



Transcranial Direct Current Stimulation for Negative Symptoms of Schizophrenia: Why the Reader Must Choose a Clinically Relevant Outcome

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

A recent, large, randomized controlled trial (RCT) of 10 twice-daily sessions of active vs sham transcranial direct current stimulation (tDCS), delivered across 5 consecutive days to schizophrenia patients with high negative symptom burden, found that active treatment was superior to sham treatment by a mean of 2.65 points on the Positive and Negative Syndrome Scale, negative subscale (PANSS-N), at 6 weeks. This was the primary endpoint of the study. Because a difference of 2.65 PANSS-N points between the average active vs sham tDCS patient is a very small advantage, it appears that the finding was statistically but not clinically significant; why this is so is explained in the context of how the PANSS-N is scored. The study also found that, with response defined as 20% attenuation of PANSS-N scores, significantly more (40% vs 4%) active than sham group patients responded at 6 weeks. This was one of many secondary outcomes that the study examined. Because response is a clinically important endpoint, it appears that the finding was clinically as well as statistically significant; why this is so is also explained in the context of PANSS-N scoring. As a final poser, whereas the advantage for active tDCS for both outcomes persisted at 12 weeks, at neither 6 nor 12 weeks was active treatment superior to sham treatment on a global measure of functioning; this suggests that the advantage for active tDCS does not translate into real-life gains. The reader is provided with an understanding of how to critically read a paper that describes an RCT; of how to interpret a continuous outcome measure that describes the average patient versus a categorical outcome measure that describes a clinically important outcome in an entire group; and, most important of all, of the need to choose an outcome that is relevant to clinical practice.

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Schizophrenia is a major mental illness that is characterized by positive symptoms, negative symptoms, cognitive impairment, behavioral disturbances, and disturbances in social, occupational, and other areas of functioning.

Negative Symptoms

Negative symptoms of schizophrenia are best understood as emotional, interactional, and other attributes that are expected to be present in a fully functional, healthy individual but are often compromised in patients with the disorder. Negative symptoms include attenuated emotional reactions, decreased verbal output, decreased social interaction, decreased interests, decreased motivation, and decreased experience of pleasure, among others; the symptoms included in this list depend on what instrument is used in assessment. Negative symptoms are associated with functional impairments in everyday life, and with reduced quality of life.

Negative symptoms may be secondary to positive symptoms, extrapyramidal symptoms, depression, and/or decreased opportunities for psychosocial stimulation. Negative symptoms may also be primary, that is, symptoms that represent a core part of the illness and that chronically persist even when there have been no positive symptoms, depressive symptoms, or extrapyramidal symptoms for long and when there has been adequate psychosocial stimulation.¹

Atypical antipsychotic drugs are generally more effective in the attenuation of negative symptoms than are typical antipsychotic drugs.² Among atypical antipsychotics, clozapine² and cariprazine³ have demonstrated especial efficacy against negative symptoms. Amisulpride, in particular, has demonstrated efficacy against primary negative symptoms when used in low doses that preferentially block presynaptic D₂ dopamine receptors.⁴

Many other treatments have shown efficacy against negative symptoms, including antidepressant drugs,⁵ cholinesterase inhibitors,⁶ minocycline,⁷ modafinil,⁸ ondansetron,⁹ and others. Among brain stimulation techniques, both repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) have been found to reduce negative symptom burden in schizophrenia.¹⁰

Transcranial Direct Current Stimulation

tDCS, formerly called brain polarization therapy,¹¹ is a noninvasive form of electrical brain stimulation that involves the continuous passage of low amplitude (1–3 mA) direct current through electrodes, at least one of which is sited on the scalp¹²; where the electrodes are placed depends on the purpose of tDCS. Patients who receive tDCS are fully conscious all through the treatment session, which is usually 20–30 minutes in duration.^{12,13}

tDCS increases the negativity of the resting membrane potential of neurons in the area of cerebral cortex underlying the cathode and decreases the negativity in the resting membrane potential of

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neurons in the area of cortex underlying the anode^{12,13}; thus, cathodal stimulation results in cortical inhibition and anodal stimulation facilitates cortical excitation. These changes facilitate neuroplasticity. It may be hypothesized, therefore, that anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) may improve activation of DLPFC neural circuits and reduce the severity of negative symptoms of schizophrenia; this has indeed been observed in some studies of the use of tDCS to treat refractory auditory hallucinations in schizophrenia.^{14,15}

In this context, Valiengo et al¹⁶ described the largest randomized controlled trial (RCT) of tDCS that was specifically designed to study the efficacy of the treatment against negative symptoms in schizophrenia patients. The present article summarizes the RCT and critically examines its findings and the implications for the field.

