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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

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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.

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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).

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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

the visualization of the distribution of the studies in the limits of the funnel (e.g., whether studies are distributed symmetrically and fall within the funnel margins). We also evaluated the impact of each study in the overall results by excluding one study at a time (sensitivity analysis).

2.6. Meta-regression

Meta-regression was performed utilizing the random-effects model modified by Knapp and Hartung (2003) (Knapp and Hartung, 2003) using only one of the following variables at a time: (1) technique (rTMS, tDCS, other), (2) brain region modulated, (3) age, (4) blinding, (5) baseline scores, (6) duration of stimulation (in weeks), (7) number of sessions, (8) duration of the illness, and (9) scale used to evaluate negative symptoms. The protocol characteristics of rTMS and tDCS were assessed separately to try to determine a better protocol for future studies.

2.7. Safety evaluation

We used patients' dropouts for safety assessment (odds ratio).

3. Results

3.1. Overview

Our systematic review yielded 440 studies after duplicates were removed. In an initial eligibility evaluation, we excluded 366 articles (Fig. 1). In a more detailed subsequent analysis, we excluded 43 that did not meet our eligibility criteria for full-text evaluation. In the end, 31 studies, from 1999 to 2017, complied with inclusion criteria and were selected for the quantitative analysis (total of 1272 subjects) (Fig. 1). From the included studies, 24 focused on rTMS, including iTBS (Bais et al., 2014; Barr et al., 2012; Cordes et al., 2010; de Jesus et al., 2011; Dlabac-de Lange et al., 2014; Fitzgerald et al., 2008; Gan et al., 2015; Hajak et al., 2004; Holi et al., 2004; Jin et al., 2005; Klein et al., 1999; Li et al., 2016; Mogg et al., 2007; Novak et al., 2006; Prikryl et al., 2013; Quan et al., 2015; Rabany et al., 2014; Rosa et al., 2007; Rosenberg et al., 2012; Saba et al., 2006; Wobrock et al., 2015; Wölwer et al., 2014; Zheng et al., 2012). From these, two studies used deep rTMS and were included in the rTMS subgroup for the analysis of effect size. The impact of including the dTMS research in the rTMS subgroup was evaluated through meta-regression. Seven studies focused on tDCS (Brunelin et al., 2012; Fröhlich et al., 2016; Fitzgerald et al., 2014; Hoy et al., 2014; Palm et al., 2016; Smith et al., 2015; Gomes et

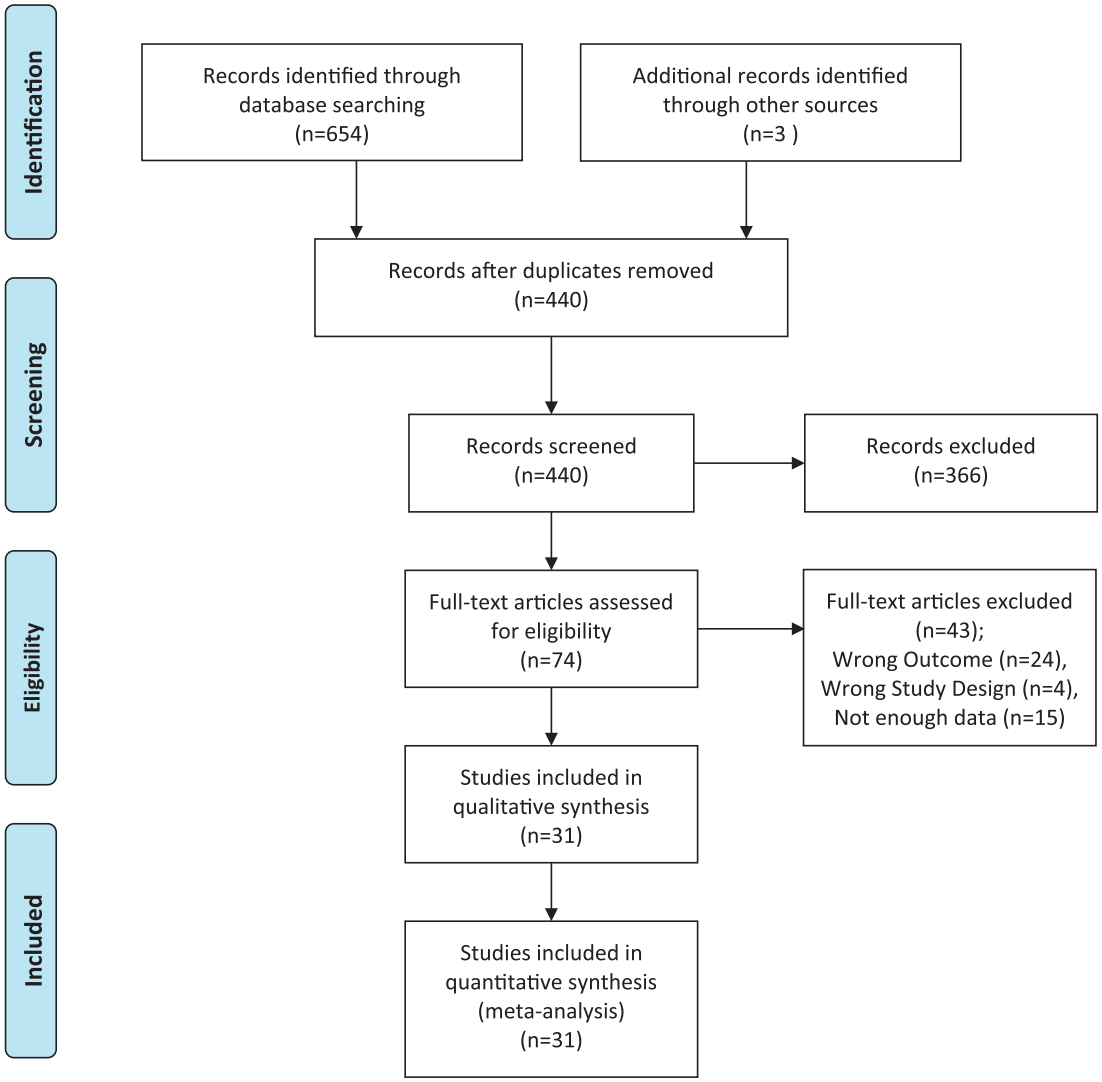

Fig. 1. PRISMA flow diagram.

al., 2015), and one on tVNS (Hasan et al., 2015). No included studies evaluated the effects of TNS, DBS, tACS, or VNS.

