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Original article

Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have shown promise in the treatment of schizophrenia.
Objective: To quantify the efficacy of double-blind randomized controlled trials (RCT) of tDCS and rTMS for the positive and negative symptoms of schizophrenia and identify significant moderators relating to patient-related features and stimulation parameters.
Methods: Systemic review and meta-analyses of the relevant literature published until February 1st, 2017 to assess treatment efficacy and quantify the contribution of potential moderator variables.
Results: We identified 7 RCTs on tDCS (involving 105 participants) and 30 RCTs on rTMS (involving 768 participants). Compared to sham, tDCS improved all symptom dimensions but the effect reached significance for negative symptoms (Hedge's $g = -0.63$, $p = 0.02$). Efficacy for positive but not negative symptoms was linearly associated with cumulative tDCS stimulation. Compared to sham, rTMS improved hallucinations (Hedge's $g = -0.51$, $p < 0.001$) and negative symptoms (Hedge's $g = -0.49$, $p = 0.01$) but was associated with modest, non-significant worsening of positive symptoms (Hedge's $g = 0.28$, $p = 0.13$). Higher pulse frequency (>10 Hz), motor threshold intensity of 110%, left prefrontal cortical treatment site and trial duration over 3 weeks were associated with improvement in negative symptoms and worsening in positive symptoms (all $p < 0.03$).
Conclusions: The symptom dimensions in schizophrenia may respond differently to brain stimulation interventions in a way that may reflect the interaction between disease- and treatment-related mechanisms. Our findings underscore the need for further research into patient selection prior to treatment assignment and greater refinement of stimulation protocols.
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1. Introduction

Schizophrenia is a severe and complex disorder presenting with positive (hallucinations, delusions, disorganized thinking and agitation) and negative (affective flattening, amotivation, and alogia) symptoms [1]. Approximately 10% of patients are resistant to standard treatments at disease onset and this proportion increases to around 40% with chronicity [2–6]. In response, there is increased interest in the therapeutic potential of novel approaches involving noninvasive neuromodulation, and particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS involves the use of a rapidly fluctuating electrical current to generate a magnetic field which, when applied to the scalp, can influence neuronal excitability to a depth of approximately 2 cm below the skull [7,8]. Randomized controlled trials (RCTs) in schizophrenia suggest that rTMS is moderately effective in the treatment of auditory hallucinations [9] and negative symptoms [10,11]. These studies also report that duration of illness and stimulation parameters relating to target region, pulse frequency and motor threshold as well as overall treatment duration were significant moderators of efficacy [9–11]. tDCS involves the application of weak electrical currents (typically 2 mA) that flow through the brain from anodal to cathodal scalp electrodes. These weak electrical currents are thought to modulate the resting membrane potentials of neurons, reducing (cortical) excitability at the cathode while increasing it at the anode [12]. tDCS in schizophrenia has been evaluated mostly in connection to auditory hallucinations; the results have been mixed and the role of moderator variables remains unclear [13–19].

This study addresses two key knowledge gaps. First, we used quantitative meta-analysis to evaluate the efficacy of rTMS and tDCS on the positive, negative and general symptoms of schizophrenia using data from the available RCTs. Second, we

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quantified the moderator effects relating to patient-related characteristics (sex, age, duration of illness and antipsychotic dose) and stimulation parameters. The stimulation parameters considered were target brain regions, trial duration, electrical current amplitude (for tDCS trials only), pulse frequency and motor threshold (for rTMS trials only) and cumulative stimulation, new composite measure of stimulation "dose". In addition, we provide an online, freely accessible and searchable database listing the variables used in this study to enable future work by other researchers.

2. Materials & methods

2.1. Search strategy and selection criteria

We conducted a systematic search of the major electronic databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [20] to identify studies published between January 1 st 1996 and February 1st 2017. Our start date was determined by the first publication of an RCT using rTMS in schizophrenia and was extended by 3 years to include any other reports. Selection criteria were: (a) Peer-reviewed, original studies of patients with schizophrenia and related psychoses diagnosed according to standardized criteria; (b) Double-blind randomized sham controlled design; (c) Symptom ratings using the Auditory Hallucinations Rating Scale (AHRS) [21] and/or the Positive and Negative Syndrome Scale (PANSS) [22]; (d) Sufficient data to calculate effect size using Hedges' g; (e) information about study drop-outs/withdrawals. Based on the criteria set-out by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group (http://www.gradeworkinggroup.org/) the studies selected would be rated as 4 (highest rating). Conference abstracts, open label trials, case reports and case series were not included. Details of the search strategy and the study selection process are provided in supplemental material (PRISMA flowcharts Figs. S1 and S2), supplemental datasheet and Fig. S3.

