Strategies for replacing non-invasive brain stimulation sessions: recommendations for designing neurostimulation clinical trials

Abstract

Introduction: Despite the potential impact of missed visits on the outcomes of neuromodulation treatments, it is not clear how this issue has been addressed in clinical trials. Given this gap in the literature, we reviewed articles on non-invasive brain stimulation in participants with depression or chronic pain, and investigated how missed visits were handled.

Areas covered: We performed a search on PUBMED/MEDLINE using the keywords: "tDCS", "transcranial direct current stimulation", "transcranial magnetic stimulation¨, "depression", and "pain". We included studies with a minimum of five participants who were diagnosed with depression or chronic pain, who underwent a minimum of five tDCS or TMS sessions. A total of 181 studies matched our inclusion criteria, 112 on depression and 69 on chronic pain. Of these, only fifteen (8%) articles reported or had a protocol addressing missed visits. This review demonstrates that, in most of the trials, there is no reported plan to handle missed visits.

Expert commentary: Based on our findings and previous studies, we developed suggestions on how to handle missed visits in neuromodulation protocols. A maximum of 20% of missing sessions should be allowed before excluding a patient and these sessions should be replaced at the end of the stimulation period.

Keywords: missing session, missed visit, dosing, adherence, transcranial direct current stimulation, transcranial magnetic stimulation, depression, chronic pain.

Introduction

Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) use electrical or magnetic current to modulate neural excitability and brain plasticity [1]. These non-invasive brain stimulation techniques (NIBS) have been shown to improve depression's symptoms, pain, as well as motor and cognitive deficits [2–5]. From a clinical perspective, to achieve persisting behavioral effects, participants should attend multiple neurostimulation visits [6,7]. However, daily visits can be burdensome and might promote low adherence. This decreased adherence is costly, affect intervention's effectiveness, and biases the final potential positive results of an intervention [8–10]. Various strategies to improve adherence exist, yet there are very few established approaches once a neurostimulation visit is missed [8,9].

To study how missed neurostimulation visits are managed, we reviewed randomized clinical trials (RCT) that used tDCS and TMS to treat depression and chronic pain. We first selected depression and we wanted to confront our results with another condition to explore if the issue of missed visits was exclusive of depressive syndromes or may be generalized to other conditions. We selected these conditions since they are highly prevalent and commonly associated with poor adherence (*e.g. missed visits*) [11,12]. In addition, these disorders are frequently studied in neurostimulation trials which have shown promising results for symptom reduction (for reviews see [13–17]). Based on our findings, we proposed a strategy to handle these missed visits.

Methods

We searched PUBMED/MEDLINE for clinical trials published before 2017, using the keywords: “tDCS”, “transcranial direct current stimulation”, “transcranial magnetic stimulation¨, “depression”, and “pain”. Two different searches were performed to reduce the chances to exclude eligible articles. The exact highly sensitive search strategy [18], can be found in supplementary table 1.

Once the search was performed, we extracted the data and perform of first screening based on the titles and abstracts. Inclusion criteria were: i) Papers written in English; ii) A minimum of 5 tDCS or TMS sessions; iii) A sample size ≥5 participants; iv) Studies on depression or chronic pain. Exclusion criteria were: i) Case reports and case series; ii) Follow-up studies; iii) Observational studies; iv) Articles using the same sample but with different endpoints (only the first published trial was included); v) Animals studies.

For the articles that matched our inclusion and exclusion criteria, a full-text review was done and, if no further exclusion criteria were identified, a quantitative analysis of each article was performed.

This systematic review did not involve human subjects. We only reviewed published articles and data published in these articles. As reviews and meta-analyses do not involve human subjects, they do not require IRB review [19].

Results

3.1 Depression

In total, we extracted 1136 articles that used tDCS and TMS for the treatment of depression. Of these, 112 (fifteen on tDCS and ninety-seven on TMS) matched our

inclusion/exclusion criteria and were further quantitatively analyzed (Figure 1). After a systematic review of these 112 papers, 9 mentioned missed visits in their protocol. Details regarding each study protocol are reported in Tables 1 and 2.