Studies' sample sizes ranged from 11 to 157 subjects, with mean ages of 38.8 years (SD = 7.27) and 39.93 years (SD = 7.75) for the sham and active groups, respectively (Table 1).

Quality assessment revealed that all studies were properly randomized and sham-controlled, with patient and evaluator blinded. Also, all studies scored at least 4 in the Jadad scale (ranging from 0 to 5) (Moher et al., 1996). Sham rTMS was performed in four different ways: (1) with a sham coil that produced an acoustic artifact and scalp sensation similar to the real stimulation (Bais et al., 2014; Hajak et al., 2004; Jin et al., 2012; Li et al., 2016; Mogg et al., 2007; Prikryl et al., 2013; Rosenberg et al., 2012; Saba et al., 2006; Wobrock et al., 2015); (2) with the coil held 90° vertically to the scalp (minimal magnetic field was induced, producing an auditory artifact) (Barr et al., 2012; Dlabac-de Lange et al., 2014; Fitzgerald et al., 2008; Gan et al., 2015; Holi et al., 2004; Klein et al., 1999; Quan et al., 2015; Zheng et al., 2012); (3) with the coil placed at a 45-degree angle to the scalp, delivering the current to the face and scalp (de Jesus et al., 2011; Rabany et al., 2014; Wobrock et al., 2015); and (4) with a deactivated coil (Cordes et al., 2010; Hasan et al., 2015; Jin et al., 2005; Rosa et al., 2007). All Sham tDCS protocols were performed in similar ways, with reduced real stimulation time (Brunelin et al., 2012; Fitzgerald et al., 2014; Fröhlich et al., 2016; Palm et al., 2016; Smith et al., 2015). Please refer to Table 2 for the protocols of stimulation adopted for each study.

Regarding the scales used, 83.9% of the studies used the PANSS (Table 1) to evaluate negative symptoms (Bais et al., 2014; Barr et al., 2012; Brunelin et al., 2012; Cordes et al., 2010; Dlabac-de Lange et al., 2014; Fitzgerald et al., 2008; Fitzgerald et al., 2014; Fröhlich et al., 2016; Gan et al., 2015; Hajak et al., 2004; Holi et al., 2004; Jin et al., 2005, 2012; Klein et al., 1999; Mogg et al., 2007; Novak et al., 2006; Palm et al., 2016; Quan et al., 2015; Rosa et al., 2007; Saba et al., 2006; Wobrock et al., 2015; Wölwer et al., 2014; Zheng et al., 2012), 12.9% used the SANS (Li et al., 2016; Prikryl et al., 2013; Rabany et al., 2014; Rosenberg et al., 2012), and one study (3.2%) used the BPRS(de Jesus et al., 2011).

3.2. Primary outcome

We calculated the effect size for the endpoint. We found that 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, considered small and medium-sized effect sizes as per the Cochrane guidelines, respectively), but active taVNS was not (Hedges' $g = 0.44$; 95% CI -0.53–1.41) (Fig. 2).

Table 1
Characteristics of the included studies.

TMS studies characteristics					Active TMS			Sham TMS		
Author	Study design	Scale	Primary outcome	Jadad scale	N	Fem (N)	Mean age (y)	N	Fem (N)	Mean age (y)
Klein et al., 1999	Parallel	PANSS	SO	5	18	7	30.2	17	6	29.5
Hajak et al., 2004	Parallel	PANSS	SO	5	10	2	37.9	10	4	41.7
Holi et al., 2004	Parallel	PANSS	SO	5	11	NA	38.5	11	NA	34.8
Jin et al., 2005 3 Hz	Factorial	PANSS	PO	5	9	NA	NA	8	NA	NA
Jin et al., 2005 Alpha	Factorial	PANSS	PO	5	9	NA	NA	8	NA	NA
Jin et al., 2005 20 Hz	Factorial	PANSS	PO	5	11	NA	NA	8	NA	NA
Novak et al., 2006	Parallel	PANSS	PO	5	8	1	35.3	8	3	32.8
Saba et al., 2006	Parallel	PANSS	SO	5	9	NA	30.7	9	NA	30.6
Mogg et al., 2007	Parallel	PANSS	PO	5	8	1	50.8	9	0	33.6
Rosa et al., 2007	Parallel	PANSS	SO	5	6	2	29.8	5	3	33
Fitzgerald et al., 2008	Parallel	PANSS	PO	5	12	2	37.2	8	2	33.2
Cordes et al., 2010	Parallel	PANSS	SO	5	20	4	34.3	15	3	34.4
de Jesus et al., 2011	Parallel	BPRS	SO	5	8	3	46	9	2	36.5
Barr et al., 2012	Parallel	PANSS	PO	5	13	6	40.4	12	2	47.9
Jin et al., 2012 Frontal	Factorial	PANSS	SO	4	16	NA	NA	26	NA	NA
Jin et al., 2012 Parietal	Factorial	PANSS	SO	4	16	NA	NA	26	NA	NA
Rosenberg et al., 2012	Parallel	SANS	SO	5	9	2	40.8	9	1	38.4
Zheng et al., 2012 iTBS	Factorial	PANSS	SO	4	19	NA	56.5	17	NA	55.6
Zheng et al., 2012 10 Hz	Factorial	PANSS	SO	4	19	NA	56.8	17	NA	55.6
Zheng et al., 2012 20 Hz	Factorial	PANSS	SO	4	18	NA	56.4	17	NA	55.6
Prikryl et al., 2013	Parallel	SANS	PO	5	23	NA	31.6	17	NA	33.9
Bais et al., 2014 Left	Factorial	PANSS	SO	4	15	7	33.9	16	6	37.3
Bais et al., 2014 Bilateral	Factorial	PANSS	SO	4	16	7	37.2	16	6	37.3
Dlabac-de Lange et al., 2014	Parallel	PANSS	PO	4	16	2	32.3	16	4	41.8
Rabany et al., 2014	Parallel	SANS	PO	2	20	7	33.1	10	2	35.9
Wölwer et al., 2014	Parallel	PANSS	SO	3	18	4	34.3	14	3	34.4
Quan et al., 2015	Parallel	PANSS	PO	5	78	34	46.8	39	11	46.8
Wobrock et al., 2015	Parallel	PANSS	PO	5	76	14	36.2	81	25	34.9
Gan et al., 2015	Parallel	PANSS	PO	4	33	NA	NA	37	NA	NA
Li et al., 2016	Parallel	SANS	PO	4	25	13	45.2	22	11	44.9

