Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Non-invasive brain stimulation for negative symptoms in schizophrenia: An updated systematic review and meta-analysis

Caio Osoegawa [a], July Silveira Gomes [a,b], Ruth Bartelli Grigolon [a], Elisa Brietzke [a,c,d], Ary Gadelha [a,b], Acioly L.T. Lacerda [a,e], Álvaro Machado Dias [a], Quirino Cordeiro [a], Ronaldo Laranjeira [a], Danilo de Jesus [d], Zafiris Jeff Daskalakis [d], Jerome Brunelin [f], Joachim Cordes [g], Alisson Paulino Trevizol [c,d,*]

[a] Federal University of São Paulo, Brazil
[b] Schizophrenia Program, Federal University of São Paulo (PROESQ), Brazil
[c] Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Canada
[d] University of Toronto, Canada
[e] Center for Research and Clinical Trials Sinapse-Bairral, Instituto Bairral de Psiquiatria, Brazil
[f] Lyon Neuroscience Research Center, Lyon 1 University, Lyon, France
[g] Department of Psychiatry and Psychotherapy, Heinrich-Heine University of Düsseldorf, Germany

ARTICLE INFO

Article history:
Received 27 September 2017
Received in revised form 17 January 2018
Accepted 17 January 2018
Available online xxxx

Keywords:
Meta-analysis
Schizophrenia
Transcranial magnetic stimulation
Transcranial direct current stimulation
Non-pharmacological therapies
Systematic review

ABSTRACT

Background: Schizophrenia is a mental disorder with significant socioeconomic burden. Although current pharmacological treatments are effective for treating positive symptoms, medications have little-to-no effect in the treatment of negative symptoms.
Objective: To assess the efficacy of non-invasive brain stimulation (NIBS) for negative symptoms in schizophrenia in randomized clinical trials (RCTs).
Methods: A systematic review in Medline and Cochrane Library databases was performed up to May 31, 2017. The primary outcome was Hedges' *g* for continuous scores in a random-effects model. Heterogeneity was evaluated with the I^2 and χ^2 tests. Publication bias was assessed using Begg's funnel plot.
Results: 31 RCTs ($n = 1272$) were included, most with small-to-modest sample sizes. Both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) were superior to sham (Hedges' $g = 0.19$; 95% CI 0.07–0.32; and 0.5; 0.02–0.97, respectively). Only one study evaluated the use of transcutaneous auricular vagus nerve stimulation (taVNS). The funnel plot and Eggers test showed that the risk of publication bias was low. In relation to heterogeneity, we found an I^2 of 0% ($p = 0.749$) and 51.3% (0.055) for rTMS and tDCS, respectively.
Conclusion: Both rTMS and tDCS were superior to sham stimulation for ameliorating negative symptoms in schizophrenia. We found no considerable heterogeneity or publication bias in our analysis, corroborating the strength of our findings. Not enough studies on other NIBS techniques, such as taVNS, were found for an isolated analysis. Further RCTs with larger sample sizes are needed to clarify the specific impact of NIBS on negative symptoms in schizophrenia.

1. Introduction

Negative symptoms in schizophrenia consist of affective flattening, anhedonia, alogia, asociality, and avolition. These symptoms are the main predictors of functional outcomes resulting in poorer social and occupational functioning, in particular for patients with a young age of onset of the disorder (Immonen et al., 2017). Antipsychotic pharmacological treatment has evolved in the last five decades, resulting in significant control over positive symptoms but yielding small to no effective results for negative symptoms (Green and Harvey, 2014; Kahn and Keefe, 2013; Robinson et al., 2015). Non-invasive brain stimulation (NIBS) techniques include repetitive transcranial magnetic stimulation (rTMS) (Farzan et al., 2012; Rabany et al., 2014), transcranial direct current stimulation (tDCS) (Gomes et al., 2015), trigeminal nerve stimulation (TNS) (Trevizol et al., 2016b), transcutaneous vagus nerve stimulation (tVNS) (Trevizol et al., 2016d), deep transcranial magnetic stimulation (dTMS), and transcranial alternating current stimulation (tACS).

