Review article

Transcranial Direct Current Stimulation: a potential novel treatment for alcohol addiction and abuse

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Abstract

Alcohol use disorder (AUD) is a major global health concern. Many treatment modalities have been used in past to help decrease the use of alcohol. Recently, a growing interest has been seen in neuromodulation as a novel treatment means to reduce alcohol addiction behavior. Studies on the effect of Transcranial Direct Current Stimulation (tDCS), especially over dorsolateral prefrontal cortex (DLPFC) have been conducted that have shown to reduce craving and relapse behavior in AUD. Adverse effects associated with tDCS are found to be minor and are temporary in nature. However, the results are preliminary as only few studies are done. More research on AUD done using tDCS will help improve our knowledge and understanding on the various factors involved in AUD besides helping to prevent the cycle of craving, relapse and abstinent.

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Introduction

AUD is the third most common cause of disease burden globally[1]. Despite many treatment options, AUD affects 18 million adult in the USA[2]. Exposure to alcohol-related cues has been shown to provoke craving by a conditioned appetitive response[3]. Although craving may not guarantee relapse rate and may in fact be a protective factor in some cases[4], AUD is known to follow a craving, relapse and abstinent cycle[5]. An urgent need is felt to help decrease and prevent AUD by developing new treatment modalities[6].

Cortical brain stimulation was introduced by Giovanni Aldini in 1802 when he publically demonstrated for the first time electrical stimulation of exposed human cortex[7,8] and treated a patient suffering from melancholia[8]. Most recently, direct current stimulation received attention as many studies done on human subjects showed positive effects of direct current stimulation with only minor side effects[9]. tDCS is a non-invasive technique[10] that uses two scalp electrodes – anode which increases the cortical exhibiting and cathode that decreases cortical excitability[11, 12]. Low intensity current is applied for a constant period of time[10]. The effects of tDCS have been shown to last for some time - 30-120 mins[13] even after the end of stimulation period[11, 12] tDCS has been shown to be effective in ameliorating the signs and symptoms of various psychiatric disorders including major depressive disorder, schizophrenia, obsessive-compulsive disorder[14, 15, 16]. Very recently, interest has arisen in the potential effect of tDCSon addiction as it has also shown to be effective in reducing craving and relapse rate in people with alcoholic problems[17-21]. In this article, we would review studies done using tDCS in people with AUD.

Method

A systemic literature search was done using terms "tDCS and substance use" or "tDCS and addiction." We also searched European and International Journals using the term "tDCS and substance abuse" and "tDCS addiction."

Pubmed/Medline search yielded 37 studies. Out of 37 studies, 12 studies measured the effect of tDCS on addiction/substance use.3 studies were excluded as they were done on cocaine-use; another 3 were excluded as they were done on smoking. One study was excluded as the study was done on methamphetamine and another was not done on human subjects. One study that used Alcohol Use Disorders Identification Test (AUDIT) as screening tool was included in this review as it was done on

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subjects with hazardous drinking pattern. For the final review, only 5 studies were included.

Studies included were – a) subjects who met DSM-IV, ICD -10 criteria for alcohol dependence or were identified as people with hazardous drinking pattern as evidenced by AUDIT score of more than 8; b) age no less than 17; c) use of sham trial with a current for no more than 60 seconds; d) Number of subjects no less than 10.

Clinical trials done on alcohol use disorder using tDCS

A randomized, double-blind, sham-controlled, crossover study was done on subjects (n=13) who met the DSM-IV diagnosis of alcohol dependence. Subjects received three types of treatment on DLPFC – left anodal/right cathode, right anodal/left cathode and sham treatment (2 mA for 20 mins) with a 48 hour interval between the sessions. The investigators used slopes to find the outcome measures with T0- baseline assessment, T1- assessment after cue but before tDCS, T2- after tDCS and before 2nd alcohol cue and T3- after second alcohol cue. Significant increase in craving was found by the cues used in the study ($p<0.0001$). Age and gender were significantly correlated to increase in craving observed from T0-T1 ($p= 0.0162$ and $p = 0.0076$, respectively). Significant decrease in craving was found between anodal left/ cathodal right ($p = 0.02$) and cathode right/anode left ($p<0.0001$) vs. sham tDCS. No significant difference was found between the two treatment groups ($p=0.53$). No significant effect of age, gender or years of drinking was observed ($p>0.05$). Significant negative correlation was seen post-treatment between treatment and cue provoked craving. Positive correlation was found between sham tDCS group and cue proved craving post treatment ($p<0.007$). Increase on "worried/ concerned" item on Visual Analogue Scale (VAS) scale for mood domain was found after right anodal/ left cathodal stimulation ($p=0.02$) which was not found with left anodal/right cathodal stimulation vs. sham. No significant adverse effect was reported in three groups. Discomfort at stimulation site was the most common adverse effect. Small sample size, failure to use neutral cue are limitations of the study. Also the application of bilateral tDCS, either ways (right anode/left cathode or left anode/right cathode) resulted in reduction of craving. Hence, it cannot be known if reduction in craving behavior was due to right vs. left stimulation[17].