Study characteristics					Active tDCS			Sham tDCS		
Author	Study design	Scale	Neg. symptoms		N	Fem (N)	Mean age (y)	N	Fem (N)	Mean age (y)
Brunelin et al., 2012	Parallel	PANSS	SO	5	23	3	40.4	21	5	35.1
Fitzgerald et al., 2014 Bilateral	Factorial	PANSS	SO	5	6	NA	NA	5	6	NA
Fitzgerald et al., 2014 Unilateral	Factorial	PANSS	SO	5	7	NA	NA	6	7	NA
Smith et al., 2015	Parallel	PANSS	SO	5	17	3	46.7	16	6	44.8
Palm et al., 2016	Parallel	PANSS	PO	5	10	5	38.4	10	0	34.1
Fröhlich et al., 2016	Parallel	PANSS	SO	5	13	4	43.3	13	2	40
Gomes et al., 2015	Parallel	PANSS	SO	5	12	2	39.17	10	3	36.5

N = number of subjects in each condition; PO = primary outcome; SO = secondary outcome; NA = not available; PANS: positive and negative syndrome scale; SANS: scale for the assessment of negative symptoms; BPRS: brief psychiatric rating scale;

3.3. Quantitative assessment of heterogeneity and bias

In general, heterogeneity was low and not significant for NIBS (I^2 = 2.3%, p = 0.429) and rTMS (I^2 = 0%, p = 0.749). For tDCS, we observed an I^2 of 51.3% (p = 0.055). An I^2 of 30% to 60% may represent moderate heterogeneity, even though we the p-value is considered non-significant using the conventional level of 0.05. For all the NIBS techniques included, the funnel plot shows that the studies were evenly and symmetrically distributed throughout the funnel, with no studies located out of the funnel margins (Fig. 3). The Egger's test was not significant (p = 0.179), corroborating the small risk of publication bias observed in the funnel plot. Similarly, the funnel plots for rTMS and tDCS showed a low risk of publication bias, with the Egger's test having p = 0.8 and p = 0.392, respectively (Fig. 3). The sensitivity analysis demonstrated that, when excluding one study at a time, the significant difference is maintained for the overall and the rTMS studies' results (Fig. 4-A and -B). Therefore, no particular study could be driving the results of our analysis overall or for rTMS. However, the sensitivity analysis for the tDCS subgroup showed that the exclusion of the studies with higher effect sizes, one at a time, resulted in the loss of the significance of the superiority of active tDCS over sham tDCS (Fig. 4-C). Although this finding reduces the robustness of the difference between active tDCS and sham tDCS, the results are still positive, and the superiority of the technique is, with the currently available data, significant.

Table 2
Protocols of stimulation of the included studies.