What the Study Did

The authors¹⁶ recruited 100 patients with *DSM-IV* schizophrenia, all of whom had been stable for at least the past month, and all of whom had clinically significant negative symptoms, operationalized as a score of at least 20 points on the Positive and Negative Syndrome Scale, negative subscale (PANSS-N). The mean age of the sample was about 35 years. The sample was 80% male. The mean duration of illness was about 14 years. About three-quarters of the sample was unemployed.

These patients were randomized to receive active or sham tDCS. tDCS was administered in a course of two 20-minute sessions a day for 5 days, using electrodes that were 5 × 7 cm in area. The anode was centered over the left DLPFC and the cathode, over the left temporoparietal junction, corresponding to F3 and T3P3, respectively, in the 10–20 EEG electrode positioning system. The current was ramped up and down at the start and end of the tDCS session; administration of 2 mA current was otherwise continued all through the tDCS session in patients receiving active tDCS and only for 30 seconds between ramp periods in those receiving sham tDCS. All patients were continued on their current psychotropic prescription, except for antidepressants, which were washed out 4 weeks or longer before the study. One sham and 4 active tDCS patients dropped out of the study; reasons for dropout were not stated.

What the Study Found

Both groups improved by a mean of 2–3 PANSS-N points at the 5-day treatment endpoint; there was little difference between groups. At the end of week 6, however, improvement with active tDCS was significantly greater than that with sham tDCS (by a mean of 2.65 points on the PANSS-N; Cohen $d = 0.57$); this was the primary outcome of the study. The advantage for active tDCS was slightly attenuated but remained statistically significant at week 12.

Analysis of individual PANSS-N items showed that active tDCS was superior to sham treatment on all but 2 items: passive/apathetic withdrawal and stereotyped thinking.

Thus, improvement was spread out across the PANSS-N and not limited to a few items.

With response defined as at least 20% attenuation of PANSS-N scores, the response rate in active vs sham tDCS groups was 40% vs 4% at week 6 (number needed to treat [NNT], 2.8) and 38% vs 4% (NNT, 2.9) at week 12. However, when the threshold for response was raised to 25% attenuation of PANSS-N scores, at 6 weeks only 12% vs 0% of active vs sham patients were deemed to have responded, implying that, in most responders, patients barely met criteria for response.

These benefits with active tDCS were attenuated in patients who had previously received clozapine, in those receiving higher doses of antipsychotic medication (classified in haloperidol equivalents), in those classified as treatment-resistant and ultra-treatment-resistant, and in those with a larger number of past hospitalizations.

Importantly, at both 6- and 12-week time points, active tDCS was no better than sham treatment on other outcomes, assessed using the Scale for Assessment of Negative Symptoms (SANS), PANSS positive subscale, PANSS total scale, Auditory Hallucinations Rating Scale, and Calgary Depression Scale for Schizophrenia (CDSS). Active tDCS was not significantly superior to sham treatment on the CDSS even when analysis was limited to patients whose cutoff on the scale suggested a comorbid diagnosis of major depression, though this analysis may have been underpowered (subsample sizes not reported). Last but not least, active and sham tDCS groups did not differ in Global Assessment of Functioning (GAF) outcomes.

Burning sensation at the electrode site was reported by 42% vs 14% of true vs sham tDCS patients, respectively. Patients were no more accurate in guessing their treatment assignment than could be expected on the basis of chance.

Summary of the Findings

This large RCT¹⁶ found that 5 days (10 sessions) of anodal stimulation of the left DLPFC was associated with a small but statistically significant reduction in negative symptom scores in schizophrenia patients with high negative symptom burden. The benefits developed across the course of 6 weeks and persisted at 12 weeks.

