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## Review article

## A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders

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## ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique, which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of mental illness. tDCS has been implemented in numerous therapeutic trials across a range of patient populations, with a rapidly increasing number of studies being published each year. This systematic review aimed to evaluate the efficacy of tDCS in the treatment of psychiatric disorders. Four electronic databases were searched from inception until December 2015 by two independent reviewers, and 66 eligible studies were identified. Depression was the most extensively researched condition, followed by schizophrenia and substance use disorders. Data on obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa were also obtained. The quality of included studies was appraised using a standardised assessment framework, which yielded a median score corresponding to “weak” on the three-point scale. This improved to “moderate” when case reports/series were excluded from the analysis. Overall, data suggested that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Nevertheless, the tDCS field is still in its infancy, and several methodological and ethical issues must be addressed before clinical efficacy can truly be determined. Studies probing the mechanisms of action of tDCS and those facilitating the definition of optimised stimulation protocols are warranted. Furthermore, evidence from large-scale, multi-centre randomised controlled trials is required if the transition of this therapy from the laboratory to the clinic is to be considered.

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## 1. Introduction

Mental disorders constitute a major public health issue, directly accounting for 7.4% of disease burden worldwide (Murray et al., 2012) and 17.8% in the European Union (Wittchen et al., 2011). They are the leading cause of years lived with disability globally (Whiteford et al., 2013), impacting personal well-being, social relationships and work productivity, and are associated with substantial loss of quality of life (Alonso et al., 2004). Despite an increase in the rate of treatment, psychiatric morbidity has remained relatively stable over the past two decades (Kessler et al.,

2005; Wittchen et al., 2011), thus there is a need to develop novel therapeutic strategies to improve clinical outcomes.

Recent advances in functional neuroimaging have facilitated an improved understanding of the disturbances in neural circuitry that underlie mental disorders (Frangou, 2014; Price and Drevets, 2013). Consequently, there has been increased interest in neuro-modulation methods which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of illness, with the objective of improving behavioural outcomes whilst generating information about disease mechanisms. These emerging brain-directed interventions adhere to an experimental therapeutics approach, which is now widely regarded as the gold-standard strategy for treatment-focused psychiatric research (Insel, 2014; Insel and Gogtay, 2014; Medical Research Council, 2010).

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique which delivers low-amplitude direct currents to the brain via two surface sponge electrodes (anode and cathode) attached to distinct areas of the scalp with a rubber

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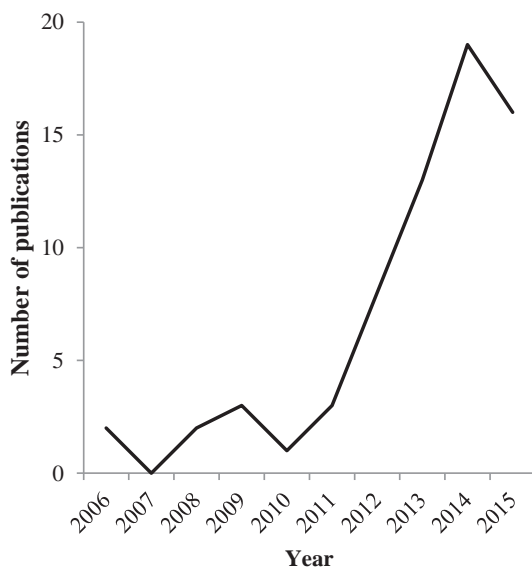
headband (Wagner et al., 2007). The current penetrates the skull and enters the brain from the anode, travels through the tissue, and exits via the cathode (George and Aston-Jones, 2010). tDCS presents several practical advantages over alternative neuromodulation modalities – it has a favourable safety-feasibility profile, offers a convincing placebo, can be applied bilaterally, and is portable and inexpensive.