A placebo-controlled tDCS study over left DLPFC was done on alcoholics that met diagnostic criteria of alcohol dependence by ICD-10, using Lesch's typology (Lesch I, n= 16; II, n = 7; III, n = 14; IV, n = 12) during their abstinence period on event-related potential (ERP) and frontal function. Type II showed least amount of alcohol intake (7.2 drinks/d) as compared to Type IV (22.0 drinks/d), Type III (12.1 drinks/d) and Type I (21.5 drinks/d). Anode was placed on F3 and cathode on contralateral supra-deltoid area. Treatment was given for 10 mins at 1mA of current. Frontal Assessment Battery (FAB) scores were significantly improved ($p=0.038$) after tDCS session only in Type IV group as compared to other groups. No significant difference was seen on obsessive-compulsive drinking scale (OCDS) items in any group. Monitoring of P3 waveform segment 250-400 ms was used to examine the effect of alcohol relates vs. neutral sound. Alcohol related sound showed a small significant increase in magnitude of P3 at Fz site during vs. before active stimulation ($p<0.001$). Significant large difference was seen in mean magnitude of P3 in tDCS group as compared to sham ($p<0.0001$) at Fz site. At Fz site, during tDCS treatment P3 was shown to be decrease which was in contrast to after tDCS session which showed an increase. Increase in mean P3 amplitude at Pz site and decrease at Cz was seen in during vs. before stimulation as compared to sham. Significant reduction in mean P3 amplitude was seen pre-sham vs post-sham and during tDCS vs. post-tDCS for neutral sounds in Fz and between pre-sham and post-sham and pre-tDCS and post-tDCS at Cz and Pz sites. Mean P3 amplitude was decreased post-tDCS in Type II alcoholics and increased in Type IV alcoholics ($p<0.0001$). Increase in mean P3 amplitude was seen at Pz and Cz sites in Lesch's IV and decrease in Lesch's II at Pz sites. The study recruited less number of subjects and hence lack of power might explain lack of significant effect on other alcoholic types and lack of correlation between P3 and FAB in Lesch's IV group[18].

A randomized trial was done on Lesch's type IV alcohol-dependent patients (n= 13; sham tDCS = 7; tDCS treatment = 6) who also met DSM-IV criteria for alcohol dependence using cue-reactivity paradigm. This cue-reactivity paradigm consisted of three alcohol cue and 3 neutral pictures. F3 region was used for placing anode and right supra-deltoid region for cathode. 2 mA Current was given for 20 mins once per week for 5 consecutive weeks. 2 subjectson active tDCSand 6 subjects receiving sham tDCS relapsed which was not statistically significant ($p=0.053$). A trend for improvement was

seen in subjects on tDCS group as compared to sham group (p=0.082). Significant improvement on Hamilton scale for depression (HAM-D) (p=0.005) and Obsessive Compulsive Drinking Scale (OCDS) (p=0.015) was seen in treatment group as compared to sham at end point. No significant difference was on anxiety symptoms or quality of life. In sham-tDCS increase in ERP amplitude was seen for both neutral and alcohol related cues. In tDCS treatment group, increase in ERP potential for neutral cue was seen in frontopolar cortex (FPC) and orbitofrontal cortex (OFC) and no change for anterior cingulate cortex (ACC) and DLPFC. For alcohol related cue, tDCS treatment group showed increase in ERP amplitude in FPC, OFC and DLPFC and decrease in ACC. In sham tDCS group, current density increased in both sides whereas in treatment group minor changes in current density were seen for both neutral and alcohol related cues. The investigators call for a more intensive treatment schedule to better understand the effect of tDCS[19].