Findings' summary

Three out of fifteen articles on tDCS reported the occurrence of missed neurostimulation visits [7,20]. Brunoni *et al*. (2013) defined participants who missed three or more consecutive neurostimulation visits out of 12 (25% of missed visits) as drop-outs [7]. These participants were excluded from statistical analyses. Not excluded from analysis were the 103 participants that completed the intervention, where 41 finished all sessions, 37 had one absence and 25 had two. In the other article, Brunoni *et al*. (2014) randomized 37 participants, and had 21 dropouts [20]. Even though the same dropout rule was used, the amount that dropped due to missed neurostimulation visit(s) was not specified. Vanderhasselt *et al.* (2015) used the same threshold of two consecutive missing sessions, in such cases extra tDCS sessions were performed to complete the total number of sessions [21]. The exact number of patients who missed one or more sessions was not reported. Concerning RCTs on TMS, five articles out of 97 detailed the possibility for patients to miss one or more sessions in their methodology and one article reported missed visits as a reason for dropout in the study flowchart. George *et al.* (2010) defined completers as patients having less than 4 rescheduled, missed or partially completed sessions, and fully adherent as patients having a maximum of 1 rescheduled, missed, or partially complete sessions (n=15 sessions) [23]. Out of 190 patients, 120 were fully adherent (63%) and 154 were considered as completers (81%). In another trial, George *et al.* (2014) defined true completers as patients receiving all treatment sessions with the entire number of pulses, even though this was

an inpatients study [24]. 27 out of 41 patients were considered as true completers (66%), 9 did not receive the full treatment (22%) and 5 dropped-out (12%). The authors found that the decline in suicidal thinking was more pronounced in the completers group. In another study by Leuchter *et al.* (2015), participants underwent 30 TMS sessions (5 per week for 6 weeks) [26]. A maximum of six missed neurostimulation visits was used to define dropout (20% of missed visits). Patients who did not complete 80% of the scheduled sessions were excluded from the analysis (67 out of 202 patients). They also demonstrated that participants needed to receive at least 80% of the rTMS doses (24 out of 30 sessions) to have a statistically significant antidepressant effect. However, neither the rational nor the numbers of dropouts were reported, and replacement of the missed neurostimulation visits was not detailed. Blumberger *et al.* (2012) allowed a maximum of 2 consecutive sessions to be missed or 4 for the entire protocol consisting of 15 sessions [25]. 30 out of 74 patients did not completed the 6-week protocol; the reasons for drop-outs were not detailed. The same team allowed up to 1 missed session per week (20%) and these sessions were replaced at the end of the protocol [26]. However, the proportion of patients who missed one or more sessions was not described. Finally, Levkovitz *et al.* (2015) reported in the study flowchart that two participants were excluded from the study after missing two sessions [27]. No further details were described.

3.2 Pain

Overall, we extracted 473 articles that studied neurostimulation for the treatment of chronic pain. From these 473 articles, 69 (35 on tDCS and 34 on TMS) matched our criteria and were systematically reviewed (Figure 2). After our quantitative analysis, we only identified 3

articles (4%) mentioning strategies to manage missed neurostimulation visits. The information regarding each study protocol is detailed in tables 3 and 4.

Findings' summary:

For tDCS, Auvichayapat *et al.* (2012) and Castillo-Saavedra *et al.* (2016) withdrew participants when they missed a single neurostimulation visit [28], while Fagerlund *et al*. (2015) withdrew only after two or more neurostimulation visits were missed [29]. These visits were never replaced.

Out of the 34 trials on TMS, only two of them mentioned management of *missed* neurostimulation visits. Ambriz-Tutut *et al*. (2016) removed a subject due to "poor compliance", however they do not explicitly describe their definition of adherence [30]. Malavera *et al*. (2016) excluded participants that missed one or more day(s) of stimulation [31].

Discussion

According to the Health World Organization, adherence is defined as, *"the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* [32], while no specific cut-off for good or poor adherence has been defined yet. Despite the apparent prevalence in clinical research, there is no established gold standard to manage missed visits.