During the past decade, tDCS has been implemented in numerous trials across a range of patient populations and psychiatric conditions, with a rapidly increasing number of studies being published each year (Fig. 1). This systematic review critically evaluates the clinical efficacy of tDCS in people with mental illness, and is warranted given the limited efficacy of existing therapies, the evidence that psychiatric disorders are neural circuit-based disorders that could benefit from brain-directed interventions, and the appealing characteristics of tDCS in comparison to other forms of neuromodulation. Although several reviews and meta-analyses have previously addressed this topic, the majority have either studied major depression (Berlim et al., 2013; Brunoni et al., 2012a; Kalu et al., 2012; Meron et al., 2015; Shiozawa et al., 2014d) or schizophrenia alone (Mondino et al., 2015c), or used unsystematic search procedures (Brunoni et al., 2012b; Kuo et al., 2014; Tortella et al., 2015) which promote a number of biases (Schmidt and Gotzsche, 2005). To our knowledge, one prior publication has systematically reviewed the therapeutic effects of tDCS across all psychiatric disorders (Mondino et al., 2014). Given the high growth rate of publication in the field, we have provided an up-to-date and comprehensive synthesis of the full evidence base, which is inclusive of all psychiatric conditions and study designs, and which uses a standardised quality assessment.

## 2. Material and methods

### 2.1. Selection criteria

Studies in English of any design that investigated the clinical efficacy of tDCS in individuals with psychiatric disorders were eligible for inclusion. Studies of participants with neurological



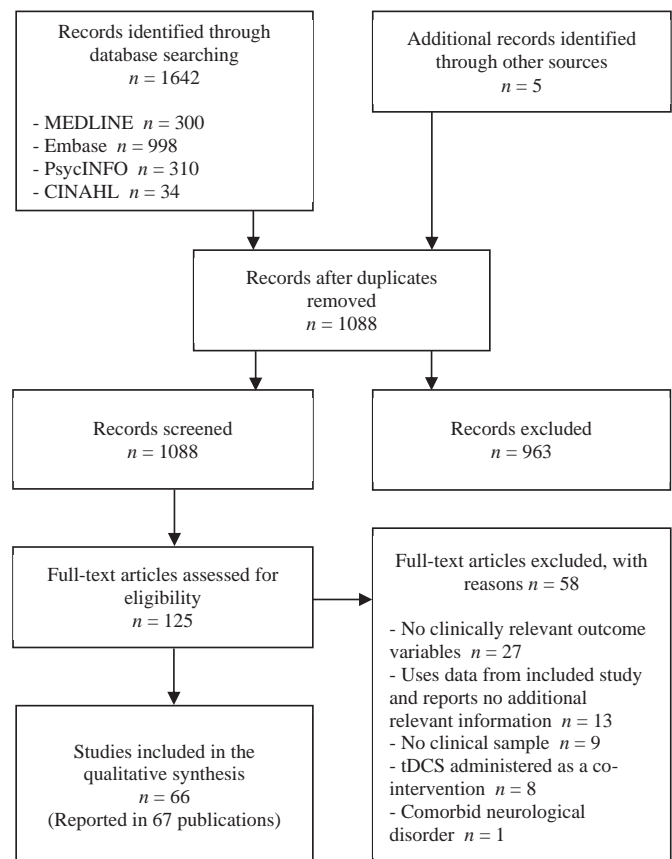
**Fig. 1.** Number of publications included in this review by year between 2006 and 2015. Note: databases were searched for papers published online or in print until 3rd December 2015.

conditions were excluded, as were those that did not report any symptom outcome variables. Publications were not restricted based on whether details of a Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases diagnosis were given, and those involving co-interventions were eligible for inclusion if the effects of tDCS *per se* were discernible.

### 2.2. Search strategy

Four electronic databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched (via OvidSP and EBSCOhost) from inception until 3rd December 2015 using the following Medical Subject Headings and keywords: transcranial direct current stimulation, tDCS, and transcranial DC stimulation, in combination with mental disorder, mental illness, psychiatric disorder, psychiatric disease, addict\*, anorexi\*, anxiety disorder, auditory verbal hallucinations, bipolar disorder, bulimi\*, catatonia, craving, dependence, depersonalization, depressi\*, eating disorder, mania, obsessive compulsive disorder, OCD, panic disorder, personality disorder, phobi\*, posttraumatic stress disorder, psychosis, PTSD, and schizophrenia. These searches were supplemented by internet searches and hand-searches of reference lists of relevant papers and reviews. Citation tracking in Web of Science was also performed.

