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Review Article

Transcranial direct current stimulation and neuroplasticity genes: implications for psychiatric disorders

Chhabra H, Shivakumar V, Agarwal SM, Bose A, Venugopal D, Rajasekaran A, Subbanna M, Kalmady SV, Narayanaswamy JC, Debnath M, Venkatasubramanian G. Transcranial direct current stimulation and neuroplasticity genes: implications for psychiatric disorders.

Background and Aim: Transcranial direct current stimulation (tDCS) is a non-invasive and well-tolerated brain stimulation technique with promising efficacy as an add-on treatment for schizophrenia and for several other psychiatric disorders. tDCS modulates neuroplasticity; psychiatric disorders are established to be associated with neuroplasticity abnormalities. This review presents the summary of research on potential genetic basis of neuroplasticity-modulation mechanism underlying tDCS and its implications for treating various psychiatric disorders.
Method: A systematic review highlighting the genes involved in neuroplasticity and their role in psychiatric disorders was carried out. The focus was on the established genetic findings of tDCS response relationship with BDNF and COMT gene polymorphisms.
Result: Synthesis of these preliminary observations suggests the potential influence of neuroplastic genes on tDCS treatment response. These include several animal models, pharmacological studies, mentally ill and healthy human subject trials.
Conclusion: Taking into account the rapidly unfolding understanding of tDCS and the role of synaptic plasticity disturbances in neuropsychiatric disorders, in-depth evaluation of the mechanism of action pertinent to neuroplasticity modulation with tDCS needs further systematic research. Genes such as NRG1, DISC1, as well as those linked with the glutamatergic receptor in the context of their direct role in the modulation of neuronal signalling related to neuroplasticity aberrations, are leading candidates for future research in this area. Such research studies might potentially unravel observations that might have potential translational implications in psychiatry.

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Summations

- The review provides an insight into identifying the neuroplasticity genes that are responsible for the disruption of signalling pathways in psychiatric disorders that might be potentially relevant for the effects of transcranial direct current stimulation (tDCS).
- tDCS-induced cortical excitatory and neuroplastic changes are brought to the front, because there is an increased assessment of tDCS for schizophrenia treatment (even in treatment refractory patients), despite the debated mechanism of action of tDCS.
- Of the genes implicated in plasticity, BDNF and COMT interaction studies with tDCS have been reviewed; however, there is spars literature to obtain definitive conclusions.

Consideration

- Despite the emerging promising effects of tDCS treatment in psychiatric disorders, compelling observations to support aberrant neuroplasticity in several psychiatric disorders and robust evidence to support plasticity-modulating effects of tDCS, very few research studies have examined the potential relationship of neuroplasticity genes with the effects of tDCS in psychiatry. This is an important area that requires further systematic research to yield potential translational implications.

Introduction

tDCS is a non-invasive neuromodulatory brain-stimulation technique (1,2) that delivers low-intensity, direct current to cortical areas facilitating or inhibiting spontaneous neuronal activity (3). Although published studies report improvements in clinical and cognitive symptoms in various neuropathological and psychiatric illnesses, the mechanism by which tDCS impacts neural networks is not well-delineated and this requires thorough systematic research (3).

tDCS and neuroplasticity: schizophrenia

tDCS has recently received interest as an emerging add-on treatment modality, especially for schizophrenia patients who have persistent auditory hallucinations even after adequate treatment with antipsychotic medications (4). Its clinical utility has been demonstrated to a lesser extent for the treatment of negative symptoms (5,6). tDCS involves the passage of a weak, direct current that flows between electrodes placed over the scalp with resultant polarity-specific changes in neuronal excitability. The anodal stimulation increases and the cathodal stimulation decreases the neuronal excitability, possibly due to sub-threshold polarity-specific depolarisation or hyperpolarisation, respectively, of neuronal membranes. In schizophrenia, tDCS can be potentially effective in reducing auditory hallucinations by decreasing hyperactivity of the temporo-parietal junction (7). Indeed, pilot studies have demonstrated significant clinical improvement with tDCS, with respect to auditory hallucinations (7–9), negative symptoms (6,7) and insight into the origin and reality of these psychotic experiences (10). Moreover, in these preliminary findings, the results seem to have a large effect size and the benefits lasted for sufficient duration, which makes them potentially clinically relevant (7). Recently, it has been shown that the improvement in auditory hallucination severity may be due to adaptive modulation of neuroplasticity (11,12).