Our analysis of 181 papers revealed that missed visits are widely underreported in NIBS RCTs on depression and chronic pain, since less than 10% of the trials (n=15) mentioned this issue. More precisely, in depression, 8% of the trials reported missed visits and most of them how they managed this issue, while for pain, only 4% of trial did report missed visit but did not

provide any further details on how to handle this problem. In studies detailing missing visits, the rate of patients who were not fully adherent is extremely high, ranging from 30 to 60%, reflecting the importance of taking this factor into account when designing a trial and when reporting the results.

Herein, we discuss the importance of missed visit(s) and provide recommendations regarding potential methods to deal with this issue based on the current literature of tDCS and TMS. To do this, we discussed the following questions: (i) When should missed visit(s) be considered a protocol violation and the participant excluded?; (ii) Should missed neurostimulation visit(s) be replaced at the end of the stimulation period?; (iii) When do missed neurostimulation visits bias results?

(i) When should (and if) missed visits be considered protocol violation and the participant excluded?

Although it is well-defined that multiple sessions of tDCS and TMS have cumulative effects, the impact of spaced sessions in abolishing, potentiating or having no effect still needs to be further clarified [16,33–35]. This was explored by Zanão *et al.* (2014), based on their previous trial [36] where some patients did not attend all visit [37]. They showed that missing one or two tDCS visits (out of 10) did not alter the treatment effectiveness [37]. Likewise, Leuchter *et al.* (2015), demonstrated that participants needed to receive at least 80% of the rTMS doses (24 out of 30 sessions) to have a statistically significant antidepressant effect [26]. In addition, George *et al.* (2014) reported that patients receiving the full treatment demonstrated higher improvement in their symptoms as compared to non-completers [24].

The results from Zanão et al (2014) and Leuchter et al (2015) reflect pharmacological trials' guidelines, in which poor adherence is frequently considered as less than 80% of medication taken correctly [38]. Regardless, there is no universally accepted definition of adequate adherence, despite its potential impact on treatment effectiveness [39]. For instance, if aspirin is taken once a month, it does not prevent myocardial infarction (3% adherence, 1/30 days), while, when it is taken once a week, it can help decreasing the incidence of myocardial infarction (14% adherence, 4/30 days). These properties are summarized in different models by Kravitz et al (2014). In linear and curvilinear models, the percent of benefit increases as adherence increases. In ON-OFF models, benefit is only achieved when adherence nears 100%. Finally, in threshold models, benefit is limited below a certain point and maximal above that point [40]. As such, minimum adherence expectations should reflect an intervention's properties and trials' objectives. Under the assumption that tDCS and TMS efficacy follows Kravitz´s models, guaranteeing that the participant receives a sufficient treatment dose to maximize the outcome is relevant [40–43]. Therefore, based on the reviewed literature, in these populations, and in NIBS trials with at least 5 or more stimulation visits, it seems reasonable to allow up to 20% of neurostimulation visits to be missed.

(ii) Should missed visit(s) be replaced at the end of the stimulation period?

Regarding the studies on tDCS in depression, missed neurostimulation visits were only replaced at the end of the treatment period in three trials [7,20,21]. In Brunoni *et al.* (2013), only about 40% of the participants received the full intervention as designed, while about 60% had at least one session replaced at the end of the treatment period [7]. Replacement of visits had no impact on the final results as long as the participants were adherent to 80% of the intervention.

To ensure treatment efficacy and that all participants received the same number of treatment sessions, it may be favorable to replace missed visits at the end of the designated stimulation period. In addition, the replacement sessions allow for a more flexible schedule, which could promote increased adherence and reduce the number of dropouts. In order to have a good balance between the flexibility required when working with participants with depression and chronic pain, and the mandatory rigor for RCTs, an additional interval (e.g. 1 week) could be included in the protocol to account for the replacement of missed visits at the end of the planned stimulations session.