TMS parameters

Author	Brain cortex	Stimulation or inhibition	F (Hz)	Pulses per session	Total of pulses	Number of sessions	Duration of sessions (s)	Weeks	Blinding
Klein et al., 1999	Right PFC	Inhibition	1	120	1200	10	480	2	90°
Hajak et al., 2004	Left DLPFC	Stimulation	10	1000	10,000	10	NA	2	Similar accoustic and scalp sensation effect
Holi et al., 2004	Left DLPFC	Stimulation	10	1000	10,000	10	700	2	90°
Jin et al., 2005 A	Bilateral DLPFC	NA	3	120	1200	10	1200	2	Deactived coil
Jin et al., 2005 B	Bilateral DLPFC	NA	Alpha	320–520	3200–5200	10	1200	2	Deactived coil
Jin et al., 2005 C	Bilateral DLPFC	NA	20	800	8000	10	1200	2	Deactived coil
Novak et al., 2006	Left DLPFC	Stimulation	20	2000	20,000	10	13	2	90°
Saba et al., 2006	Left TPJ	Inhibition	1	300	3000	10	600	2	Similar accoustic and scalp sensation effect
Mogg et al., 2007	Left DLPFC	Stimulation	10	2000	20,000	10	1200	2	Similar accoustic and scalp sensation effect
Rosa et al., 2007	Left TPJ	Inhibition	1	960	9600	10	960	2	Deactived coil
Fitzgerald et al., 2008	Bilateral DLPFC	Stimulation	10	1000	15,000	15	600	3	90°
Cordes et al., 2010	Left DLPFC	Stimulation	10	1000	10,000	10	1200	2	Deactived coil
De Jesus et al. 2011	Left TPJ	Inhibition	1	NA	23,040	20	1200	4	45°
Barr et al., 2012	Bilateral DLPFC	Stimulation	20	750	15,000	20	NA	4	90°
Jin et al., 2012 A	Bilateral Parietal Cortex	Stimulation	Alpha	NA	NA	NA	NA	NA	Deactived coil+similar accoustic
Jin et al., 2012 B	Bilateral Frontal Cortex	Stimulation	Alpha	NA	NA	NA	NA	NA	Deactived coil+similar accoustic
Rosenberg et al., 2012	Left TPJ	Stimulation	1	600	6000	10	600	2	Similar accoustic and scalp sensation effect
Zheng et al., 2012 iTBS	Left DLPFC	Stimulation	iTBS	NA	6000	5	900	NA	Reverse side of coil plane to the scalp
Zheng et al., 2012 10 Hz	Left DLPFC	Stimulation	10	1200	6000	5	900	NA	Reverse side of coil plane to the scalp
Zheng et al., 2012 20 Hz	Left DLPFC	Stimulation	20	1200	6000	5	900	NA	Reverse side of coil plane to the scalp
Prikryl et al., 2013	Left DLPFC	Stimulation	10	2000	20,000	10	800	3	Similar accoustic and scalp sensation effect
Bais et al., 2014 A	Left TPJ	Inhibition	1	1200	14,400	12	1200	2	Similar accoustic and scalp sensation effect
Bais et al., 2014 B	Bilateral TPJ	Inhibition	1	1200	14,400	12	1200	2	Similar accoustic and scalp sensation effect
Dlabac-de Lange et al., 2014	Bilateral DLPFC	Stimulation	10	2000	60,000	30	1200	3	90°
Rabany et al., 2014	Left DLPFC	Stimulation	20	1680	33,600	20	924	3	NA
Wölwer et al., 2014	Left DLPFC	Stimulation	10	1000	10,000	10	1200	2	Similar accoustic and scalp sensation effect
Quan et al., 2015	Left DLPFC	Stimulation	10	800	8000	10	1200	2	90°
Wobrock et al., 2015	Left DLPFC	Stimulation	10	1000	15,000	15	NA	3	45°
Gan et al., 2015	Left DLPFC	Stimulation	10	NA	NA	10	NA	2	NA
Li et al., 2016	Left DLPFC	Stimulation	10	1500	30,000	20	1050	4	Similar accoustic and scalp sensation effect

tDCS Parameters

Author	Anode	Cathode	Intensity	Duration of sessions (s)	N of sessions	Weeks	Blinding
Brunelin et al., 2012	Left DLPFC	LTPJ	2 mA	1200	1	1	Reduced stimulation time (40s)
Fitzgerald et al., 2014 A	Both DLPC	Both TPJ	2 mA	1200	2	3	Reduced stimulation time (40s)
Fitzgerald et al., 2014 B	Left DLPFC	LTPJ	2 mA	1200	2	3	Reduced stimulation time (40s)
Smith et al., 2015	Left DLPFC	Contralateral supraorbital ridge	2 mA	1200	1	1	Reduced stimulation time (40s)
Palm et al., 2016	Left DLPFC	Contralateral supraorbital ridge	2 mA	1200	1	1	Sham dual mode tDCS: mimics sensorial arctifacts
Fröhlich et al., 2016	Left DLPFC	LTPJ	2 mA	1200	1	2	Sham dual mode tDCS: mimics sensorial arctifacts
Gomes et al., 2015	Left DLPFC	Right DLPFC	2 mA	1200	1	1	Reduced stimulation time (40s)

F (Hz) = frequency in hertz; PFC = prefrontal corex; DLPFC = dorsolateral prefrontal cortex; TPJ = temporoparietal junction; TBS = theta burst stimulation; NA = not available; Blinding code: 1.0 = 90°; 2.0 = deactivate coil; 3.0 = reduced stimulation time; 4.0 = similar acoustic and scalp sensation effect; 5.0 = Sham dual mode tDCS: mimics sensorial artifacts.

3.4. Sub-analysis

Meta-regression showed no particular influence of any variable on the results (Table 3), and there was no difference between protocols of stimulation. Regarding rTMS studies, in most protocols, the dorsolateral prefrontal cortex (DLPFC) was stimulated, with 12 studies using rTMS to stimulate the left DLPFC (Cordes et al., 2010; Gan et al., 2015; Hajak et al., 2004; Holi et al., 2004; Li et al., 2016; Novak et al., 2006; Prikryl et al., 2013; Quan et al., 2015; Rabany et al., 2014; Wobrock et al., 2015; Wölwer et al., 2014) and five studies stimulating the DLPFC bilaterally (Barr et al., 2012; Dlabac-de Lange et al., 2014; Fitzgerald et al., 2014; Fitzgerald et al., 2008; Jin et al., 2012). All tDCS studies applied the