The first study to show long lasting beneficial modulatory effect of repetitive tDCS (klauss) on alcohol use disorder was a randomized (1:1), sham controlled, single-center study done to investigate the effect of repetitive bilateral tDCS (left cathodal/ right anodal) on DLPFC on relapse rate and to find the effect of tDCS on cognitive functions that are predominantly under frontal lobe control in detoxified alcoholics (n= 33; sham = 17, tDCS = 16). Current (2mA) was given for 5 consecutive days, twice daily for 13 minutes with 20 minutes break (13:20:13 schedule). 8/16 and 15/17 subjects relapsed from tDCS and sham group respectively at the end of 6-month observation i.e. subjects receiving tDCS treatment relapsed three times less in comparison to sham group. No significant difference was found on OCDS scores, HAM-D, Hamilton scale for anxiety (HAM-A), FAB and Mini Mental Status Examination (MMSE) scores. A trend towards improvement on Individual's overall perception of quality of life (Q1) was only seen on an abbreviated instrument of quality of life of the World Health Organization (WHOQOF-BREF) scale (p=0.06). This perception of better quality of life may be due to long abstinent period or may be due to feeling the environment safer. No significant change was seen on other WHOQOF-BREF domains. The only adverse effect reported was itching sensation or rare mild redness. Low number of participants and a telephonic interview used to know the relapse rate were study limitations[20].

A sham-controlled study was done to examine the effect of tDCS on alcohol craving on heavy alcohol users (n=41) using two variants of implicit association tests (IATs) – affective IAT (positive and negative words) and motivational IAT (approach and avoidance).The study measured the effect of tDCS on left DLPFC and right inferior frontal gyrus (IFG). Subjects were divided in three groups – DLPFC group (n= 14), IFG group (n=15) and sham group (n=12). Current of 1 mA was given for 10 mins. Anode was placed on F3 for DLPFC group and on crossing of Fz and Cz and Fz and T3 for IFG group. Cathode was placed on contralateral supraorbital region for all three groups. No subject dropped out from the study. Significant decrease in craving was found post-tDCS stimulation in DLPFC group (p=0.024). No significant effect was found in IFG group on craving (p=0.43). No significant effect of tDCS was found on either group on motivational IAT. Significant Reduction in reaction time was observed for attribute words in DLPFC group (p=0.0004) which was not found in IFG group. No significant correlation was seen between bias scores and AUDIT, alcohol time line follow back (TLFB) or alcohol approach and avoidance questionnaire (AAAQ) Inclined scores. The lack of significant effect on bias scores may be due to inclusion of only heavy drinkers or lack of power [21].

Discussion

Effect of tDCS on Alcohol related craving

Exposure to alcohol related cues has been shown to increase DLPFC activity in people suffering from AUD[22]. This is in contrast to people who drink socially that do not display an increase in DLPFC[22]. Increased activity in DLPFC has been linked with compulsive drug seeking behavior and has shown to disrupt cognitive inhibitive mechanisms resulting in relapse[23]. This may be due to the fact that DLPFC is linked to mesolimbic pathway via mesofrontolimbic connections[24]. Mesolimbic pathway is linked to reward behavior and is a critical pathway involved in addiction and drug seeking behavior[24]. This is supported by the den Uyl TE et al. study which showed that anodal DLPFC stimulation reduces even small predilections towards alcohol. Hence, craving to drugs may increase the activity in DLPFC through mesolimbic pathway[25]. Three studies were done to measure the effect on craving using anode placed over left DLPFC[17-21]. In only one study, right DLPFC anodal was also used[17]. In all three studies, craving was reduced, more pronounced when left DLPFC was used as anode. It was not clear as to which half of hemisphere is predominantly involved in reducing

craving. It was suggested that possible modulation of one half of DLPFC may lead to opposite effects on the other half[17]. This indicates that a situation of balance may be required or essential for craving behavior and the disturbance of this balance between the two DLPFCs may lead to reduction in craving[17, 26]. Functional imaging has shown that both left[22] and right[27] DLPFC are activated on exposure to alcohol related cues. This is also supported by the work of Wilson et al., 2004[28] that showed both sides of DLPFC may be required in drug-related cues. It is also possible that tDCS may exert its influence on drug-related cues and craving by modulating the adjoining areas of DLPFC such as OFC[29, 30] that have connections to subcortical regions[31]. However in den Uyl TEet al. study[21], anodal stimulation of right IFG failed to show significant decrease in craving (alcohol) despite showing increase in response inhibition in an earlier study[32].

Another possible mechanism may be that tDCS may diminish DLPFC activity in the memory related to substance abuse or attention bias associated with substance abuse[33]. This is supported by the study which show decrease attention to substance abuse related cues[34]. Again, in den Uyl TE et al. study[21] such an effect was not seen.