To support this recommendation – replacing missing sessions at the end of the stimulation period – one of the trials included in this review compared the efficacy of rTMS when applied every day (5 days per week) for 4 weeks, with rTMS applied every other day (3 days per week) [44] for 6 weeks. After 4 weeks, participants in the daily treatment group, who had received 20 sessions, showed more improvement than participants in the spaced treatment group, who had received 12 sessions, showing the importance of the number of treatments sessions given to induce a significant clinical effect. However, at the end of the 6-week period, once the spaced treatment group had accrued the total 18 sessions, the outcomes were statistically comparable between the two groups (5 days per week vs 3 days per week). The results of this study reflect that spacing the treatments with one day intervals, had no effect on treatment efficacy if the entire number of sessions were provided, which support our recommendation to replace the missed visit at the end of the stimulation period.

In future RCTs, a comparison between the impact of replaced sessions versus non-replaced session on treatment effectiveness could be a valuable approach to understand this

dosing issue. Using the analysis of Leuchter et al (2015) as a model [26], researchers could compare data collected under per-protocol analysis, to intention to treat analysis and replaced session analysis. This would help to assess the impact of missed visits on clinical outcomes and to find cut-off points for poor adherence.

(iii) When do missed neurostimulation visits bias final results?

Many drug trials report on the effects of poor adherence with a negative impact on the outcomes. For instance, in a multicentric RCT including more than 1000 participants with coronary heart disease, the authors identified a significant difference in term of complications between participants with an adherence of more or less than 75% [45]. They reported that nonadherence (i.e., <75%) was associated with a greater rate of subsequent cardiovascular events, up to two times more than in participants with good adherence (i.e., >75%). In other trials, the threshold is slightly different (e.g., 80% [38]).

Based on the BCM – Bienenstock, Cooper, and Munro – and metaplasticity theories, it can be mentioned that the effects of long-term potentiation (LTP) and long-term depression (LTD) are limited and after a certain number of interventions no further neuroplastic changes are expected [46,47]. With neurostimulation, hyperactive neurons reduce input by increasing their thresholds (LTP to LTD) while hypoactive neurons do the opposite (LTD to LTP) [47]. This parallels pharmacologic dosing, and drug half-lives, and is a window into understanding dosing mechanisms in NIBS. Briefly, these physiological considerations may support the results seen in George *et al.* (2010), Brunoni et al (2013), Zanão et al (2014) and Leuchter et al (2015). For this reason, neurophysiological methods to assess the impact of missed neurostimulation visits are desirable.

Conclusion

In future RCTs using neurostimulation, it is important to detail both the timing of missed visit(s) and how this issue was handled when reporting the results. Concerning the impact of missed neuromodulation visits, it would be interesting to compare the results of participants who did not miss any visits versus participants who missed one, two or more visits, if the sample is large enough. This might help researchers and clinicians to understand how missed visits could affect the results and how many treatment sessions could be missed without impacting the outcome. Based on the current literature, allowing 20% of missed visits, while replacing these sessions at the end of the designated stimulation period, seems to be a valuable balance between the rigor requested by RCTs and the expected clinical translation. It also seems to be beneficial as a method to decrease results bias of this important question.

Our review shows that missed visits are an important issue that has not been adequately addressed in neurostimulation RCTs in depression and chronic pain. A better understanding of the impact of missed neurostimulation appointments is essential to avoid erroneous conclusions on its efficacy. This will help scientists and clinicians to understand the genuine impact of non-adherence and establish better strategies that optimize participants' engagement in their treatment.

Expert commentary: Missed visits are common in neurostimulation trials especially in populations with poor adherence such as depression and chronic pain. In the present review, we noticed that most RCTs did not report missed visits and less than 10% of the RCTs reviewed clearly stated how these missed visits were managed when they occurred. We proposed a plan to handle this issue by allowing up to 20% of appointments to be missed and replacing those visits

at the end of the designated stimulations period as successfully done in several RCTs [20,21,27,48]. This method seems to have an appropriate balance between the rigor required in RCT and the flexibility needed for patients with depression or chronic pain, or other conditions inclined to missed treatment visits. On the other hand, we have found evidence that 20% of missed neurostimulation visits may not impact the clinical results [37]. However, nothing is known about the possible impact on the long-term effects of this treatment since the neuroplastic strengthening would not have been as strong as if patients would have received daily stimulation sessions. Future RCTs assessing the effect of 20%, or more, of missed visit need to be conducted including long-term assessments (e.g., 6 months). In our opinion, the duration of the effects is another important point to take into account.