Developments in functional neuroimaging and biomarkers have resulted in better understanding of the cortical and subcortical areas

* Corresponding author at: Mood Disorders Psychopharmacology Unit, University Health Network, 399 Bathurst St, 9th Floor, Room 325, Toronto, ON M5T 2S8, Canada.
E-mail address: alisson.trevizol@mail.utoronto.ca (A.P. Trevizol).

https://doi.org/10.1016/j.schres.2018.01.010
0920-9964/

involved in the pathophysiology of the negative symptoms of schizophrenia. The idea of modulating such dysfunctional areas in a more controlled, focused way, in contrast to electroconvulsive therapy (ECT), enabled the rise of NIBS in the last decades. Both rTMS and tDCS have proved efficacious for neuroplasticity enhancement, boosting treatment response for refractory symptoms in different neurological and psychiatric disorders (Fusar-Poli et al., 2015; Brunoni et al., 2017). Although promising results have been previously reported for the effects of rTMS and tDCS on negative symptoms in schizophrenia (Shi et al., 2014), they are still controversial (Fusar-Poli et al., 2015). With the purpose of reviewing all randomized controlled trials of NIBS for negative symptoms in schizophrenia, we conducted a systematic review and meta-analysis. We hypothesized that active NIBS is superior to sham NIBS for the treatment of negative symptoms in schizophrenia.

2. Materials and methods

The systematic review was performed following the PRISMA guidelines (Moher et al., 2009). Two authors (CO and JG) performed independent selections of the articles, without knowing what choice one or the other had, using the Rayyan platform (Ouzzani et al., 2016). The open access to independent selection was conducted after data extraction, and consensus resolved any discrepancy. The present systematic review and meta-analysis is registered at the International Prospective Register of Ongoing Systematic Reviews (systematic review registration – PROSPERO 2017: CRD42017064238).

2.1. Literature review

We reviewed the following references and databases:

(a) MEDLINE and Cochrane Library using the following keywords: (1) "Schizophrenia Spectrum and Other Psychotic Disorders"; (2) "Schizophrenia, Paranoid"; (3) "Schizophrenia, Disorganized"; (4) "Schizophrenia, Catatonic"; (5) "Schizophrenia, Childhood"; (6) "Schizotypal Personality Disorder"; (7) "transcranial direct current stimulation"; (8) "transcranial magnetic stimulation"; (9) "tDCS"; (10) "rTMS"; (11) "VNS"; (12) "vagus nerve stimulation"; (13) "transcranial vagus nerve stimulation"; (14) "taVNS"; (15) "trigeminal nerve stimulation"; (16) "TNS"; (17) repetitive transcranial magnetic stimulation (19) "brain stimulation"; (20) "non-invasive brain stimulation"; (21) "NIBS"; (22) "tACS"; (23) "rTMS." The following Boolean terms were imputed: [(1) OR (2) OR (3) OR (4) OR (5) OR (6)] AND [(7) OR (8) OR (9) OR (11) OR (12) OR (13) OR (14) OR (15) OR (16) OR (17) OR (18) OR (19) OR (20) OR (21) OR (22) OR (23)]. We searched for studies listed in MEDLINE and Cochrane Library up to April 30, 2017.

(b) Study references in retrieved articles and reviews, particularly those included in the meta-analyses by Fusar-Poli et al. (2015) and by Shi et al. (2014).

2.2. Eligibility criteria

(1) Method of randomization specified in the manuscript; (2) use of a validated method of blinding for the studied NIBS technique; (3) provided data (on the manuscript or upon request) for the estimation of the outcomes, i.e., mean and standard deviation (SD) values. We excluded case reports and series of cases, non-controlled trials, and trials assessing conditions other than schizophrenia or interventions other than rTMS, tDCS, TNS, transcutaneous vagus nerve stimulation (tVNS), deep transcranial magnetic stimulation (dTMS), and transcranial alternating current stimulation (tACS). We didn't exclude articles based on language.