Neuroplasticity, the ability of the human brain to actively grow and change itself, has been a path-breaking revelation in the field of neuroscience (13,14). Alterations in this fascinating neurobiological phenomenon have been used as a framework to understand complex psychiatric disorders such as schizophrenia (15,16). Schizophrenia is increasingly being understood as a disorder of disrupted neuroplasticity (16,17). The biology of neuroplasticity and how it interacts with the disease process in schizophrenia have been the focus of much of the recent work, as the most influential molecular determinants of neural plasticity also have relevance for the pathophysiology of schizophrenia. The important genes among the determinants of neuroplasticity with functional significance in schizophrenia are disrupted-in-schizophrenia 1 (DISC1) (18), neuregulin 1 (NRG1) and ErbB4 signalling pathway (19), dystrobrevin binding protein 1 (dysbindin) (17,20,21), V-akt murine thymoma viral oncogene homolog 1 (AKT1) (22), brain-derived neurotrophic factor (BDNF) (23) and the *N*-methyl-D-aspartate (NMDA) receptor (24). A majority of genetic links, their molecular products and their interactions converge towards glutamate signalling, GABA (gamma aminobutyric acid) and its receptors, the dopamine system and the cell migration and neuronal development pathways (17). Further, dorsolateral prefrontal cortex (DLPFC)-mediated executive functions deficits that are universally reported in schizophrenia have been conceptualised as markers of deficit in neuroplasticity, as neural mechanisms associated with working memory are also closely related to those governing neural plasticity (16). Studies using non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and tDCS have shown the presence of plasticity deficits in schizophrenia patients as well as their unaffected first-degree relatives (25–27). These findings suggest that aberrant cortical plasticity may be an inheritable trait, and possibly a biomarker, for schizophrenia.

tDCS and neuroplasticity: other psychiatric disorders

Recently, tDCS has been studied with various psychiatric disorders and has shown encouraging preliminary observations. It has been studied as a potential therapeutic treatment for depression (28–30), alcohol craving and dependence (31–33) and anxiety disorders (34,35), apart from schizophrenia where tDCS has been in active use for treatment of auditory verbal hallucinations (7). tDCS

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application is now being explored in the treatment of dementia as well (36). All the above-mentioned psychiatric illnesses have shown to have aberrations in neuroplasticity (37,38). A single recent study by Player et al. (39) showed that neuroplasticity was increased after 13–21days of tDCS (2–2.5 mA for 20–30 min) in depressive patients. tDCS treatment led to significant mood improvement, but overall did not correlate with improved neuroplasticity. tDCS and alcohol craving inhibition is a new area of study. Studies with tDCS have reported positive outcomes, paving way for streamlining of the tDCS protocol in this area. Being in the exploratory phase of tDCS, not many studies are focussed on the underlying neuroplasticity changes brought about by tDCS. Of the limited studies, da Silva et al. (33) have examined the effects of repeated anodal tDCS (2 mA, 35 cm 2.20 min) over the left DLPFC on relapse to the use of alcohol in alcoholics in a sham-control setting. They reported that, when compared with the sham tDCS group, active tDCS was able to block the increase in neural activation triggered by alcohol-related and neutral cues in the prefrontal cortex (PFC) as indexed by event-related potential. Further studies exploring links with the biology of neuroplasticity are required in this area.

Disparate lines of evidence support the role of modulation of neuroplasticity as one of the key mechanisms underlying the beneficial effects of tDCS. For example, observations from magnetic resonance spectroscopy studies have implicated reduction of GABA (inhibitory neurotransmitter) through anodal tDCS and reduction in glutamate levels (excitatory neurotransmitter) through cathodal tDCS (40). Findings from animal studies have related the direct current effects to acute and lasting changes of neuronal activity and have implicated NMDA in long-term potentiation (LTP) of motor cortex through anodal tDCS (41,42). In this context, emergent findings also indicate glutamate-dependent LTP-like plasticity changes induced by tDCS stimulation (3,43). It is noteworthy that prolonged passage of current for sufficient duration to brain areas can lead to lasting changes in neuronal excitability of those areas (44,45). The applied external electric field modulates transmembrane potential differences by altering the concentration of intracellular ions across synapses, thereby modifying spike firing probability (3) inducing time-bound neuroplastic changes.