One current limitation of tDCS and TMS use is their unfeasibility to be applied at home, thus, requiring patients to go to laboratories or hospital every day to receive these treatments, which could increase the probability of missing sessions. Therefore, an option to improve adherence to neurostimulation treatments is the development of home-based devices.

We hope that this review will encourage researchers to develop plans to handle missed visits in their protocol and to clearly detail this issue when reporting the results. In addition, we expect that future RCTs comparing different proportions of missed visits on direct and long-lasting effects, will help to answer this critical question “how many missed neurostimulation visits will impact the clinical results?” It is essential to tackle this question to facilitate the clinical translation of neurostimulation treatments.

Five Year View

Within the next five years we believe that device trials will develop a clearer understanding of dose-response curves in relation to tDCS and TMS. We expect there to be a minimum and maximum tolerated doses tailored and required per condition. With the development of clinical trials aiming to investigate NIBS dose-response, we will be able to predict the effects of not attending a neurostimulation visit. This will change the interpretation of attrition on outcomes, and statistical methods to handle missing data. It will also create new strategies for administering NIBS and offer new protocol designs options (e.g., allowing one or more missed visit) that might be closer to what is feasible in clinical practice.

Key issues:

- Missed neurostimulation visits occur in non-invasive brain stimulation clinical research.
- There is no standardized method for dealing with missed neurostimulation visits. Some trials exclude the participants immediately, others allow for a predetermined amount of absentee to occur.
- We have found published evidence that 20% of missed neurostimulation visits may be an allowable quantity of absentee, to maintain effects of NIBS.
- However, the long-term effects of missed visits is yet to be determined, and therefore it can be better to replace the missed neurostimulation visit at the end of the neurostimulation period to ensure that all participants receive the same dose of NIBS in a clinical trial.

Disclosure

The authors have no disclosure to report.

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Figures:

Figure 1: Flow chart for missed visits in depression.

Figure 2: Flow chart for missed visits in chronic pain.

References

1. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat. Neurosci.* [Internet]. 16(May 2016), 838–44 (2013). Available from: http://www.nature.com.login.ezproxy.library.ualberta.ca/neuro/journal/v16/n7/abs/nn.3422.html.

2. Nitsche MA, Cohen LG, Wassermann EM, *et al.* Transcranial direct current stimulation: State of the art 2008. *Brain Stimul* [Internet]. 1(3), 206–223 (2008). Available from: http://www.ncbi.nlm.nih.gov/pubmed/20633386.

3. Boggio PS, Rigonatti SP, Ribeiro RB, *et al.* A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *Int J Neuropsychopharmacol* [Internet]. 11(2), 249–254 (2008). Available from: http://www.ncbi.nlm.nih.gov/pubmed/17559710.

4. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. *Bipolar Disord* [Internet]. 8(2), 203–204 (2006). Available from: http://www.ncbi.nlm.nih.gov/pubmed/16542193.

5. Shiozawa P, Fregni F, Benseñor IM, *et al.* Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int. J. Neuropsychopharmacol.* [Internet]. 17(9), 1443–52 (2014). Available from: http://www.ncbi.nlm.nih.gov/pubmed/24713139.

6. Castillo-Saavedra L, Gebodh N, Bikson M, *et al.* Clinically Effective Treatment of Fibromyalgia Pain With High-Definition Transcranial Direct Current Stimulation: Phase II Open-Label Dose Optimization. *J. Pain* [Internet]. 17(1), 14–26 (2016). Available from: http://www.ncbi.nlm.nih.gov/pubmed/26456677.