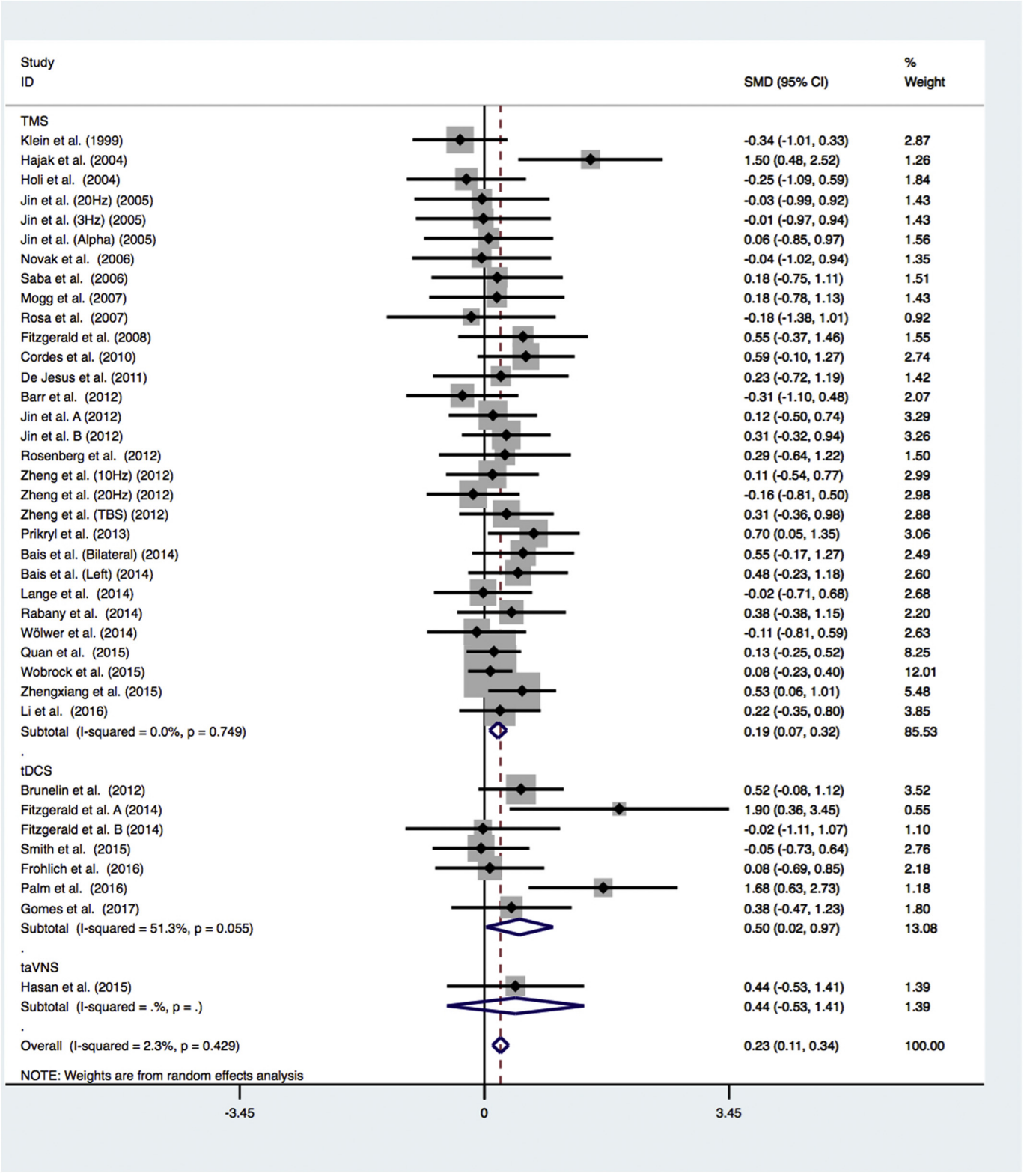

Fig. 2. Forest plot of effect sizes (Hedges' *g*) CI, confidence interval. The forest plot graphically illustrates the strength of treatment effects concerning each elected study; the vertical line represents the overall effect.

anode over the left DLPFC, inducing excitability of this brain area. Cathode positioning varied: (1) Three studies positioned it over the left temporoparietal junction (Brunelin et al., 2012; Fitzgerald et al., 2014; Fröhlich et al., 2016), (2) two over the right supraorbital area (Palm et al.; Smith et al.), (3) and one over the right DLPFC (Gomes et al., 2015). The exception was the study conducted by Fitzgerald et al. (2014), in which the stimulation of the DLPFC was performed bilaterally, and the cathode was positioned over the temporoparietal junction bilaterally. The other protocols consisted of (1) inhibiting the temporoparietal junction bilaterally (Bais et al., 2014); (2) stimulating the temporoparietal junction (LTPJ) (Rosenberg et al., 2012), more specifically halfway between T3 and P3 (de Jesus et al., 2011; Rosa et al., 2007; Saba et al., 2006); and (3) stimulating the parietal cortex bilaterally (Jin et al., 2012). The taVNS study stimulated the left auricular branch of the vagus nerve (Hasan et al., 2015).

A categorical analysis of safety using dropout as the outcome showed no difference between active NIBS and sham NIBS (Fig. 5) (Odds Ratio = 1.02, 95% CI 0.94–1.11; 1.02, 0.93–1.11; and 1.03, 0.83–1.27, for NIBS, rTMS, and tDCS, respectively).

4. Discussion

In this systematic review, we included 31 randomized sham-controlled clinical trials ($n = 1272$). Active NIBS was superior to sham NIBS for the treatment of negative symptoms in schizophrenia (g = 0.23; 95% CI 0.11–0.34). Considering the different techniques, active rTMS had robust positive results over sham stimulation (g = 0.19), with a narrower interval (95% CI 0.07–0.32) than tDCS (g = 0.5; 95% CI 0.02–0.97). Only one study evaluating the use of taVNS met the eligibility criteria. The risk of publication bias was low, as assessed by the funnel plot. Between-study heterogeneity was not considerable ($I^2 = 2.3\%$; p = 0.429), strengthening the present results. These are in line with previous meta-analytical studies that showed a small-to-moderate effect of rTMS on the reduction of negative symptoms in schizophrenia (Dougall et al., 2015; Shi et al., 2014) and complementary to a previous meta-analysis (Fusar-Poli et al., 2015), in which a non-significant difference between sham NIBS and active NIBS was observed. Our meta-analysis differs from these, since we included all types of NIBS and compared the effect of active treatment over sham on negative symptoms in schizophrenia. Additionally, our rTMS included studies focused on prefrontal areas due to the outcome of this systematic review (negative symptoms), emphasizing the knowledge in this theme.