Positives of the Study

This was a large, 2-center RCT; the results can therefore be expected to have a substantial impact on the field. Although the investigators administered tDCS on just 5 (consecutive) days, with just 10 sessions in all, benefits that developed across 6 weeks persisted to the 12-week study endpoint. If a brief course of tDCS has such persistent effects, pharmacologic interventions for negative symptoms may not be necessary. This is noteworthy because pharmacologic augmentation strategies that improve negative symptoms may carry an adverse effect burden; in contrast, tDCS, as administered in this study, was very well tolerated.

It is also possible that booster sessions of tDCS may maintain treatment gains, though this will need to be

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separately studied. If booster treatments are effective in maintaining improvement, and especially if the treatment gains with tDCS are clinically meaningful, tDCS could become an important, inexpensive, well tolerated option for schizophrenia patients with high negative symptom burden.

Statistical Significance vs Clinical Significance

Consider the hypothetical situation where houses built in one town have a carpet area that is approximately 1 mm² larger than that of houses built in the next town. From a statistical perspective, the houses in the first town are indubitably larger. From a practical perspective, the advantage will not translate into the conscious enjoyment of a larger living space. Examining statistical vs clinical significance in RCTs is much the same. tDCS produced statistically significant reduction in PANSS-N scores. Was the reduction clinically significant?

The PANSS-N comprises 7 items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. Each item is scored from 1 to 7, with descriptions of absent (scored as 1), minimal, mild, moderate, moderately severe, severe, and extreme (scored as 7). Thus, the minimum score on PANSS-N is 7 and the maximum score is 49.

In the tDCS study,¹⁶ the primary outcome was change in the PANSS-N score at 6 weeks. The mean PANSS-N score at baseline was approximately 25 in each of the 2 groups. This translates to a mean score of 25/7; that is, 3.57 points per PANSS-N item. An item score of 3 represents a rating of “mild,” and an item score of 4 represents a rating of “moderate.” So, on average, at baseline each item in the average patient was rated as being between mild and moderate in intensity.

Mean PANSS-N scores at 6 weeks were 20.51 vs 23.26 in active and sham groups, respectively (data taken from supplementary materials). This corresponds to a mean item score of about 2.93 and 3.32, respectively. That is, on average, at the 6-week time point each item in the active group was rated as just below “mild” and each item in the sham group was rated as just above “mild.” Would such decimal differences around a rating of “mild” be clinically noticeable? Note that it is reasonable to average the improvement across the PANSS-N items because active treatment was significantly better than sham treatment on 5 of the 7 items.

A telling point is that SANS scores did not differ significantly between groups at either 6 or 12 weeks, so active tDCS was effective against PANSS-N-rated negative symptoms but not against SANS-rated negative symptoms! Furthermore, GAF scores did not differ significantly across groups; at both baseline and 6 and 12 week endpoints, the GAF scores were in the “serious impairment” zone. The authors suggested that it could take time for improvement in negative symptoms to lead to better functional outcomes. However, active tDCS was superior to sham treatment for negative symptoms at both 6- and 12-week time points; in contrast, it was not superior to sham treatment for global functioning at either time point. If SANS scores are not

significantly improved, and if 3 months is insufficient to observe functional improvement, could the improvement in PANSS-N negative symptoms truly be clinically significant?

What About the Response Rates?

The discussion in the previous section examined the PANSS-N score as a continuous outcome in the average patient. What about the response rate, which was one of several secondary outcomes examined by the authors? The response rate in active vs sham treatment groups was 40% vs 4% at week 6 and 38% vs 4% at week 12. Considering that the cutoff for response rates is usually set at a value that is clinically meaningful, and considering that a 20% improvement in negative symptoms scores could reasonably be expected to result in noticeable differences between baseline and endpoint, it does seem that active tDCS was associated with clinically significant benefits.

As a group, patients in the active group improved from 25.00 at baseline to 20.51 at week 6; this translates to a 17.96% improvement for the group as a whole. As a group, patients in the sham group improved from 25.10 to 23.26; this translates to a 7.33% improvement for the group as a whole. One can easily understand, now, how 40% of the active group made it to the response cutoff (20% improvement in PANSS-N) whereas only 4% of the sham group did. A 40% vs 4% difference is striking.