Titles and abstracts of retrieved publications were imported into EndNote, duplicates were removed, and papers that were deemed highly unlikely to be relevant were disregarded. Full-text versions of the remaining articles were then obtained and screened according to the pre-specified eligibility criteria. All papers that did not meet the inclusion criteria were excluded, with the reasons



**Fig. 2.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

documented (Fig. 2). The entire search process was conducted independently by two reviewers (M.K. and E.B.) and disagreements at the final stage were resolved by consensus.

### 2.3. Quality assessment and data extraction

The quality of included studies was appraised using a standardised evaluation framework – the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (Thomas et al., 2004) – which is suitable for use with multiple study designs. The instrument assesses six methodological domains: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Each component is rated as strong, moderate, or weak on a three-point scale and these scores are averaged to provide a global rating. The quality assessment was performed independently by two reviewers (M.K. and E.B.) and discrepancies were discussed until an agreement was reached.

The principal reviewer (M.K.) extracted data from all included studies into an electronic summary table which was then checked by another reviewer (E.B.). Information collected related to patient population, sample size, study design, stimulation protocol, measurement of clinical efficacy, and relevant findings. Due to the methodological diversity of the included studies, a narrative synthesis is presented.

## 3. Results

### 3.1. Characteristics of included studies

We identified 66 studies (reported in 67 publications, including data from 1021 participants) that met the inclusion criteria for this review (Fig. 2). The majority (30 studies) evaluated the efficacy of tDCS for the treatment of major depression in patients with major depressive disorder (MDD) or bipolar disorder (BP). The remaining studies were of patients with schizophrenia (23 studies), substance use disorders (SUDs; 7 studies), obsessive compulsive disorder (OCD; 4 studies), generalised anxiety disorder (GAD; 1 study), and anorexia nervosa (AN; 1 study). There were 23 randomised controlled trials (RCTs) and 41 open-label studies (2 had blind-raters) including 24 case reports/series. In addition, there was one double-blind, sham-controlled case report and one study with a hybrid design involving both double-blind, sham-controlled and open-label conditions. All studies had adult-only samples which differed substantially in size, ranging from 1 to 120 participants ( $M = 18.09$ ,  $SD = 19.99$ ).

All but four of the studies had stimulation protocols comprising multiple sessions; however, the duration, number, and frequency of these sessions, as well as the tDCS parameters employed, varied considerably across trials (Tables 2–5). The unilateral or bilateral dorsolateral prefrontal cortex (DLPFC) was targeted in 59 of the 66 studies. Other hypothesis-driven sites of stimulation were the temporoparietal junction (TPJ), cerebellum, occipital lobe, orbitofrontal cortex (OFC), frontotemporal region, pre-supplementary and supplementary motor areas (pre-SMA/SMA), and Wernicke's area.

### 3.2. Quality of included studies

The median global rating derived from the EPHPP Quality Assessment Tool for Quantitative Studies was 3 (weak). Overall, the weakest scores were obtained for the selection bias component of the tool because 38% of studies were case reports/series and a further 26% did not adequately describe the participant selection process. A high number of weak ratings were also assigned for the

blinding component because 62% of the studies were open-label. The strongest-scoring dimension was data collection methods because 63 of the 66 studies used at least one standardised outcome measure with known reliability and validity. Where relevant, withdrawals and dropouts were generally addressed and reported accurately, and only 5 studies had a retention rate lower than 80% at the final stage of data collection. Of the 18 studies that involved 2 or more independent experimental groups, 16 reported no baseline between-group differences with respect to important variables, 1 noted that the active group had more severe symptoms pre-tDCS, and 1 study did not provide this information. A numerical summary of the component ratings is provided in Table 1. Since the high proportion of case reports/series notably impacted the results of the quality assessment, average scores were calculated with and without these studies included.