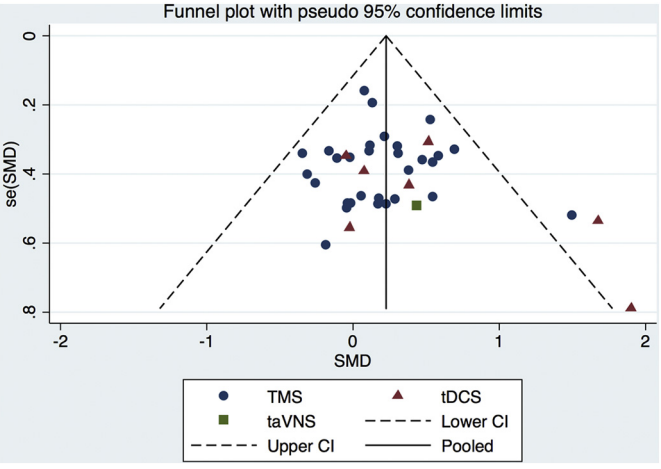

Fig. 3. Begg's funnel plot The funnel plot was used to assess the existence of publication bias. Most studies are within the limits determined by the graphic for both interventions, indicating a low risk of bias.

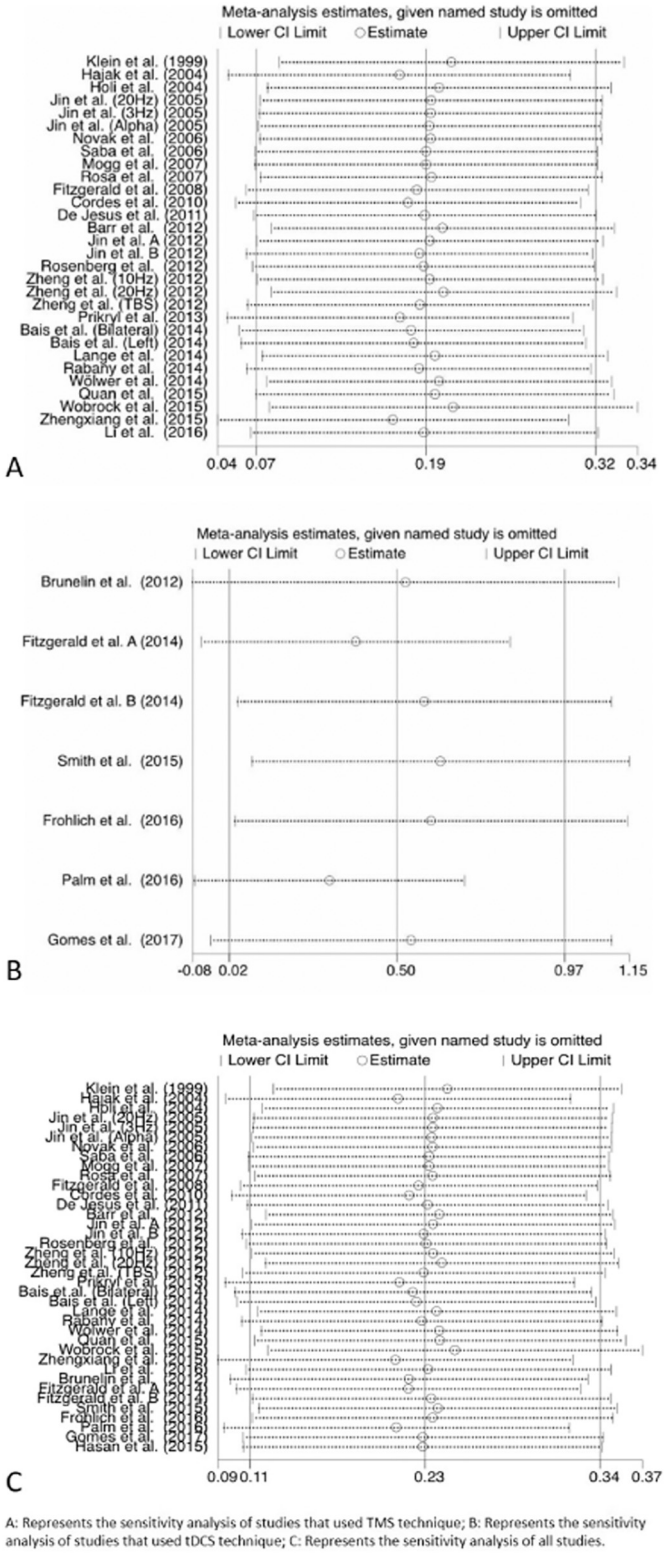

Fig. 4. Sensitivity analysis of the impact of the NIBS in the negative symptoms The figure shows the sensitivity analysis of the studies conducted with A: rTMS, B: tDCS and C: tDCS, rTMS, and taVNS. No study was able to modify the final results for rTMS and NIBS in an overall analysis. However, the exclusion of one of the studies conducted by Brunelin et al. (2012), Fitzgerald et al. (2014), and Palm et al. (2016) would result in a non-significant difference. Although this finding reduces the robustness of the difference between active tDCS and sham tDCS, the results are still positive, and the superiority of the technique is, with the currently available data, significant.

Table 3
Metaregression.

Metaregression tDCS				
	β	95%CI	t	p-value
N of sessions	1.322	0.199; 8.774	0.38	0.72
N of weeks	1.426	0.607; 3.352	1.07	0.334

Metaregression tDCS				
	β	95%CI	t	p-value
N of sessions	1.068	0.835; 1.367	0.56	0.582
Duration of sessions	1	0.999; 1.000	0.64	0.528
Frequency of stimulation	1.025	0.725; 1.448	0.15	0.882
Stimulation of the left DLPFC or inhibition of the right DLPFC	1.361	0.934; 1.984	0.104	0.104
Pulses per session	1.228	0.963; 1.565	0.092	0.092
Total N of pulses	1.057	0.897; 1.245	0.7	0.491

Four different neuromodulation techniques (rTMS, tDCS, dTMS, and tVNS) for the treatment of negative symptoms in schizophrenia were evaluated. Subgroups analyses were performed to assess possible confounders related to each technique, such as the protocol of stimulation used. It is noticeable that rTMS has been better studied in past decades than other techniques. In this review, we included 23 trials using rTMS since Klein et al. (1999) published the first randomized, sham-controlled trial on the subject. The first tDCS randomized, sham-controlled clinical trial was released only in 2012 by Brunelin et al., and we were able to include six other studies with similar quality. The increasing number of trials published in this area corroborate the need for a more up-to-date meta-analysis comparing different NIBS techniques.