So, what’s wrong here? Why is it that when the data are examined in one way they suggest that the difference between active and sham tDCS does not appear to be clinically significant, but when the data are examined in another way, the difference appears striking?

Resolving the Arguments

Resolving the arguments pivots around a key question: is a 20% improvement in PANSS-N scores clinically meaningful? The baseline PANSS-N mean score was 25. So a 20% improvement would imply a reduction of 5 points on the scale. This 5-point reduction could be a fall from moderately severe to absent on 1 PANSS-N item; or from moderate to minimal on 2–3 items; or from moderate to mild on 5 items; etc. All scenarios suggest that the improvement would be noticeable, that is, clinically significant. This does suggest that the 20% threshold to define response is valid.

The answer to the question posed at the end of the previous section is that there is no contradiction! The difference between active and sham tDCS may not be discernable *in the average patient*; however, *taken as a group*, there are many more patients who turn out to be “above average” (treatment responders) with active tDCS than with sham tDCS. This is a subtlety that needs to be pondered upon. Heads and tails can sit on the same coin.

Revised Summary of the Findings

At both 6 and 12 weeks, schizophrenia patients with prominent negative symptoms were much more likely to show clinically significant improvement with active tDCS than with sham tDCS, as delivered and assessed in this study.

Why Did the Contradictory Arguments Arise?

Looking back, it seems obvious that the 40% vs 4% response rate should have been given credence at the very outset, preventing the digression into the analysis of mean PANSS-N improvements in the average patient. However, that digression was necessitated by the study investigators who set PANSS-N improvement rather than response rate as the primary outcome of the study.

If so, is it permissible for us, as readers of the study, to assign more importance to what the investigators set as one of many secondary outcomes? It depends. Investigators need a primary outcome for many reasons, an important one being that they base sample size estimation on the primary outcome. Readers, however, may have a different a priori question, and so it could be reasonable to ask, a priori, whether more patients will show clinically meaningful improvement with active tDCS instead of to ask whether the average patient will improve more with active tDCS.

Note that if, to the reader, the a priori question was whether or not functional outcomes were improved by active tDCS, then the answer, straightaway, is No! An unanswered question is whether clinically meaningful improvement in GAF scores was more likely with active than with sham tDCS; unfortunately, we do not have an answer to this question because no cutoff for response rate is set for the GAF.

Three Clinical Messages

There are 3 clinical messages; you pay your money and you take your choice. (1) At both 6 and 12 weeks, the average schizophrenia patient with high negative symptom burden will show significantly greater PANSS-N improvement with active tDCS (as delivered in this study) than with sham tDCS; however, this difference would probably not be clinically discernible in the average patient. (2) Examined as a group, at both time points significantly more patients will show clinically meaningful decrease in PANSS-N scores with active tDCS than with sham treatment. (3) Greater improvement in PANSS-N ratings or higher response rates with active tDCS do not translate into greater improvement in global functioning at either time point.

Which of these the reader selects as a take-home message depends on what the reader's purpose is when considering whether or not to administer tDCS to a schizophrenia patient with prominent negative symptoms.

Parting Notes

Negative symptoms may be primary or secondary, and secondary negative symptoms may arise in different ways, as explained early in this article. The authors of the tDCS study¹⁶ did not describe their patients using these categories. Whereas one might expect that randomization would have balanced the groups in these regards, the information, if available, could have thrown light on the efficacy of tDCS in the different categories.

The authors did not provide information about whether or not their patients had previously received and failed pharmacologic interventions that have been suggested to

be useful for negative symptoms. This information could have helped better position tDCS in the context of existing experimental treatments for negative symptoms.

The authors did, however, state that patients receiving antidepressants underwent a 4-week washout; however, they did not record whether the antidepressant washout was associated with worsening of negative or depression symptom scores.

The lack of substantial superiority of active over sham tDCS may be a common feature across treatments for negative symptoms in schizophrenia, and not limited to tDCS alone.

Finally, this dissection of the clinical relevance of continuous versus categorical outcomes can be applied to all RCTs, across indications and treatments. If the response rate does not differ significantly between treatment groups, or if functional outcomes do not differ significantly between treatment groups, it is unlikely that statistically significant differences in illness ratings will be clinically meaningful.

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