Studies thus far suggest that tDCS-induced LTP is mediated through changes in various neurochemical levels. In relation to this, few animal studies have been reported. A rat model of cerebral infarction demonstrated that tDCS intervention from day 7 to day 14 after stroke improved motor function and downregulated peroxidase (PX1) mRNA expression after stroke (46). In an ischaemic rat model, immunohistochemical staining showed that the early tDCS treatment reinforced notable MAP-2 (microtubule-associated protein 2) expression, and the late treatment group had enhanced levels of mainly GAP-43 (growth-associated protein 43) in both the peri-lesional and contra-lesional cortex (47). Extending further, c-fos and zif268 (zinc finger protein 225) (egr1/NGFI-A/krox24) are strongly implicated in schizophrenia (48,49). tDCS on rat brain slices showed that c-fos and zif268 were rapidly induced following neuronal activation, and increased zif268 expression played an important role in the induction and maintenance of LTP (50).

Aims of the study. This review attempts to summarise the literature pertinent to neuroplasticity modulation by tDCS and to identify the potential path it might lay to provide insights into the genetic correlates of tDCS response in psychiatric disorders. In addition, the aim of this review was to suggest the potential usefulness of non-pharmacological treatments in the optimisation of 'pharmacogenetic' investigation strategies, focussing mainly on tDCS. The relevant literature was obtained through PubMed (search till September 2014) using the following keywords: tdcs[All Fields] AND ('genotype'[MeSH Terms] OR 'genotype'[All Fields]) -7; tdcs[All Fields] AND ('polymorphism, genetic'[MeSH Terms] OR ('polymorphism'[All Fields] AND 'genetic'[All Fields]) OR 'genetic polymorphism'[All Fields] OR 'polymorphism'[All Fields]) -10; tdcs[All Fields] AND ('genes'[MeSH Terms] OR 'genes'[All Fields] OR 'gene'[All Fields]) -20; (direct[All Fields] AND ('Current'[Journal] OR 'current'[All Fields]) AND stimulation[All Fields]) AND ('polymorphism, genetic'[MeSH Terms] OR ('polymorphism'[All Fields] AND 'genetic'[All Fields]) OR 'genetic polymorphism'[All Fields] OR 'polymorphism'[All Fields]) -15; ('schizophrenia'[MeSH Terms] OR 'schizophrenia'[All Fields]) OR ('psychiatry'[MeSH Terms] OR 'psychiatry'[All Fields])AND ('neuronal plasticity'[MeSH Terms] OR ('neuronal'[All Fields] AND 'plasticity'[All Fields]) OR 'neuronal plasticity'[All Fields]) -767 (papers selected relevant to gene polymorphism and neuroplastic defects). From these articles identified through PubMed search, relevant cross references were identified (Fig. 1).

tDCS, cortical excitability and neuroplasticity

Despite its increasing use in experimental and clinical settings, the cellular and molecular mechanisms underlying tDCS are yet to be established definitively. Elucidating the properties and foundations of

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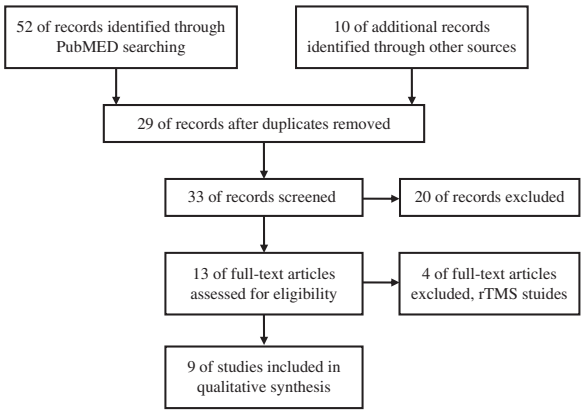

Fig. 1. Schematic overview of the selection of articles.

neuroplasticity has been an area of important focus in current activities of brain research (44). Based on scientific documentations, recently it has been hypothesised that tDCS alters neuronal excitability and motor performance (40). Physiological after-effects of tDCS also appear to be associated with LTP (51–53).