Effect of tDCS on Alcohol relapse rate

Two studies were identified that investigated the effect of tDCS on relapse probability[19, 20]. Repetitive tDCS over left DLPFC (F3) as cathode and right DLPFC (F4) as anode for 5 consecutive days was shown to reduce the risk of relapse by at least 50% besides improving the quality of perception of life[20]. In contrast, no significant reduction in relapse rate was seen in da Silva et al., study[19] that used left DLPFC as anode and right supra-deltoid region as cathode once a week for 5 consecutive weeks although an improvement in mood was reported. This may reflect that repetitive stimulation is advantageous over single stimulation to reduce relapse rate. Single stimulation may exert its influence only on DLPFC while repetitive tDCS may effect adjoining areas supposedly OFC, ACC and FPC[19]. Another factors accounting for the different results may be the different placement of electrodes or because of the fact that at baseline, active group in da Silva study used alcohol more than twice as compared to the sham. The mechanism by which tDCS may help reduce relapse is not well known although it is speculated that cathodal tDCS on DLPFC may disengage brain reward circuit leading to reduction in relapse rate[20] or enhance the attention to drug related cues without producing a reward effect[35].

Effect of tDCS frontal lobe functions in alcoholic subjects

Cue-reactivity paradigms have been used earlier to understand addiction[36]. Positive correlation has been found between cue-reactivity paradigms and P3 component of ERP alcohol[37]. P3 is involved in attention and memory regions of the brain that are involved in stimulus processing[38, 39]. People with AUD have been shown to have low P3 amplitude in cingulate, medial and superior frontal regions [40]. This is suggestive of poor frontal lobe activity in alcoholic subjects[40]. In study comparing the different types of Lesch alcoholics, Lesch type IV seem to be more sensitive to effects of tDCS as it showed maximum increase in P3 amplitude on alcohol exposure than other Lesch types and in contrast to Lesch type II alcoholics that showed decrease in P3 amplitude[18]. Anodal left dlPFCwas also shown to improve executive functioning in Lesch Type IV (as seen by FAB scores). This shows that tDCS can improve cognition in Lesch Type IV alcoholics although no significant effect of tDCS was apparent on MMSE[18].

Efficacy and Safety of tDCS

tDCS has been shown to successfully reduce craving and relapse rate besides improving the overall perception on life[17-21] when applied on DLPFC[41-45]. One distinct advantage of tDCS is its seemingly quick mechanism of action which is in contrast to psychopharmacological management of substance-abuse that takes long time[17-21]. tDCS modulates cortical excitability of human cerebral cortex[35] that last even after the stimulation is over i.e. effect of 9 min of tDCS stimulation has been shown to last for at least an hour [11, 12]. During the stimulation, electric current induced by tDCS causes subthreshold neuronal depolarization by opening/closing of voltage-gated ions[46, 47]. Post-stimulation effects are believed to involve NMDA receptors[48,49]. Other mechanism by which DLPFC may exert its effect is by having a detrimental effect on self-interested impulses[26, 50, 51]. Its efficacy may also be accounted by its role in exerting effect on surrounding cortical or subcortical structures or on opposite hemisphere[10,52,53] such as OFC[54]. OFC along with amygdala and striatum is involved in emotional aspects of decision making[42]. Thus, DLPFC stimulation may affect both the executive and affective part of decision making[50]. Modulation of DLPFC activity may have an influence on reward pathway[55]. D2 receptor blocker, sulpride has shown to block the effect of tDCS almost completely[56]. Thus, multiple mechanism of

action of tDCS application at DLPFC may explain its effectiveness.

Most common side effects seen with tDCS application areheadache, redness and local itching that are mild in intensity and temporaryin nature (17-21). The use of sham-control in tDCS is both easy and efficient i.e. turning the devise off either manually or automatically after 30-60 seconds has not been shown to break the blind (57).Chances of seizures induction by tDCS is not significantly high as the current is low (58). Hence, tDCS appears to be a promising tool in understanding the pathophysiology of alcohol use and ways to help people with alcohol use disorder.

Conclusion

Preliminary studies examining the role of tDCS in subjects with alcohol use disorder show promising results. However, the effect of tDCS on alcohol is not fully known. Most studies focus on applying the electrodes on DLPFC. Only one experiment was done to see the effect of tDCS on other parts of brain – right IFG that failed to show any significant effect. This is important as ERP was shown to be increased in OFC and FPC parts of brain besides DLPFC on exposure to alcohol related cues. Other study showed that left anodal DLPFC is more efficient as compared to right anodal DLPFC. All studies support the safety of tDCS stimulation, the only significant side effects being itching/tingling and redness which istemporary in nature. More studies using different montages, different placement of electrodes and different outcome measures will help enhance our understanding of alcohol addiction and ways to counteract them.

