44 ± 15.95	6 F/ 3 M	14.49 ± 5.43	27.51 + 11.04	28.80 + 15.16	52.22 ± 17.13
Non-responders	22 (56.4%)	42.00 ± 16.24	12 F/10 M	14 .35 ± 5.38	27.51 ± 11.04	28.80 ±15.16	57.42 ± 17.04

	Unilateral left DLPFC TMS (n=24)	Unilateral right DLPFC TMS (n=15)	Comparisons between groups
Baseline HAM-D 17	16.33 ± 5.30	18.4 ± 6.10	p=0.269
% Change in HAM-D- unilateral sessions (mean ± std. dev)	-13.08 ± 23.47	-7.61 ± 27.59	p=0.156
% Change in HAM-D: bilateral sessions (mean ± std. dev)	4.14 ± 45.86	-27.56 ± 35.71	**p=0.0138**

Setting threshold for significance at 0.05/3 using the Bonferroni correction for multiple comparisons, tests comparing changes in HAM-D 17 scores between patients who initially received unilateral left DLPFC vs. unilateral right DLPFC showed there was a significantly **greater reduction in HAM-D 17 scores among patients moving from unilateral right DLPFC TMS to bilateral TMS. Baseline HAM-D 17 scores did not differ significantly between groups**.

CONCLUSIONS, LIMITATIONS, AND FUTURE DIRECTIONS

- Although these patients displayed inadequate response to TMS treatment within their course which lead to implementation of bilateral TMS treatments, our findings show a continued increased improvement in depression symptoms as a function of an increasing number of overall TMS sessions, as 7 patients (18.0%) met criteria for partial remission, and 10 (25.6%) met criteria for full response.
- n=22 (56.4%) of patients did not respond to treatment, even after moving from unilateral to bilateral TMS.
- These findings show that patients moving from unilateral right DLPFC TMS to bilateral TMS had a significantly greater reduction in HAM-D scores following the switch to bilateral TMS as compared to those initially receiving unilateral TMS to the left DLPFC. Further analysis into the potential factors influencing this result (e.g.- clinical characteristics of patients being selected for right DLPFC TMS) is warranted.
- Limitations of this analysis include a small sample size and an observational study design. Further research is needed to more thoroughly assess the clinical efficacy of moving from unilateral to bilateral treatment in cases of inadequate response to unilateral TMS. Additionally, future research should also investigate potential clinical predictors for individual response to bilateral TMS.

References

1. Camprodon, J. (2016). Transcranial Magnetic Stimulation. In *Psychiatric Neurotherapeutics* (Current Clinical Psychiatry, pp. 165-186). New York, NY: Springer New York.
2. Rizvi, S., & Khan, A. (2019). Use of Transcranial Magnetic Stimulation for Depression. *Curēus (Palo Alto, CA), 11*(5), E4736.