### 3.3. Study findings

#### 3.3.1. Major depression

A number of studies have provided evidence that unilateral DLPFC stimulation (anodal tDCS to the left DLPFC [l-DLPFC], cathodal tDCS to a contralateral intra- or extra-cephalic region) can ameliorate symptoms of major depression (Table 2). The earliest of these were conducted by Fregni and colleagues (Fregni et al., 2006a, 2006b) who found that five sessions of sham-controlled tDCS induced significant improvements in mood (indexed by the Hamilton Rating Scale for Depression [HRSD] and the Beck Depression Inventory [BDI]) in two small samples of MDD patients ( $N = 10$ ,  $N = 18$ ). Their findings were later extended by Boggio et al. (2008a) who demonstrated that, in 40 MDD patients, 10 sessions of anodal tDCS to the l-DLPFC led to persisting reductions in HRSD and BDI scores when compared with both sham tDCS and an active control (anodal tDCS to the occipital cortex). Lasting improvements in depressive symptoms following 10 sessions of anodal l-DLPFC tDCS were also recorded in 8 HIV-MDD co-diagnosed individuals (Knotkova et al., 2012) and one 92-year-old MDD patient (Shiozawa et al., 2014a).

Other studies of anodal tDCS to the l-DLPFC in major depression have yielded less encouraging results. For example, Palm et al. (2009) reported that 16 sessions of tDCS did not exert a meaningful therapeutic effect in a patient with treatment-resistant MDD, and Wolkenstein and Plewnia (2013) recorded no tDCS-related changes in positive or negative affect (indexed by the Positive and Negative Affect Schedule [PANAS]) in 22 MDD patients following real versus sham tDCS (though a single session protocol was used). More ambiguous findings have also been documented: a 2-week course of sham-controlled tDCS had no effect on clinical

**Table 1**

Median and mean component ratings from the EPHPP Quality Assessment Tool for Quantitative Studies.

Component	Ratings			
	All included studies ( $N = 66$ )		Excluding case reports/series ( $n = 41$ )	
	Median	Mean	Median	Mean
Selection bias	3	2.65	2	2.44
Study design	2	2.05	1	1.44
Confounders	1	1.21	1	1.21
Blinding	3	2.24	1	1.83
Data collection methods	1	1.08	1	1.12
Withdrawals and dropouts	1	1.23	1	1.23
Global rating	3	2.35	2	1.93

Ratings: 1 = strong; 2 = moderate; 3 = weak.

**Table 2**  
Studies in patients with major depression (in chronological order).

Study	N <sup>a</sup>	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Fregni et al. (2006a)	10	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 5 sessions (1 per day for 5 alternate days)	HRSD, BDI	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Fregni et al. (2006b)	18	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 5 sessions (1 per day for 5 alternate days)	HRSD	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Boggio et al. (2008a)	40	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS of the DLPFC; (ii) tDCS of the occipital cortex (active control); (iii) sham tDCS	Left DLPFC	Right supraorbital area	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD-21, BDI	Improvement in depressive symptoms after tDCS to the DLPFC versus sham tDCS and tDCS to the occipital cortex, maintained for at least 1 month.	
Ferrucci et al. (2009b)	14	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 min, 10 sessions (2 per day for 5 consecutive days)	BDI, HRSD, self-reported mood (VAS)	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month.	
Ferrucci et al. (2009a)	32	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, particularly in patients with severe depression who maintained improvements for at least 1 month.	
Palm et al. (2009)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 16 sessions (1 per day then 2 per day over 27 days)	BDI, HRSD, CGI	Improvement in depressive symptoms post-tDCS, but no change in CGI score.	
Loo et al. (2010)	35	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	1	35	20 min, 5 sessions (1 per day for 5 alternate weekdays) plus 5 further sessions (active for both groups) at the same treatment frequency	MADRS, HRSD, CGI-S, BDI, PGI-I	No improvement in depressive symptoms after active versus sham tDCS.	Sessions 6–10 were active for all participants, but they were not made aware of this until the blind was broken. Those who received 5 sham sessions initially were offered the opportunity to receive 5 further active sessions.
Brunoni et al. (2011b)	31	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month. Depression severity was positively related with symptom improvement.	
Martin et al. (2011)	11	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right upper arm	2	35 (100 for extracephalic electrode)	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-SR, MADRS-SR	Improvement in depressive symptoms post-tDCS.	Participants were non-responders or relapsers from Loo et al. (2012).
Blumberger et al. (2012)	24	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks)	HRSD, MADRS, BPRS, BDI-II	No improvement in depressive symptoms after active versus sham tDCS.	