The neuroplasticity-modulating effects of tDCS can be determined by measuring the activation of brain areas through the variation in the cortical excitability in the electrode underlying areas and those nearby. tDCS provides current non-invasively and painlessly to induce focal, prolonged but yet reversible shifts of cortical excitability (45,52). However, the excitability changes are not reported when the current stimulation is of short duration (4 s), as reported in studies that utilised pharmacological design to monitor tDCS-induced cortical changes (44,51). Repeated tDCS within a specific time window is able to induce LTP-like plasticity in the human motor cortex (54).

A growing body of evidence supports the effects of tDCS on cortical excitation with and without cognitive task performance. The studies either reported anodal or cathodal stimulation effects or both. Working memory was found to be influenced by tDCS, as evidenced by improved performance in a three-back sequential-letter working memory task during anodal stimulation of the left DLPFC (53,55). In addition, tDCS has been shown to induce neuroplasticity in healthy individuals (56), and specific anodal tDCS has been shown to induce LTP-like plasticity (12,57). Applying large electrode anodal tDCS causes amplitudes of motor-evoked potential (MEP) components to decrease significantly, whereas it causes those of early somatosensory-evoked potential components (N20 and P25) to increase (58). A sham-control study (59) reported significant improvements in motor function following unilateral and bilateral stimulation when compared with sham stimulation immediately after 30 and 60 min. Finally, a study on regional cerebral blood flow (rCBF) demonstrated that real tDCS increased rCBF in specific brain areas compared with sham and this persisted for up to 50 min after the end of tDCS (60). Similar findings, such as anodal tDCS increasing rCBF in sub-cortical brain regions compared with cathodal tDCS, have also been shown (61).

In addition, the impact of tDCS on cortical excitability can also be measured by tracking the brain functional connectivity changes. Preliminary evidence for tDCS-induced neuroplastic alterations that might be related to functional connectivity changes in the human brain has been shown recently (62). A study was also performed on motor rehabilitation with tDCS (63). In this study, tDCS was installed with functional near-infrared spectroscopy that provided insight into the neuroplasticity changes through modulation in functional connectivity in relation to modulated muscle output. Further, in healthy individuals, application of anodal tDCS over DLPFC with cathode over contra-lateral supraorbital area was used to examine the dynamic interactions within and across intrinsic resting-state networks before and after stimulation. The results revealed a re-distribution of activity across resting-state networks (64,65).

Genetic variations within BDNF and COMT genes and the impact of tDCS

Genetic variation is one of the major factors that play a determining role in the response of the brain to injury and diseases (66,67). As already stated above, genes related to neuroplasticity seem to be critical in the pathogenesis of schizophrenia. In recent studies, two important neuroplasticity-modulating genes were identified that are significantly linked with schizophrenia pathogenesis – BDNF and COMT (68–71). In this respect, BDNF and COMT have been evaluated to assess the impact of tDCS and how the response improvement is influenced by genetic variations within these genes.

It has been shown that the BDNF genotype might have a significant effect on the neuroplasticity effect of tDCS. For instance, in a study that examined the potential effects of BDNF polymorphism on the neuroplasticity effects of tDCS, it was observed that the carriers of the Val66Met allele displayed enhanced plasticity for facilitatory tDCS as well as for inhibitory tDCS (72). A study has been conducted on adult mice M1 brain slice carrying a forebrain-specific deletion of the BDNF gene to demonstrate the tDCS interaction (41). Current was applied in parallel to the vertical M1 fibres (0.75 mV/mm for

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15 min), but before tDCS few slices were incubated in CSF containing the BDNF scavenger for 1.5 h. Brain slices with deletion in the BDNF gene exhibited no synaptic potentiation, whereas slices without gene deletion displayed intact tDCS-LTP (transcranial direct current stimulation induced long-term potentiation). However, after incubation with the BDNF scavenger, tDCS-LTP was abolished in the later slices, suggesting activity-dependent BDNF secretion during tDCS. Further expanding the study, healthy human individuals received anodal tDCS or sham tDCS targeting the left M1 hand knob and cathode over the contra-lateral forehead. It was suggested that genotype × stimulation interaction was not significant and anodal tDCS may induce a facilitatory effect on BDNF-dependent motor skill learning in both genotypes (val/val or val/met).

