TECHNICAL COMMENTARY

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Transcranial direct-current stimulation

Introduction

Transcranial Direct-Current Stimulation (tDCS) is a non-invasive form of brain stimulation, which is 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[1]. 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)[2]. 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 five systematic reviews that met our inclusion criteria[3-7].

- Moderate to low quality evidence finds a large effect of greater improvement in auditory hallucinations with tDCS given twice-daily or over 10 sessions. Over 10 sessions may also improve negative symptoms.
- Moderate quality evidence finds a medium-sized effect of greater improvement in working memory, but not other cognitive domains, with prefrontal tDCS.

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Aleman A, Enriquez-Geppert S, Knegtering H, Dlabac-de Lange JJ

Moderate effects of noninvasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: Meta-analysis of controlled trials

Neuroscience and Biobehavioral Reviews 2018; 89: 111-8

View review abstract online

Comparison	**Effectiveness of adjunctive transcranial direct current stimulation (tDCS) vs. placebo/sham.**
Summary of evidence	**Moderate to low quality evidence (small sample, inconsistent, imprecise, direct) suggests tDCS may improve negative symptoms.**
Negative symptoms **Measured with the SANS or PANSS negative subscale**	
A medium-sized trend effect of greater improvement in negative symptoms with tDCS; 5 RCTs, N = 134, SMD = 0.50, 95%CI -0.07 to 1.07, p = 0.08, I^2 = 62%, p = 0.03	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Kennedy NI, Lee WH, Frangou S

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

European Psychiatry 2018; 49: 69-77

View review abstract online

Comparison	**Effectiveness of adjunctive transcranial direct current stimulation (tDCS) vs. placebo/sham.**
Summary of evidence	**Moderate to low quality evidence (small samples, inconsistent, unable to assess precision, direct) finds a medium-sized effect of greater improvement in negative symptoms with active tDCS, with no effect on positive symptoms (including auditory**

	hallucinations).
Overall symptoms **Measured with the PANSS (total score)**	
No significant differences between groups; 6 RCTs, N = 163, *g* = -0.48, 95%CI not reported, *p* = 0.12, I^2 = 73% There were no moderating effects of age, sex, and treatment dose.	
Negative symptoms **Measured with the PANSS (negative subscale)**	
A significant medium-sized effect of greater improvement in negative symptoms with tDCS; 7 RCTs, N = 190, *g* = -0.63, 95%CI not reported, *p* = 0.02, I^2 = 70% There were no moderating effects of age, sex, and treatment dose.	
Positive symptoms **Measured with the PANSS (positive subscale)**	
No significant differences between groups; 7 RCTs, N = 190, *g* = -0.10, 95%CI not reported, *p* = 0.59, I^2 = 42% There were no moderating effects of age, sex, and treatment dose.	
Auditory hallucinations **Measured with the AHRS and PANSS**	
No significant differences between groups; 5 RCTs, N = 143, *g* = -0.28, 95%CI not reported, *p* = 0.38, I^2 = 77% The efficacy of active tDCS increased significantly with greater treatment dose. There were no moderating effects of age and sex.	
Risks	The most common adverse effect was itching under the electrode.
Consistency in results	Inconsistent
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Kim J, Iwata Y, Plitman E, Caravaggio F, Chung JK, Shah P, Blumberger DM, Pollock BG, Remington G, Graff-Guerrero A, Gerretsen P

A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?"

Journal of Psychiatric Research 2019; 110: 117-26

View review abstract online

Comparison	**Effectiveness of adjunctive transcranial direct current stimulation (tDCS) vs. placebo/sham.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) finds a large effect of greater improvement in auditory hallucinations with active tDCS given twice-daily or over 10 sessions. Over 10 sessions may also improve negative symptoms.**

Auditory hallucinations

Measured with the AHRS, PSYRATS, and PANSS

No significant differences between groups;

7 RCTs, N = 242, SMD = 0.50, 95%CI -0.09 to 1.09, $p = 0.10$, $I^2 = 79\%$

Studies that applied twice-daily stimulation showed a large improvement with tDCS;

4 RCTs, N = 138, SMD = 1.04, 95%CI 0.20 to 1.89, $p = 0.02$

Studies that applied 10 or more sessions showed a large improvement with tDCS;

5 RCTs, N = 186, SMD = 0.86, 95%CI 0.22 to 1.51, $p = 0.009$

There was no improvement with once-daily stimulation, or in studies that applied a left fronto-temporoparietal placement.

