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# Transcranial direct current stimulation in psychiatry: Clinical neurobiology & translational implications

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Transcranial direct current stimulation (tDCS) is a safe, well-tolerated, non-invasive, neuromodulation technique that applies direct current (in the range of 1-2 mA) using bio-conducting electrodes; tDCS causes polarity-specific neuromodulation of underlying brain regions.[1,2] tDCS is attracting increasing interest for interventional & investigative applications in psychiatry.

The mechanistic basis of tDCS involves several components.[2] It is important to note that tDCS does not evoke an action potential; relative depolarization (at the anodal electrode) or relative hyperpolarization (at the cathodal electrode) is one of components of mechanistic effect of tDCS.[1] tDCS also causes alteration of neurotransmitters (glutamate, GABA and several others). In addition, alteration of brain-derived neurotrophic factor as well as involvement of glial cell also are postulated to mediate the effects of tDCS. [summarized in 2] In addition, tDCS results persisting after-effects on neuroplasticity that might last up to about a day after stimulation; such effects of tDCS are likely to be mediated through glutamate synapses that are influenced by gama-aminobutyric acid (GABA)through calcium-dependent interactions.[1] Furthermore, repeated sessions of tDCS is likely to cause longer-lasting alterations of cortical excitability and activity that resemble long-term potentiation or depression.[1] The genesis of psychiatric disorders like schizophrenia and depression are postulated to be due to abnormalities in calcium-dependent synaptic plasticity processes amongst several other mechanisms.[3] It is possible that long-lasting neuroplasticity modulation following repeated sessions of tDCS underlies the ameliorative treatment effects in these disorders.[3]

Extensive research studies have been conducted to assess the safety and tolerability of tDCS. A systematic review that collated data on repeated sessions of tDCS in 4130 participants across 158 studies. Verum tDCS was comparable with sham tDCS in terms of adverse effects.[4] This offers robust support to the safety & tolerability of tDCS.[4] Data from several ongoing tDCS studies at NIMHANS also support the safety of tDCS.

While the safety and tolerance of this technique is well-established, the clinical efficacy of tDCS in psychiatric disorders is yet to be definitively established. Controlled studies have support for efficacy of tDCS in treatment of non-treatment resistant depression,[5] addiction/craving (alcohol, nicotine, cocaine)[3] and auditory verbal hallucinations in schizophrenia.[6] There is emerging evidence from several studies which support the utility of tDCS in treatment of obsessive-compulsive disorder and attention deficit hyperactivity disorder.[3] Nonetheless, evidence for therapeutic application of tDCS in psychiatric disorders needs further systematic work since some studies did not show significant result; in addition, it needs to be noted that most of the positive studies are of small sample size. Hence, large-scale, preferable multi-site studies are required for comprehensive and systematic evaluation of the effects of tDCS in several psychiatric disorders.[3]

In a study done at NIMHANS, using a randomized, double-blind, sham-controlled design (RCT), we examined the "effect of add-on tDCS [anode corresponding to left dorsolateral prefrontal cortex and cathode to left temporo-parietal junction; 2-mA, twice-daily sessions for 5-days] to treat refractory AVH in schizophrenia patients (N=25); following this RCT phase, schizophrenia patients who had less than 30% reduction in AVH severity were treated with an open-label extension (OLE) active stimulation to evaluate the effect of cross-over to verum tDCS. In the RCT phase, greater reduction of AVH score was observed in active tDCS group as compared to sham group. In the OLE phase, sham-to-verum crossed over patients (N=13) showed significantly greater reduction in AVH severity than their corresponding change during RCT phase. Together, these observations added further support to the beneficial effects of add-on tDCS to treat refractory AVH schizophrenia".[7]

There are certain aspects of tDCS that needs to be clarified; for example, it has been questioned that whether 2-mA current is strong enough to reach the brain to result neuronal modulation,[8] and inconsistent reports from treatment as well investigative studies.[9] While these doubts are being addressed, for example – Contextually, it needs to be acknowledged that there are reports that demonstrate this current strength of 2 mA delivered at the scalp is indeed capable of generating biologically relevant electrical field in certain deeper brain structures like thalamus or subthalamus.[10] It has been recommended that systematic research is required to unravel the biological underpinnings of neuromodulatory effects of tDCS as well potential parameters that might influence the inter-individual variability in response.[11] Recent advances in the form of availability of high-definition tDCS with improved focality, concurrent application of computational neuromodelling with neuronavigation to minimise inter-individual variations due brain structural differences have the immense potential to facilitate personalized neuromodulation.[12] tDCS has the advantage to offer safe, cost-effective, scalable, home-based application procedures that needs further systematic research.[13]

Another domain of increasing concern pertains to regulatory, legal & ethical aspects of tDCS especially due to the access of "over-the-counter (OTC)" tDCS devices. Contextually, it is important to note that the International Federation of Clinical Neurophysiology "*warns against the use of DIY devices and methods unless they have shown both efficacy and safety and recommends that any use of tDCS / related techniques in the treatment of a medical indication (at home or in the clinic) should be done with a medical grade device or consumer device and under supervision of medical provider and trained personnel*" (https://goo.gl/uZsXAb).[14] In conclusion, as summarized in a recent commentary by this author [2] – "tDCS is a simple, low-cost, technique that has robust safety and tolerance with an emerging evidence base for its efficacy in select psychiatric conditions. Systematic, large-sample, multi-site studies need to replicate these preliminary evidence leads; concurrently, studies should address neuroethical (eg, safety of long-term use, application for cognitive enhancement in healthy population, use in vulnerable populations like children, pregnant women) and regulatory challenges associated with tDCS to evolve best practice guidelines. Together, this might facilitate translation of tDCS to clinical services in psychiatry".

## Conflict of interest

There are no potential conflicts of interest to report.

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