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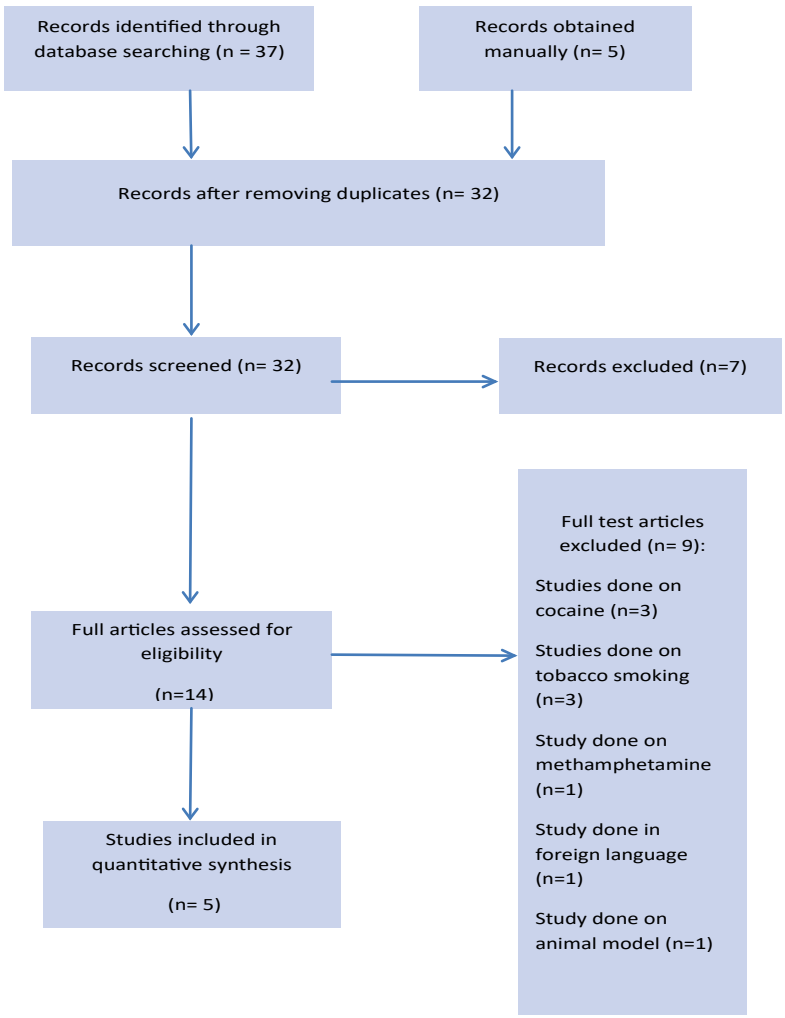