Increasing age was associated with lower effect sizes. There were no associations with gender, sample size, or baseline AHRS scores.

Positive symptoms

Measured with the PANSS

No significant differences between groups;

9 RCTs, N = 313, SMD = 0.03, 95%CI -0.24 to 0.31, $p = 0.81$, $I^2 = 32\%$

There was also no improvement with once-daily, twice-daily, 10 or more sessions, fronto-temporoparietal placement, or bi-frontal placement.

There were no associations with age, gender, sample size, or baseline PANSS scores.

Negative symptoms

Measured with the PANSS and SANS

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No significant differences between groups; 9 RCTs, N = 313, SMD = 0.27, 95%CI -0.09 to 0.62, *p* = 0.14, I^2 = 57% *Studies that applied 10 or more sessions showed improvement with tDCS;* 7 RCTs, N = 257, SMD = 0.41, 95%CI 0.01 to 0.81, *p* = 0.04 There was also no improvement with once-daily or twice-daily sessions, or bi-frontal placement. Increasing age was associated with lower effect sizes. Increased baseline PANSS scores were associated with larger effect sizes. There were no association with gender.	
Risks	Not reported
Consistency in results	Inconsistent for hallucinations and negative symptoms.
Precision in results	Imprecise for hallucinations
Directness of results	Direct

Narita Z, Stickley A, DeVylder J, Yokoi Y, Inagawa T, Yamada Y, Maruo K, Koyanagi A, Oh H, Sawa A, Sumiyoshi T

Effect of multi-session prefrontal transcranial direct current stimulation on cognition in schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2019; 216: 367-373

View review abstract online

Comparison	**Effectiveness of prefrontal adjunctive transcranial direct current stimulation (tDCS) vs. placebo/sham.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, precise, direct) finds a medium-sized effect of greater improvement in working memory, but not other cognitive domains, with prefrontal tDCS.**
Cognition	
A medium-sized, significant improvement in working memory with prefrontal tDCS; 9 RCTs, N = 270, SMD = 0.49, 95%CI 0.16 to 0.83, *p* = 0.004, I^2 = 39% There were no significant effects for other cognitive domains (speed of processing, attention and vigilance, verbal learning, visual learning, and reasoning and problem solving). There were no moderating effects of diagnosis (schizophrenia vs. schizoaffective disorder), sample	

size, age, montage, current intensity, number of sessions, or total duration of the intervention.	
Risks	Not reported
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Osoegawa C, Gomes JS, Grigolon RB, Brietzke E, Gadelha A, Lacerda ALT, Dias AM, Cordeiro Q, Laranjeira R, de Jesus D, Daskalakis ZJ, Brunelin J, Cordes J, Trevizol AP

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

Schizophrenia Research 2018; 197: 34-44

View review abstract online

Comparison	**Effectiveness of adjunctive transcranial direct current stimulation (tDCS) vs. placebo/sham.**
Summary of evidence	**Moderate to low quality evidence (small sample, inconsistent, imprecise, direct) finds a medium-sized effect of greater improvement in negative symptoms with active tDCS.**
Negative symptoms **Measured with the PANSS (negative subscale)**	
A significant, medium-sized effect of greater improvement in negative symptoms with tDCS; 7 RCTs, N = 169, SMD = 0.50, 95%CI 0.02 to 0.97, $p < 0.05$, $I^2 = 51\%$, $p = 0.05$	
Risks	There were no differences in dropout rates.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

AHRS = Auditory Hallucinations Rating Scale, CI = confidence interval, *g* = Hedges' standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = sample size, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome, PSYRATS = Psychotic Symptom Rating Scales Scale, RCT = randomised controlled trial, SANS = Scale of assessment of negative symptoms, SMD = standardised mean difference, vs. = versus

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[8].

† 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[8].

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[9]. lnOR 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

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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[10].

‖ 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.

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