7. Brunoni AR, Valiengo L, Baccaro A, *et al.* The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA psychiatry* [Internet]. 70(4), 383–91 (2013). Available from: http://www.ncbi.nlm.nih.gov/pubmed/23389323.

8. Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance, compliance, and compliance. *Mol. Interv.* 11(2), 107–10 (2011).

9. Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. *N. Engl. J. Med.* 301(26), 1410–1412 (1979).

10. Nüesch E, Trelle S, Reichenbach S, *et al.* The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *BMJ*. 339, b3244 (2009).

11. Kim Y. Missing data handling in chronic pain trials. *J. Biopharm. Stat.* 21(2), 311–25

(2011).

12. Hung C-I. Factors predicting adherence to antidepressant treatment. *Curr. Opin. Psychiatry* [Internet]. 27(5), 344–349 (2014). Available from: http://www.ncbi.nlm.nih.gov/pubmed/25033275.

13. Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. *Brain Stimul.* 9(3), 336–346 (2016).

14. George MS. Transcranial magnetic stimulation for the treatment of depression. *Expert Rev. Neurother.* 10(11), 1761–1772 (2010).

15. Klein MM, Treister R, Raij T, *et al.* Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. *Pain* [Internet]. 156(9), 1601–14 (2015). Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4545735&tool=pmcentrez&rendertype=abstract%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/25919472%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4545735.

16. Lefaucheur J. Cortical neurostimulation for neuropathic pain : state of the art and perspectives. 157(2) (2016).

17. Brunoni AR, Moffa AH, Fregni F, *et al.* Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br. J. Psychiatry*. (2016).

18. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: *The Cochrane Collaboration*. , Table 7.7.a: Formulae for combining groups (2011).

19. Sullivan GM. IRB 101. *J Gr. Med Educ*. 3(1), 5–6 (2011).

20. Brunoni AR, Boggio PS, De Raedt R, *et al.* Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *J. Affect. Disord.* [Internet]. 162, 43–9 (2014). Available from: http://www.ncbi.nlm.nih.gov/pubmed/24767004.

21. Vanderhasselt MA, De Raedt R, Namur V, *et al.* Transcranial electric stimulation and neurocognitive training in clinically depressed patients: A pilot study of the effects on rumination. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*. 57, 93–99 (2015).

22. Levkovitz Y, Harel E V., Roth Y, *et al.* Deep transcranial magnetic stimulation over the prefrontal cortex: Evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul.* 2(4), 188–200 (2009).

23. George MS, Lisanby SH, Avery D, *et al.* Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch. Gen. Psychiatry* [Internet]. 67(5), 507–16 (2010). Available from: http://www.ncbi.nlm.nih.gov/pubmed/20439832.

24. George MS, Raman R, Benedek DM, *et al.* A two-site pilot randomized 3 day trial of high

dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. *Brain Stimul.* 7(3), 421–431 (2014).

25. Blumberger DM, Mulsant BH, Fitzgerald PB, *et al.* A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J. Biol. Psychiatry*. 13(March 2011), 423–435 (2012).

26. Leuchter AF, Cook IA, Feifel D, *et al.* Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression. *Brain Stimul.* [Internet]. 8(4), 787–94 (2015). Available from: http://www.ncbi.nlm.nih.gov/pubmed/26143022.

27. Blumberger DM, Maller JJ, Thomson L, *et al.* Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatmentresistant depression: A randomized controlled study. *J. Psychiatry Neurosci.* 41(4), E58–E66 (2016).

28. Auvichayapat P, Janyacharoen T, Rotenberg A, *et al.* Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. *J. Med. Assoc. Thai.* 95(8), 1003–1012 (2012).

29. Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. *Pain* [Internet]. 156(1), 62–71 (2015). Available from: http://www.ncbi.nlm.nih.gov/pubmed/25599302.

30. Ambriz-Tututi M, Alvarado-Reynoso B, Drucker-Colin R. Analgesic effect of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic low back pain. *Bioelectromagnetics*. (2016).