Despite the positive correlation between BDNF and tDCS, tDCS after-effects were reported not to be influenced by the BDNF polymorphism when studied with before and up to 24 h after 20 min of cathodal tDCS following single- and paired-pulse TMS-induced cortical excitability (73). The study examined the thresholds for MEPs, short-interval intra-cortical inhibition and intra-cortical facilitation and did not find any difference in relation to polymorphism, but stated that 20-min tDCS was capable of inducing a long-lasting suppression of the excitability of the human motor cortex. This finding was replicated by Brunoni et al. (74) intensively by investigating interactions of tDCS and BDNF as well as the role of its alleles as the genetic predictor for major depressive disorder (MDD). It was found that not BDNF but the 5-HTTLPR polymorphism was associated with treatment response. On the same note, many recent reports have been published on healthy individuals, suggesting once again that no correlation exists between tDCS response and BDNF Val66Met interaction. Fujiyama et al. (75) performed a study to compare the extent and time course of anodal tDCS-induced plastic changes (10, 20, 30 min, 1 mA true or sham current) in the primary motor cortex (M1) in young and older adults also assessing BDNF polymorphism interaction. The study reported that tDCS-induced plastic changes were delayed as a result of healthy aging (30 min significant change in excitability), but that the overall efficacy of the plasticity mechanism remained unaffected. In addition, BDNF Met allele did not result in significant differences in excitability increases for either age group. Similar to the study by Di Lazzaro et al. (73), MEPs were taken into account to report the effect of the BDNF Val66Met polymorphism on the after-effects of tDCS (76). This study indicated that both Met66Met and Val66Met carriers produced a late facilitation of MEPs following recording under stereotaxic guidance for 90 min after 9 min of anodal tDCS. The study clearly rules out any specific role of the BDNF Val66Met polymorphism.

Although the focus of gene X tDCS interaction studies have mainly been on BDNF, a recent study has reported that in COMT Met/Met allele carrier anodal tDCS on the DLPFC was associated with a deterioration of set-shifting ability, assessed by the most challenging level of the parametric Go/No-Go task (77). The study also suggested that the individual genetic profile may contribute to modulate the behavioural effect of tDCS.

Discussion

Recently, tDCS has gained renewed interest as a potential therapeutic technique. There have been increased optimised applications of late; however, a definitive understanding of the mechanism of action is still in the juvenile state. In this context, the neuroplastic change hypothesis is being appreciated widely. This notion could empirically be tested by studies involving genes that are primarily known to modulate synaptic plasticity changes for LTP. Apart from the tDCS studies mentioned above (Table 1), similar studies have been conducted with varied models of transcranial stimulation, and these studies have also highlighted the important role played by genetic variation on treatment response.

The emerging trend of using tDCS in the clinical setting, especially for treatment of psychiatric disorders (add-on or therapeutic), has highlighted the necessity to investigate the disrupted neuroplasticity hypothesis of these disorders (16,17). In addition, there is a need to investigate the role played by genetic insults to dynamic network connectivity signalling cascades associated with cognitive disruption (78) in psychiatric disorders. The altered neuroplasticity and multiple risk genes that are known to be involved in the pathogenesis of various mental illnesses are the putative neuroplasticity-regulating genes (DISC1, neuregulin/ErbB4, dysbindin, Akt1, BDNF and the NMDA receptor) (17,79). These risk genes have been studied to answer how alterations in their expressions may contribute to the dys-connectivity observed in these illnesses. Furthering the genetic link in schizophrenia, Greenwood et al. (80) revealed ERBB4 (encode receptor tyrosine-protein kinase erbB-4), GRID2 (encode Glutamate receptor, ionotropic, delta 2), RELN (Reelin) and NRG1 to be in extensive pleiotropy, offering a compelling importance of these genes in the neuropathology of schizophrenia and its associated heritable deficits. Genetic variation associated with reduced function in the *CREB1-BDNF-NTRK2*