Among the brain areas targeted in the included studies, the prefrontal cortex appears as the most frequently targeted. The prefrontal cortex is associated with goal-directed behavior, working memory, executive functioning, and social and emotional processing (Sakurai et al., 2015; Zhou et al., 2015). Although the neural pathways involved in negative symptomatology are not as well described as the ones involved in positive symptoms, evidence suggests prefrontal dysfunction in schizophrenia and its association with negative symptoms and cognitive deficits (Zhou et al., 2015). Among the reported dysfunctions, reduced functional activation of the frontal cortex in cognitive tasks is the most consistent finding (Sakurai et al., 2015). Furthermore, dysfunctional activation of the ventrolateral prefrontal cortex and the DLPFC is associated with negative and disorganization symptoms, respectively, while frontotemporal abnormalities have been linked to positive symptoms (Goghari et al., 2010). Recently, the thickness of the prefrontal cortex, more specifically the medial orbitofrontal cortex, was associated with the severity of negative symptoms (Walton et al., 2017). Also, normalization of the frontal cortex's excitability is one of the main consequences of effective therapeutic approaches, including antipsychotic medications (Kani et al., 2017), and the use of focal neuromodulation techniques to increase excitability of the prefrontal areas was proposed as a result. From a mechanistic point of view, rTMS works through the creation of an electromagnetic field that can generate a current that further depolarizes the targeted brain areas positioned under the coil (e.g., the DLPFC) (Du et al., 2012). Low-frequency rTMS (1 Hz) inhibits the area beneath the coil, reducing excitability, while higher frequencies enhance it by stimulating the area. On the other hand, the tDCS device delivers a continuous current through two electrodes, one positive (cathode) and one negative (anode). The area located under the anode is then stimulated, producing a reduction in membrane potential. Thus, the modulated neurons are more easily depolarized. On the other hand, the area under the cathode is inhibited, with further elevation of the membrane potential. Both techniques can modulate excitability and promote neuroplasticity, which is fundamental for a better prognosis in schizophrenia. One important difference regards energy retention in the scalp. In tDCS, a significant amount of energy is lost due to high retention by the scalp. In rTMS, in contrast, the creation of the electrical field takes place in the cortical area without the need for the current to trespass the scalp. While the efficacy of rTMS is robust for multiple psychiatric and neurological disorders, tDCS has some potential advantages, such as its low costs and the possibility of at-home use, since it is an easy-to-use technology that can be monitored remotely. Besides, the continuous current is propagated from the cathode to the anode, going through cortical and subcortical areas in its path. That feature enables the modulation of different areas based on the montage used. Computational modeling analysis allows for the creation of estimates regarding the probably stimulated and inhibited structures using each montage (Bikson et al., 2012).

In accordance with previous meta-analytical studies that reported positive results using rTMS and tDCS for the treatment of patients with other psychiatric disorders, such as PTSD, anxiety disorders, substance dependence/abuse, and major depression (Brunoni et al., 2017; Enokibara et al., 2016; Trevizol et al., 2016a, 2016c), we present compelling positive findings that substantiate the use of NIBS in the treatment of negative symptoms in schizophrenia. Stimulation of the DLPFC seems reasonable, given the underlying neurobiological model of cognitive and negative symptoms, and our results support this. However, the overall NIBS and rTMS Hedges' *g* (reflecting mean change in negative symptom scores from baseline to treatment end point) are in the small-to-moderate effect range, which may not be really substantial clinically when we are talking about improvements in negative symptoms, which are quite disabling and in which a small improvement may not mean much. The moderate effect size of 0.5 for tDCS has to be considered cautiously, given the possible heterogeneity in the studies. A few large effect size studies may have over-inflated the effect size, as demonstrated in the sensitivity analysis (Fig. 4). Though metaregression has been performed as an attempt to look for the reasons for inconsistency of results in tDCS trials, we found nothing significant. Inferences made through metaregression may have limitations and may not be an accurate way of addressing heterogeneity (Murad et al., 2014). However, we observed a trend for a positive impact on the effect size when stimulating the left DLPFC or inhibiting the right DLPFC (Table 3). In addition, the majority of the studies have looked at the effects of NIBS over the left DLPFC. Depression scores were not recorded or controlled for in the included studies, and high-frequency rTMS to the left DLPFC is an approved treatment for major depression. Improvement in depressive symptoms could potentially confound the results. Despite the positive results when comparing sham to active rTMS, the effect size found in the pooled analysis is small in both TMS and tDCS. Moreover, a substantial proportion of studies have resulted in negative results. The clinical implication of these findings may seem limited at first. However, given the long-lasting symptoms, the constant decline, and the lack of efficacy for pharmacological treatments for negative symptoms in schizophrenia, the results may represent a fruitful path to be followed in order to improve the efficacy of NIBS for negative symptoms. One of the main gaps in our current knowledge has to do with the longevity of the effect of NIBS. Although our findings point to the superiority of NIBS in comparison to sham stimulation for negative symptoms in schizophrenia, longer longitudinal studies are needed in order to better understand the potential for clinical use. Another potential limitation is related to the Jadad scale used for assessing the risk of bias of individual studies. The use of the Jadad scale has been discouraged lately, as it does not involve allocation concealment and puts more emphasis on the reporting of studies than their actual conduct. However, we have taken allocation concealment into consideration for a proper blinding. The Jadad scale was not used as the sole quality assessment, but each study was evaluated using both the scale and the risk as assessed by two researchers. One limitation involved in our systematic review is that it has been done only from MEDLINE and the Cochrane Library, which may not be exhaustive enough and does not include studies from the “gray literature” (Murad et al., 2014).