2.2. Data extraction and database construction

We extracted the following variables from each study: treatment modality (tDCS or rTMS), sample size per treatment condition (active or sham), sex, age, duration of illness, antipsychotic dose (converted into chlorpromazine equivalent milligrams; CPZE), frequency of treatment administration, trial duration and stimulation parameters (electrode montage and current amplitude for tDCS, target brain region, motor threshold and pulse frequency for rTMS), time point of data collection, raw difference in mean and standard deviation of pre- and post-treatment symptom scores in the active and sham condition, difference in means with associated p value and 95% confidence intervals, or exact *F* or *t* values, and number of dropouts and side-effects.

2.3. Statistical analysis

All analyses were conducted using the Comprehensive Meta-Analysis (CMA) v3.3.070 software (Biostat, Englewood, NJ, USA). Because of the imbalance in the number of studies reporting on tDCS and rTMS, data for each neuromodulation modality were analyzed separately using identical methodology. The outcomes considered were (a) reduction in auditory hallucinations as measured by a composite score derived from the AHRS and the PANSS auditory hallucination subscale computed using the "which procedure" in the CMA software; (separate confirmatory meta-analyses using the AHRS alone are reported in supplemental material); (b) reduction in positive symptoms as measured by the positive symptoms subscale of the PANSS; (c) reduction in negative symptoms as measured by the negative symptoms subscale of the PANSS; (d) reduction in overall symptom severity as measured by the PANSS total score; (e) number of dropouts; (f) type and number of side-effects.

For each outcome, we calculated weighted standardized mean differences (Hedges' g) between active and sham conditions using a DerSimonian and Laird's random effects model [23]. Studies were weighted by sample size as calculated by the Mantel-Haenszel method [24]. Effect sizes were considered small (<0.20), medium and large (>0.80) in accordance with conventional guidelines [25]. When trials comparing effects of multiple stimulation parameters were reported in the same article, we treated each trial as an independent dataset. In four studies that employed a crossover design [26–29] we used the clinical scores at initial randomization as baseline. We considered only outcome data recorded on completion of the clinical trial and not at other timepoints.

Heterogeneity was quantified using the I^2 statistic which accommodates small numbers of studies. Conventionally, an $I^2 < 25\%$ is considered as likely unimportant while an $I^2 > 50\%$ is indicative of substantial heterogeneity requiring cautious interpretation of the results [30]. A random effects model was applied to all analyses where the $I^2 \geq 25\%$. The threshold for statistical significance was set at $p < 0.002$, following Bonferroni correction considering the 4 clinical efficacy outcomes examined per modality.

For each modality, we considered moderator effects relating to patient-related characteristics and stimulation parameters. Patient-related characteristics comprised sex (expressed as the percentage of male patients within each study), age, duration of illness and antipsychotic dose (in CPZE). The stimulation parameters considered for both modalities were target brain regions and trial duration. Additional moderators were electrical current amplitude for tDCS trials and pulse frequency and motor threshold for rTMS studies. We also evaluated the usefulness of "cumulative stimulation" as composite measure of "dose" defined as:

$$\begin{aligned}(\text{tDCS cumulative stimulation}) = {} & (\text{density of administration}) \\ & \times (\text{individual session duration}) \\ & \times (\text{current amplitude})\end{aligned}$$

$$\begin{aligned}(\text{rTMS cumulative stimulation}) = {} & (\text{density of administration}) \\ & \times (\text{individual session duration}) \\ & \times (\%\text{motor threshold}) \\ & \times (\text{pulse frequency})\end{aligned}$$

For both tDCS and rTMS, administration density was defined as the ratio of total number of treatment sessions over the duration of the treatment trial. Regression analyses were used to assess the independent contribution of each continuous moderator to change in clinical outcomes based on the regression coefficient, 95% confidence interval (CI) and the R^2 statistic. Subgroup analyses were used to assess effect size for categorical variables. We retained the conventional statistical threshold of $p < 0.05$ as we considered these analyses potentially informative for future detailed examination. For each modality, we assessed tolerability by calculating the odds ratio (OR) of dropout and side-effect rates between the active versus sham condition across all studies.

3. Results

3.1. Dataset

The final dataset comprised 7 tDCS and 30 rTMS studies (Tables 1 and 2 and Tables S1 and S2). We found no evidence of publication bias (Fig. S4). For both modalities, the study samples comprised patients with persistent symptoms despite adequate

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