Introduction

Transcranial Direct-Current Stimulation (tDCS) is a non-invasive form of brain stimulation similar to transcranial magnetic stimulation, but instead of using magnets, it uses a low-intensity, constant current applied through scalp electrodes. Generally, anodal stimulation induces an increase of cortical excitability, whereas cathodal stimulation decreases cortical excitability, with effects that last beyond the stimulation period. Dose involves current intensity, duration of stimulation and size of electrodes. The use of tDCS in schizophrenia is in the early stages of investigation for relief of symptoms in people who are not satisfied with their response to antipsychotic medication.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis. Reviews reporting less than 50% of items are excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found two reviews that met our inclusion criteria. These are presented below in alphabetical order.

- Low quality evidence is unable to determine any benefits of transcranial direct current stimulation for symptoms of schizophrenia; more research is needed.
Brunoni AR, Shiozawa P, Truong D, Javitt DC, Elkis H, Fregni F, Bikson M

Understanding tDCS effects in schizophrenia: a systematic review of clinical data and an integrated computation modeling analysis

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>tDCS for patients with schizophrenia.</th>
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<tr>
<td>Summary of evidence</td>
<td>Low quality evidence (very small samples) is unable to determine any benefits of transcranial direct current stimulation for symptoms of schizophrenia; more research is needed.</td>
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**Auditory hallucinations**

1 RCT (N = 30 adults) applied tDCS twice daily for 5 days to active and sham groups, with a cathode placed on the left temporoparietal region, and an anode on the left dorsolateral prefrontal cortex (DLPFC) to simultaneously perform an inhibitory stimulation over the area related to positive symptoms, and an excitatory stimulation over the area related to negative symptoms. This study reported improvements in both auditory hallucinations and negative symptoms after the end of stimulation, with sustained clinical response after 1 to 3 months of treatment.

1 RCT (N = 12 children aged 10 to 17 years) applied tDCS for 10 days, with bilateral cathodal temporoparietal stimulation for hallucinations, and bilateral anodal prefrontal stimulation for cognitive improvement. This study reported on side effects only; 30 to 50% of children in both active and sham groups reporting tingling, itching, and fatigue.

1 case series and 3 case reports applied a cathode over the left temporoparietal region, and an anode over the left DLPFC twice daily for 5 days and reported significant improvements in hallucinations. Another case report applied a cathode over the left temporoparietal region, and an anode over the left DLPFC once or twice daily for nearly 3 years in a clozapine-refractory patient with schizophrenia. The patient showed sustained improvement, which was attenuated or lost when the sessions were performed on alternate days.

1 case report applied a cathode over the right DLPFC, and an anode over the left DLPFC, for 10 consecutive sessions in a patient with severe catatonia who was refractory to clozapine and electroconvulsive therapy. The patient showed virtually full remission of catatonia after 30 to 60 days of onset of treatment.

1 case report applied cathodal stimulation consecutively over the occipital cortex and the temporoparietal cortex, and an anode over the left DLPFC, and reported partial improvement in visual and auditory hallucinations, and enhanced global functioning.

1 case report applied a cathode over the left temporoparietal cortex, and an anode over the right supraorbital cortex for 10 consecutive days and reported improved in positive, negative and global symptoms.

1 case report applied an anode over the left DLPFC, and a cathode over the right supraorbital area.
for 10 sessions in a 19-year-old patient with paranoid, treatment-resistant schizophrenia. The patient showed reduced functional connectivity in the anterior part of the default-mode network, and a global improvement in symptoms.

<table>
<thead>
<tr>
<th>Risks</th>
<th>Tingling, itching, fatigue</th>
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<tr>
<td>Consistency in results</td>
<td>No measure of consistency is reported.</td>
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<tr>
<td>Precision in results</td>
<td>No measure of precision is reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
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Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, McGuire P

Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials

View review abstract online

Comparison
Effectiveness of adjunctive repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS) vs. placebo/sham.

Summary of evidence
Low quality evidence (inconsistent, imprecise, indirect) is uncertain as to the benefit of rTMS or tDCS over sham.

Negative symptoms
No significant effect between groups;
8 studies, SMD -0.228, 95%CI -0.775 to 0.319, \( p = 0.413, \quad \chi^2 = 73.5\%, \quad p < 0.001 \)
Authors state that this finding was not clinically significant as measured by the Clinical Global Impression Scale (severity and improvement). There were no effects of potential moderators (outcome scales, study attrition rates, illness duration, age, percentage of males, trial duration, year of publication, and quality of studies), and no evidence of publication bias.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Inconsistent</th>
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<tr>
<td>Precision in results</td>
<td>Imprecise</td>
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<tr>
<td>Directness of results</td>
<td>Indirect (rTMS and tDCS combined)</td>
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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study’s mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2. InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time.
period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity.

$I^2$ can be calculated from Q (chi-square) for the test of heterogeneity with the following formula:

$$I^2 = \left( \frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed.

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.
References