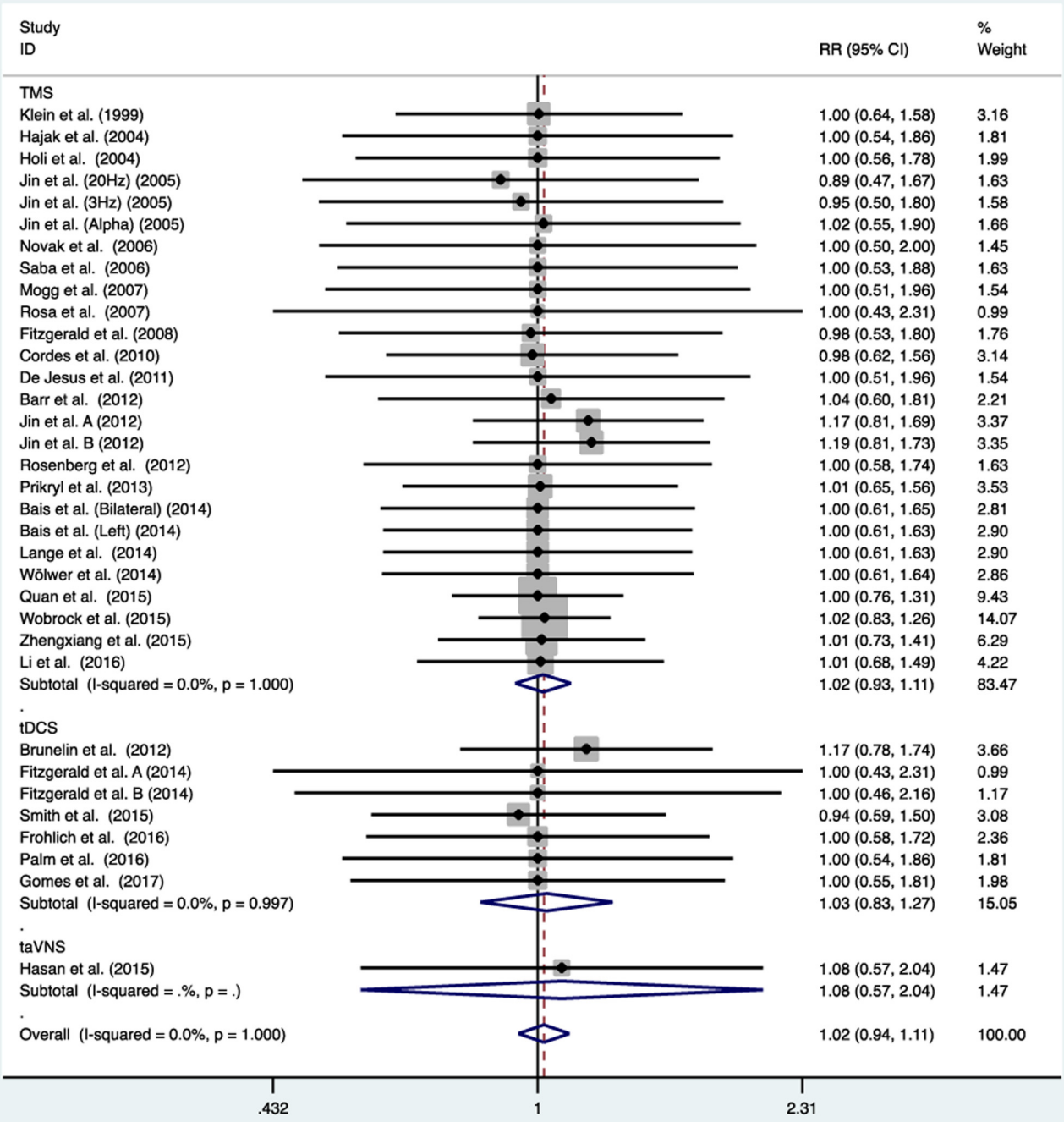

Fig. 5. Safety analysis We used patients' dropouts for safety evaluation. We performed a categorical analysis for the odds ratio assessment between groups. No difference between active and sham rTMS or tDCS was observed.

5. Conclusion

In conclusion, both active rTMS and tDCS treatments were significantly superior to sham for the treatment of negative symptoms in schizophrenia. The significance is especially robust for rTMS. We observed a non-significant trend for a better response when stimulating the left DLPFC or inhibiting the right DLPFC. The number of randomized, controlled trials on tDCS and tVNS is still small, and further studies are needed to clarify the impact of these strategies on the treatment of negative symptoms in schizophrenia.

Declaration of interest

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agreed with its submission to Schizophrenia Research. We here declare no conflict of interest related to the present manuscript.

Conflict of interest

We here declare no conflict of interest related to the present manuscript.

Contributors

Authors Osoeagawa, Gomes and Grigolon managed the literature searches and classification of the articles following the eligibility criteria. Authors Cordeiro, Trevizol, Ribeiro and Laranjeira participated in the study design and in writing the protocol to be performed and undertook the statistical analysis. Authors Brietzke, Gadelha, Lacerda and Dias participated in writing the first drafts of the manuscript. Authors de Jesus, Daskalakis, Brunelin and Cordes have considerable experience in the field of neuromodulation studies and participated in the interpretation of the results and analyses. All authors contributed to and have approved the final manuscript.

Role of funding source

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.01.010.

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