2.3. Data extraction

We extracted the following variables in accordance with a structured checklist previously elaborated by the authors: (1) metadata (authorship, year of study, etc.); (2) demographics (sample size, age, gender); (3) disorder characteristics (positive and negative syndrome scale (PANSS), brief psychiatric rating scale (BPRS), and the scale for assessment of negative symptoms (SANS); use of medication; psychometric scales, interviews, and checklists used for diagnosis and evaluation of schizophrenia symptoms); (4) characteristics of the NIBS techniques (cortical region targeted, frequency, motor threshold, duration of stimulation, train and inter-train intervals, number of sessions, side of brain, number of electrodes, intensity); (5) research methods (randomization protocol, sham technique, blinding assessment).

Although categorical outcomes might be more readily interpretable than continuous variables, we chose to analyze the primary outcome as continuous, based on the scores of the negative symptoms assessments from the PANSS, BPRS and SANS. We considered that a continuous effect size better synthesized the included studies and enabled more information, which would otherwise be lost in a categorical analysis, to be used for interpretation. To maintain homogeneity and to avoid data overlapping, we prioritized the use of the scores from the PANSS. In case it was not available, scores from other scales were used.

2.4. Quality assessment

We assessed the methodological quality of each trial by evaluating (1) methods of randomization – whether the study was randomized, and whether the authors reported the randomization method; (2) how blinding and sham NIBS were performed; (3) whether the authors reported an account of all patients; and (4) whether the authors reported the stability of psychotropic medications or medication changes in and around the period of NIBS, which could be a potential confounding factor for the outcome of improvement of negative symptoms. The Jadad scale was used for the quality assessment (JPT and A., 2008; Jadad et al., 1996).

2.5. Quantitative analysis

2.5.1. Primary outcome

All analyses were performed using the statistical packages for meta-analysis of Stata 13.1 for Mac OS X. For the primary outcome (negative symptoms), we initially calculated the standardized mean difference and the pooled standard deviation for each comparison. This procedure is convenient, since it standardizes the effect sizes across all studies based on the standard deviation of each study, enabling comparisons among different measurement instruments. In the studies conducted by Cordes et al. (2010) and Gomes et al. (2015), additional data were provided by the authors upon request. In the studies conducted by Rabany et al. (2014) and Rosenberg et al. (2012), data were extracted graphically using graph digitizer software (GetData Graph Digitizer). Three clinical trials performed by Brunelin and collaborators fit the inclusion criteria of our review (Brunelin et al., 2012; Mondino et al., 2015, 2016). Due to partial overlap in the samples from these three studies, data from the 44 subjects that were included in all three trials were requested and made available by Brunelin and collaborators, and they were grouped as one study in our analysis. Moreover, the studies conducted by Jin et al. (2005) and Zheng et al. (2012) were factorial, and the studies carried out by Jin et al. (2012), Fitzgerald et al. (2014), and Bais et al. (2014) were triple-arm. In both types of study design, each group was included as one independent study in comparison to sham, so the study will appear more than once in the graphs and tables, with particular labels.

2.5.2. Quantitative assessment of heterogeneity and bias

Heterogeneity was evaluated using the I^2 and χ^2 tests, following the recommendations from the Cochrane Handbook. We considered $p < 0.10$ for heterogeneity per the Cochrane Handbook. Publication bias was assessed utilizing Egger's test and the funnel plot, which displays confidence interval boundaries to assist publication bias through

Please cite this article as: Osoegawa, C., et al., Non-invasive brain stimulation for negative symptoms in schizophrenia: An updated systematic review and meta-analysis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.01.010