Study	Aim		Number of subjects, n	Study type	Montage used and size of electrodes	Placement of electrodes	Montage used in Sham-tDCS	Outcome Measures	Result
BoggioPS et al., 2007[17]	Effect of bilateral DLPFC on alcohol craving	DSM-IV for alcohol dependence	n=13	Randomized, sham-controlled, double-blind, cross-over study	2 mA for 20 mins; 35cm2	Anode over left and cathode over right DLPFC; Anode over right and cathode over left DLPFC	Stimulator turned off after 30 sec	AUQ, Visual analog scale for mood	Significant reduction in craving seen after anodal left/cathodal right DLPFC vs. sham (p=0.02) and anodal right/cathodal left vs. sham (p<0.0001). No significant difference seen between anodal right /cathodal left and anodal left/ cathodal right stimulation (p=0.53). Craving increased by alcohol related cues in anodal left/cathodal right (p=0.12) and anodal right/ cathodal left (p=0.64). Anodal right/ cathodal left DLPFC resulted in higher score on worried/unconcerned item vs. anodal left/cathodal right DLPFC stimulation (p=0.02)
Nakamura-Palacios EMet al.,2012[18]	Effect of tDCS over left DLPFC on P3 and frontal fucntions	ICD-10 alcohol dependence	n, Lesch type I = 16; n, Lesch type II = 7; n, Lesch type III= 14; n, Lesch type IV = 12	Randomized, crossover, sham-controlled	Two sessions each done 7-day apart -each at 1mA for 10 mins ; 35 cm2	Anode F3; cathode contralateral supradeltoid area	Stimulation turned after 20 sec	MMSE, OCDS, FAB, ERP-P3	No significant difference in MMSE score across all Lesch type except type IV that showed lower MMSE; Significant improvement on FAB scores in active tDCS group in only Lesch type IV (P=0.038). Effect alcohol related sound on mean P3 amplitude: Increase in both active and sham group at FZ site (p<0.001). significant increase at FZ site seen in after vs. before and during vs. beforein active group as compared to sham (p<0.0001); relative reduced P3 P3 in CZ and PZ site in active group vs. sham (p<0.0001); decrease in amplitude at CZ site during vs. before in the active group as compared to sham (p<0.0001); increase in amplitude at PZ site during vs. before in active group in comparison to sham (p<0.0001); For neutral sounds change in mean amplitude of P3: Significant decrease was found at FZ, CZ, PZ sites in both pre-tDCS vs. post-TDCS and pre-sham vs. post-sham; at FZ site, significant decrease in mean amplitude was found in Lesch type II in during vs. before and before vs. after. In Lesch type IV (p<0.0001), significant increase was found in during vs. before and before vs. after tDCS application (p<0.0001). At PZ site, significant decrease in mean P3 amplitude was seen in Lesch type II in during vs. before and after vs. before and increase at CZ and PZ site in Lesch type IV during vs. before and after vs. before
da silva et al., 2013[19]	Effect of anodal dlpfctDCS on alcohol relapse and craving	DSM-IV for alcohol dependence	Lesch type IV; n, tDCS = 6; n, sham =7	Randomized, sham-controlled	2mA for 20 mins once a week for 5 consecutive weeks, 35 cm2	Anode left DLPFC (F3), cathode on right supradeltoid region	Stimulator turned off after 20 sec	FAB, MMSE, OCDS, Hamilton depression, Hamilton anxiety, Quality of life, ERP	2/6 from active tDCS and 6/7 sham group remained abstinent. Significant improvement on OCDS (p=0.015) scores and Hamilton depression score (p=0.005) seen in active group vs. sham. No significant improvement seen on FAB score, MMSE, Hamilton anxiety or quality of life; increase in ERP amplitude at FPC, OFC, DLPFC and decrease over ACC seen on exposure to alcohol related cues in active group. On exposure to neutral cues, increase in ERP amplitude was seen in FPC, OFC and no significant changes in ACC and DLPFC in active group. In sham group, increase in ERP was seen for both neutral and alcohol related cues.

KlaussJ et al.,2014[20]	Effect of repititive bilateral tDCS on relapse propability and frontal cognitive functions over 6 months	DSM-IV of alcohol dependence	n, Tdcs= 16; n, sham = 17	parallel, randomized (1:1), sham controlled, blinded	2mA for 13:20:13 schedule (stimulation:rest:stimulation) one session for 5 consecutive days; 35 cm2	Left DLPFC (F3) cathode; right DLPFC (F4) anode	Stimulator turned off after 20 sec	Alcohol use relapse, FAB, MMSE, HAM-D, HAM-A, WHOQOL-BREF	8/16 in real tDCS group relapsed after a period of 6 months, 15/17 sham-Tdcs relapsed; no significant difference in FAB, OCDS, MMSE, HAM-A, HAM-D scores. Significant improvement in Q1 item of WHOQOF-BREF, Individual's overall perception of quality of life in real-tDCS group vs. sham tDCS
den UylTE et al., 2015[21]	Effect of tDCS over left DLPFC and right IFG on alcohol craving and IAT (affective and motivational)	AUDIT score > 8	n, DLPFC =14; n, IFG =15; n, sham = 12	Randomized, Sham-controlled blinded	1mA for 10 mins; 35 cm2	Anode over left DLPFC (F3), right IFG (crossing of FZ and CZ and FZ and T3); cathode over contralateral supraorbital region	Stimulator turned off after 30 sec	AUDIT, TLFB, AAAQ	Craving decreased after left DLPFC stimulation vs. sham (p=0.034). No significant effect of right IFG stimulation on craving vs. sham (p=0.43). Decrease in reaction time for attributable words in affective IAT measures after left DLPFC but not after right IFG or sham stimulation (p=0.004). No significant effect on motivational IAT for either group. No significant correlation seen between IAT and AUDIT, TLFB and AAAQ scores.

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