(continued on next page)

Table 2 (continued)

Study	N <sup>a</sup>	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Dell'Osso et al. (2012)	23	MDD and BP	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 min, 10 sessions (2 per day for 5 consecutive days)	MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 1 week.	
Knotkova et al. (2012)	8	MDD (co-diagnosed HIV)	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	2	25	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, MADRS	Improvement in depressive symptoms post-tDCS, maintained for at least 2 weeks (further improvement in MADRS scores only).	No mention of DSM/ICD diagnosis.
Loo et al. (2012) [Phase I]	58	MDD and BP	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	Improvement in depressive symptoms (MADRS scores only) after active versus sham tDCS, but an equal number of participants in each group met the criterion for response and no participants met the criterion for remission.	
Loo et al. (2012) [Phase III]	52	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks) then additional weekly sessions for 1-month (responders only)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	27 participants Met the criterion for response post-tDCS. There were 22 and 20 responders at 1-week and 1-month follow-ups, respectively.	Participants previously received active or sham tDCS in phase I of the trial (Loo et al., 2012). The group who received active tDCS in phase I had better responder rates after phase II.
Palm et al. (2012)	22	MDD and BP	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1 or 2	35	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, PANAS, BDI	No improvement in clinical depression ratings, but increase in subjectively reported positive emotions (PANAS), after active versus sham tDCS.	
Alonzo et al. (2013)	64	MDD and BP	Exploratory analysis of Loo et al. (2012)		No tDCS performed					MADRS	Improvement in dysphoria and retardation after active versus sham tDCS.	Used Loo et al. (2012) dataset.
Brunoni et al. (2013a)	82	MDD and BP (BP-II and BP-NOS only)	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS. Use of benzodiazepines was associated with a worse outcome.	
Brunoni et al. (2013b) [Phase I SELECT-TDCS]	103	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + placebo pill; (ii) sham tDCS + sertraline; (iii) tDCS + sertraline; (iv) sham tDCS + placebo pill	Left DLPFC	Right DLPFC	2	25	30 min, 12 sessions (1 per weekday for 2 consecutive weeks then 1 per week for 2 alternate weeks)	MADRS, HRSD, CGI-S, BDI	Improvement in depressive symptoms after active versus sham tDCS. Greatest effects after combined tDCS/sertraline treatment, maintained for at least 2 weeks.	
D'Urso et al. (2013)	1	MDD	Open-label, uncontrolled	(i) tDCS; (ii) tDCS + CBT	Left DLPFC	Right DLPFC	1.5	–	10 sessions (1 per weekday for 2 consecutive weeks) x 2	HRSD	Improvement in depressive symptoms post-tDCS, only partially maintained over the 4-week follow-up period. The combined treatment induced acute improvements and complete remission of symptoms at 12-month follow-up.	CBT sessions were performed weekly during tDCS treatment and throughout the following 6 months.
Martin et al. (2013)	26	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit or right upper arm	2	35 (100 for extracephalic electrode)	20 min (1 per week for 3 consecutive months then 1 per fortnight for 3 consecutive months)	MADRS, relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse.	Participants were from Loo et al. (2012) or Martin et al. (2011). Three participants commenced a new antidepressant treatment during the study.