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Table 1. Summary of studies examining the effects of neuroplasticity genes on tDCS response

Study	Design	tDCS methodology	Key findings
Antal et al. (72)	BDNF (healthy volunteers)		
	15 subjects with the Val66Met allele	24 anodal stimulation with 10 Val/Met, 7–9 min	iTBS, plasticity could be only induced in the Val66Val allele carriers
	46 subjects with the Val66Val allele	19 cathodal stimulation with 8 Val/Met, 13 min, 1 mA, 1 session	Facilitatory and inhibitory tDCS, Val66-Met allele displayed enhanced plasticity
	3 Met66Met carriers	Anode-left M1 and Cathode-contra-lateral orbit	tRNS, no difference between groups
Fritsch et al. (41)	Animal study		
	M1 slices from adult mice carrying a forebrain-specific deletion of the BDNF gene	Anodal tDCS was applied in parallel to the vertical M1 fibres (0.75 mV/mm)	$BDNF^{flox/flox}$, cre mice exhibited no synaptic potentiation
		Slices incubated in aCSF containing the BDNF scavenger TrkB-IgG (1.5 μg/ml) for 1.5 h before DCS	Cre negative $BDNF^{flox/flox}$littermates displayed intact DCS-LTP
		15 min	After incubation, DCS-LTP abolished suggesting activity-dependent BDNF secretion during DCS
Fritsch et al. (41)	BDNF		
	17 subjects with the Val66Met allele	Anodal tDCS (current density 0.04 mA/cm^2; total charge 0.048 C/cm^2) or sham tDCS	The genotype × stimulation interaction was not significant
	17 subjects with the Val66Val allele	Daily for 20 min during training, targeting the left M1 hand knob	Anodal tDCS may induce a facilitatory effect on BDNF-dependent motor skill learning in both genotypes
	1 Met66Met carriers	Cathode over the contra-lateral forehead	Significant difference between sham and anodal in Val/Val subjects
Di Lazzaro (73)	BDNF		
	30 healthy volunteers	Electrode postion: anode over left first dorsal interosseus muscle (FDI) and cathode over contra-lateral orbit	BDNF polymorphism not associated with treatment response
		1 mA 20 min	A significant suppression of cortical excitability in cathodal tDCS
			Show for 1st time that the inhibitory effects of 20 min of stimulation are still pronounced 3 h after the end of tDCS
Brunoni et al. (74)	BDNF (unipolar depression)		
	120 participants (4 groups), 30 in each group of sham with placebo/setraline and true tDCS with placebo/sertraline	6 weeks: acute treatment period, 10 daily consecutive tDCS sessions, 2 follow-up tDCS sessions given every other week	No significant effect of genetic BDNF variants on amount of MEP suppression
		Sertraline 50 mg/day started simultaneously with tDCS	No influence on tDCS after effect
		Anode over the left and the cathode over the right DLPFC	
Fujiyama et al. (75)	BDNF		
	40 healthy subjects	Cortico-spinal excitability examined using rTMS before and following 0, 10, 20, 30 min anodal tDCS (30 min, 1 mA) or sham in young and older adults	BDNF genotype not associated with increase in excitability for either age group
	20 old and 20 young	Anode-left M1 and cathode-contra-lateral orbit	tDCS induced plastic changes delayed as a result of healthy aging, but overall efficacy of plasticity mechanism remains unaffected
Plewnia et al. (77)	COMT		
	46 healthy subjects	Anodal tDCS −20 min, 1 mA to DLPFC or sham stimulation and cathode over right orbit	Anodal tDCS of DLPFC associated with deterioration of set-shifting ability, assessed by most challenging level of the PGNG
	Double blind sham-controlled crossover study	Task-parametric Go/No-Go (PGNG) test to measure sustained attention, response inhibition and cognitive flexibility measured by set-shifting	COMT Val158Met associated with detrimental effect of anodal tDCS on cognitive flexibility
Teo et al. (76)	BDNF (subjects were recruited from databases)		
	22 subjects with the Val66Met allele	1 mA, 9 min of anodal tDCS after MEP. Anode-left first dorsal interosseus muscle (FDI) and cathode-contra-lateral orbit	Auditory cortical plasticity not affected by the BDNF Val66Met polymorphism
	23 subjects with the Val66Val allele	Motor-evoked potentials (MEP) recorded under stereotaxic guidance for 90 min	Met66Met carriers behave like Val66Met carriers for tDCS-induced plasticity, and produce a late facilitation of MEPs
	20 Met66Met carriers		