31. Malavera A, Silva FA, Fregni F, Carrillo S, Garcia RG. Repetitive Transcranial Magnetic Stimulation for Phantom Limb Pain in Land Mine Victims: A Double-Blinded, Randomized, Sham-Controlled Trial. *J. Pain* [Internet]. 17(8), 911–8 (2016). Available from: http://www.ncbi.nlm.nih.gov/pubmed/27260638%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4969102.

32. World Health Organization. Adherence to Long-Term Therapies - Evidence for Action [Internet]. (2003). Available from: http://apps.who.int/medicinedocs/en/d/Js4883e/8.3.html.

33. Zan??o TA, Moffa AH, Shiozawa P, Lotufo PA, Bense??or IM, Brunoni AR. Impact of two or less missing treatment sessions on tDCS clinical efficacy: Results from a factorial, randomized, controlled trial in major depression. *Neuromodulation*. 17(8), 737–742 (2014).

34. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK. Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimul.* 5(3), 208–213 (2012).

35. Monte-Silva K, Kuo M-F, Liebetanz D, Paulus W, Nitsche M a. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). *J.*

Neurophysiol. 103(4), 1735–1740 (2010).

36. Brunoni AR, Valiengo L, Baccaro A, *et al.* The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* [Internet]. 70(4), 383–391 (2013). Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23389323&retmode=ref&cmd=prlinks%5Cnhttp://archpsyc.jamanetwork.com/data/Journals/PSYCH/926737/yoa120059_383_391.pdf.

37. Zanão TA, Moffa AH, Shiozawa P, Lotufo PA, Benseñor IM, Brunoni AR. Impact of two or less missing treatment sessions on tDCS clinical efficacy: results from a factorial, randomized, controlled trial in major depression. *Neuromodulation* [Internet]. 17(8), 737–42; discussion 742 (2014). Available from: http://www.ncbi.nlm.nih.gov/pubmed/24725075.

38. Dunlay SM, Eveleth JM, Shah ND, McNallan SM, Roger VL. Medication adherence among community-dwelling patients with heart failure. *Mayo Clin. Proc.* [Internet]. 86(4), 273–81 (2011). Available from: http://www.sciencedirect.com/science/article/pii/S0025619611600037.

39. Lars Osterberg, M.D., and Terrence Blaschke MD. Adherence to medication. *N. Engl. J. Med.* 353, 487–497 (2005).

40. L KR, Joy M. Medical Adherence Research: Time for a Change in Direction? *Med care*. 42(3), 197–9 (2004).

41. Monte-Silva K, Kuo MF, Hessenthaler S, *et al.* Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul.* 6(3), 424–432 (2013).

42. Rushmore RJ, Desimone C, Valero-Cabré A. Multiple sessions of transcranial direct current stimulation to the intact hemisphere improves visual function after unilateral ablation of visual cortex. *Eur. J. Neurosci.* 38(12), 3799–3807 (2013).

43. Nitsche MA, Cohen LG, Wassermann EM, *et al.* Transcranial direct current stimulation: State of the art 2008. *Brain Stimul* [Internet]. 1(3), 206–223 (2008). Available from: http://www.ncbi.nlm.nih.gov/pubmed/20633386.

44. Galletly C, Gill S, Clarke P, Burton C, Fitzgerald PB. A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/ week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? *Psychol. Med.* 42(5) (2011).

45. Gehi AK. Self-reported Medication Adherence and Cardiovascular Events in Patients With Stable Coronary Heart Disease<subtitle>The Heart and Soul Study</subtitle> *Arch. Intern. Med.* [Internet]. 167(16), 1798 (2007). Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.167.16.1798.

46. Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J. Neurosci.* 2(1), 32–48 (1982).

47. Cooper LN, Bear MF. The BCM theory of synapse modification at 30: interaction of theory with experiment. *Nat. Rev. Neurosci.* 13(11), 798–810 (2012).

48. Brunoni AR, Valiengo L, Baccaro A, *et al.* The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study. *JAMA Psychiatry*. 70(4), 383 (2013).