Transcranial stimulation – where we are headed

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Transcranial brain stimulation has a certain appeal understandably because of the non-invasiveness of the procedure as well as the potential for targets and their therapeutic benefits. In fact, it isn't a very novel procedure, as early as 43 A.D Roman physician, Scribonius Largus, was found to have used electricity from "torpedo fish" to treat his patients for headache. Claudius Galen another physician of the same era found the application of dead "torpedo fish" ineffective in treatment and concluded that the electricity from a live fish was responsible for its healing effects. Later in the early 19th century since the advent of the "voltaic pile", earlier versions of our modern battery, electricity was used to treat various psychiatric disorders, with varying results. During the mid-20th century with the growing stigma for electrical stimulation, advent of Electro convulsive Therapy (ECT), and the "golden era" of psychopharmacology, transcranial direct current stimulation (tDCS) lost its popularity as a mode of treatment. Trans-cranial magnetic stimulation (TMS) was introduced in in 1985 by Anthony Barker, the physics of which was described by Michael Faraday in 1881. Later in the early 1990's (George et al, 1995; Pascual-Leone et al., 1996)[1,2] repetitive Trans-cranial Magnetic Stimulation (rTMS) was increasing being used for depression and found to be effective, the protocols and methods as well as the instrument have undergone considerable change since then. rTMS finally saw its entry into clinical use after its FDA approval following sustained results in clinical efficiency (O'Reardon et al., 2007).[3] Currently this is the only FDA approved indication for neuropsychiatric use of rTMS. Other methods like the tDCS, tRNS(Trans-cranial Random Noise Stimulation), tACS (Trans-cranial Alternate Current Stimulation) and other variations of TMS are in their relative nascent stages but hold good promise for clinical use.

Transcranial Direct Current Stimulation (tDCS) is a procedure which is done using a small instrument, operated by a 9Volt battery. It has two electrodes, the anode and the cathode which are place on the desired regions of the scalp to be stimulated. The current for stimulation is drawn from the 9Vbattery source and can be controlled by a ramp switch. Various manufacturers have their own specialty of the machine, some even offering highly focused stimulation known as HD tDCS. The optimal current is around 1-2mA for about 20-30 minutes (Nitsche et al, 2000).[4] rTMS on the hand uses a much larger and expensive machine which requires a dedicated set up. This machine has a hand-held coil which is usually shaped in the form of '8' other shapes being 'bent 8 figure' and 'H' coils, which generates a magnetic field, when turned on and which in turn stimulates the cortex underneath. Due to the high energy, which passes through these coils, external sources of cooling are needed and at times can over heat and lead to reduced efficiency of stimulation. Depending on the machine being used, there are various ways in which manufacturers deal with these problems. Brainsway™ Deep TMS,[5] a new machine is found to have the best results in terms of clinical efficiency, which uses an array of multiple coils placed in a helmet – dedicated to the type of indication. This is also one of the most expensive versions of TMS.

Since its revival tDCS has been used for various conditions. Cognitive enhancement with the use of tDCS was one of the most promising and exciting forays into neuropsychiatric therapies. Investigators like Dockery et al (2009), Fregni et al, (2005) and Zwissler et al (2014)[6,7,8] have conducted work which show that different aspects of memory can be enhanced with tDCS. These findings suggest a possible utility in dementia. The fact that the nature of psychiatric disorders has a basis of variable stimulation of the neurons and external modifier should modify the pathology. With this as basis, tDCS has been applied for various disorders. tDCS was tried for various disorders with varying evidence of efficacy (Rosenthal & Wulfsohn, 1970;[9] Feighner, 1973;[10] Priori, 2003).[11] Investigators like Cruetzfeldt et al. (1962)[12] and Bindman et al. (1964)[13] have shown that adequate exposure to extra cerebral DC currents can produce lasting effects in the intra cerebral current flows in rats. Subsequent studies revealed that the long-lasting effects are protein synthesis dependent (Gartside, 1968)[14] and accompanied by modifications of intracellular cAMP (Hattori et al., 1990)[15] and calcium levels (Islam et al., 1995).[16] In monkeys, approximately 50% of the transcranially applied current enters the brain through the skull (Rush & Driscoll, 1968).[17] These estimates were confirmed in humans (Dymond et al., 1975).[18] tDCS varies from other forms of non-invasive brain stimulation in that it does not produce rapid depolarization required to produce action potential in membranes. tDCS modifies spontaneous neuronal excitability and activity by a tonic de- or hyperpolarization of resting membrane potential (Creutzfeldt et al., 1962; Purpura et al., 1965).[12,19] Various studies have been done on other neuropsychiatric conditions such as substance abuse (Conti & Palacios, 2013),[20] hallucinations (Brunelin et al., 2014),[21] depression (Loo et al., 2012),[22] chronic pain and cognitive enhancement (Ferrucci et al., 2008; Boggio et al., 2008).[23,24]

As stated above, TMS has shown good efficacy in depression. However, considering that it has been a widely-accepted form of treatment and had much higher acceptance initially, there is dearth of information for its utility in other conditions like schizophrenia, ADHD, etc. It is now understood that TMS can induce plasticity of neural networks making them more amenable for desired plastic changes to be induced artificially (Oberman LM et al, 2010; Hasan A et al, 2015).[25,26] Few studies have shown efficacy of TMS in mania, there is evidence that the right sided DLPFC (Dorso-Lateral Pre Fontal Cortex) stimulation had stronger effect in mania (Grisaru et al, 1998).[27] Amphetamine model of mania in animals was shown to be ameliorated with TMS by Shaldivin A et al, 2001.[28] Studies involving broad regions of the cortex by placing the coil over the vertex, in schizophrenic patients initially reported success (Feinsod et al, 1998; Geller et al, 1997)[29,30] but failed to show any changes when compared to sham later. Hoffman et al, (1999,2000)[31,32] used a more focused location - the left temporoparietal cortex – has shown to attenuate the hallucinatory voices, suggesting that specific and more focused stimulation leads to better clinical outcomes.

Compared to TMS, tDCS has shown better efficacy in a wider range of disorders and is easier to use and administer. It is also much inexpensive when compared to TMS. Both these techniques have similar side effect profiles.

Concluding, it is evident that there is a therapeutic use of these technologies. These effects are highly dependent on the location of stimulus, dosage and method of delivery. One of the ways in which the effects can be enhanced is by precision targeting of the stimulus area, much is being understood about the neurophysiology of these disorders after the advent of non-invasive brain stimulation. As our knowledge further improves, especially with initiatives like the human connectome project, more specific areas of stimulation would be unveiled. In the meantime, several investigators are using imaging technologies like SPECT, fMRI, etc. to precisely target the stimulation areas (Jha S et al, 2016).[33] Targeted therapy ensures identification of the desired region on individual basis and better precision of delivery of stimulus. Not many studies exist where tDCS stimulation is confirmed on an objective level. As better animal models are developed these challenges can be answered and a more cost-effective and clinically efficient therapeutic stimulation can be achieved. Currently most of the studies have examined their potential usage in resistant stage of the illness, further studies are needed to confirm their usefulness across the different stages of illness and across the range of neuropsychiatric disorders. From the few studies conducted these technologies have proven to be relatively safe to use but due to the nascent stage at which the literature exists, larger sample sizes can further confirm their safety. We now understand that these stimulation techniques modify the plasticity of neural networks, and various forms of stimulation could be further combined to enhance their effects or can be combined with medications to further the desired effects.

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