BDNF, brain-derived neurotrophic factor; DLFPC, dorsolateral prefrontal cortex; LTP, long-term potentiation.

pathway has multiple and sometimes opposing influences on risk mechanisms of depression (81). Gene candidates such as PCLO (piccolo presynaptic cytomatrix) and GRM7 (metabotropic glutamate receptor 7) have been recently shown to be associated with depression (82). In yet another study, linkage analyses (83) have strongly implicated GABRA2 (GABA A receptor, alpha 2) and CHRM2 (cholinergic muscarinic receptor 2) to be associated with alcohol dependence. GWAS analyses too have revealed that variations in the ANK3 (ankyrin G) and CACNA1C (alpha 1C subunit of the L-type voltage-gated calcium channel) genes are found to be associated with susceptibility to bipolar disorder (84). This ANK3 gene is also found to be associated with schizophrenia along with other disorders, making it a common genetic risk factor for neuropsychiatric diseases (85,86). All these genetic variations have a direct/indirect link with plasticity signalling pathways.

Of the other strong evidences for genetic misregulation in various psychiatric disorders is the presence of gene variants (single nucleotide polymorphisms, SNP) at functionally relevant positions within the genes. To further elaborate, specific alterations in DISC [non-synonymous SNPs: rs821616 (Cys704Ser), rs6675281 (Leu607Phe) and rs821597] are predicted to be associated with higher expression levels of the gene transcripts in lymphoblasts and hippocampus in the schizophrenic brain (18). Haplotype-based NRG-1 studies showed single marker SNP8NRG221533 and two microsatellite polymorphisms as the core risk factors for schizophrenia (87,88). BDNF, the most widely studied neuroplastic gene, too confirmed its strong genetic association with schizophrenia risk (89). Of all the BDNF polymorphisms, the most extensively studied rs6265 (Val66Met) polymorphism affects the activity-dependent secretion in neuronal cell cultures (90), hippocampus functions and episodic memory (91). COMT Met allele of the Val158Met gene variant has also been recently associated with stress-sensitivity in patients with schizophrenia (92). Lopez-Leon et al. (93) have found strong evidence for the association between the following major gene polymorphisms – namely, *APOE* (apolipoprotein E), variants of *GNB3* (guanine nucleotide-binding protein, beta 3), *MTHFR* rs1801133 (methylene tetrahydrafolate reductase) and *SLC6A4* (serotonin transporter) – and major depression. Of the other polymorphisms associated with psychiatric disorders, CRHR1 gene polymorphism is associated with alcohol dependence (94). Allelic differences in *SLC6A4* (rs1042173) associated with serotonin transporter (5-HTT) expression level alterations is also hypothesised to be a genetic marker for cue-induced alcohol craving among males, triggering disproportionate craving in response to alcohol consumption leading to more intense drinking (95). Leu657Phe polymorphism of the DISC1 gene is linked with bipolar disorder (79). Zhang et al. (96) have also reported a loss-of-function polymorphism in TPH2, which they found to be associated with MDD.

Despite the major evidences supporting the important risk genes involved in disrupting neuro-pathways in various mental disorders and positive effects of tDCS treatment (even in drug refractory patients), gene X tDCS interaction studies in these disorders have not been reported. In this view, exploring the gene X tDCS interaction is important due to the following factors: (i) to understand in more depth the role of individual genetic determinants for the efficacy of brain stimulation, tDCS in particular; (ii) it may in near future point towards new strategies for individualised neuro-stimulation approach by integrating genetic information in the design of studies and therapeutic interventions; and (iii) a better understanding of the mechanisms underlying inter-individual differences in cognitive response might help in exploring preventive and therapeutic strategies of psychiatric disorders using tDCS.

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Conflicts of Interest

None.

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