Valiengo et al. (2013) [Phase II SELECT-TDCS]	23 MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	MADRS	Improvement in depressive symptoms post-tDCS.	Participants were non-responders who received sham tDCS in phase I of SELECT-TDCS (Brunoni et al., 2013b).
Valiengo et al. (2013) [Phase III SELECT-TDCS]	42 MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 min, 9 sessions (1 per week for 6 alternative weeks then 1 per month for 3 consecutive months)	MADRS relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse. The mean response duration was 11.7 weeks.	Participants were responders who received active tDCS in phase I or phase II of SELECT-TDCS (Brunoni et al., 2013b; Valiengo et al., 2013).
Wolkenstein and Plewnia (2013)	22 MDD	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right deltoid	1	35	20 min, 1 session	PANAS	No change in subjective mood state after active versus sham tDCS.	
Brunoni et al. (2014a)	37 MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT	Left DLPFC	Right DLPFC	2	25	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, BDI	Both groups showed similar improvement in depressive symptoms after treatment. Active tDCS + CCT was not superior to sham tDCS + CCT.	
Brunoni et al. (2014b)	120 MDD	Exploratory analysis of Brunoni et al. (2013b)		No tDCS performed					MADRS	Improvement in concentration difficulties, pessimistic thoughts, and suicidal thoughts after active versus sham tDCS.	Used Brunoni et al. (2013b) dataset.
Dell'Osso et al. (2014)	23 MDD and BP	Follow-up of Dell'Osso et al. (2012), blind-rater		No tDCS performed					MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 months in half the sample.	Participants were from Dell'Osso et al. (2012).
Ho et al. (2014)	14 MDD	Open-label, uncontrolled	(i) Fronto-occipital tDCS; (ii) fronto-cerebellar tDCS	Left supraorbital area	(i) Bilateral occipital lobe; (ii) bilateral cerebellum	2	35 (100/50 for cathodes)	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after fronto-occipital tDCS only.	
Player et al. (2014)	18 MDD and BP-II	Double-blind, sham-controlled (n = 6); open-label, uncontrolled (n = 12)	(i) tDCS; (ii) sham tDCS (n = 6)	Left DLPFC	Right frontal area, right upper arm, or occipital-cerebellar region	2–2.5	–	20–30 min, 13–21 sessions (consecutive weekdays)	MADRS	Improvement in depressive symptoms after sham tDCS, but greater improvement after active tDCS.	Participants were from several different trials which varied in study design/tDCS parameters. Clinical results from one subject were also reported in Loo et al. (2012).
Segrave et al. (2014)	27 MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT; (iii) tDCS + sham CCT	Left DLPFC	Right lateral orbit	2	35	24 min, 5 sessions (1 per day for 5 consecutive days)	MADRS, BDI-II	Improvement in depressive symptoms post-tDCS, partially maintained for at least 3 weeks (BDI-II scores only). Combined tDCS/CCT treatment was most effective but had a delayed benefit.	
Shiozawa et al. (2014a)	1 MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	–	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 weeks.	No mention of DSM/ICD diagnosis.
Bennabi et al. (2015)	23 MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	35	30 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, MADRS, BDI	No improvement in depressive symptoms after active versus sham tDCS, but more participants in the active group met the response and remission criteria immediately, 12 days, and 30 days after treatment.	

(continued on next page)

Table 2 (continued)

Study	N <sup>a</sup>	Diagnosis	Design	Stimulation protocol for experimental condition(s)				Outcomes extracted for this review	Findings	Comments		
				Study type	Groups/conditions	Anode electrode position	Cathode electrode position				Current strength (mA)	Electrode size (cm <sup>2</sup> )
Ho et al. (2015)	4	MDD	Open-label, uncontrolled	(i) tDCS	Left fronto-temporal region	Right fronto-temporal region	2.5	35/16	30 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after tDCS. At the end of treatment, two participants met the criteria for response and one met the criteria for remission. Intensification of depressive symptoms after tDCS.	Participants had previously received multiple courses of tDCS (Chan et al., 2013; Loo et al., 2012; Martin et al., 2011, and unpublished data). No mention of DSM/ICD diagnosis. Patient had right hemispheric dominance (he was left-handed and was diagnosed with dyslexia during childhood).
Shiozawa et al. (2015)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 5 sessions (1 per day for 5 consecutive days)	HRSD	Intensification of depressive symptoms after tDCS.	No mention of DSM/ICD diagnosis. Patient had right hemispheric dominance (he was left-handed and was diagnosed with dyslexia during childhood).

BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BP, bipolar disorder; BP-II, bipolar II disorder; BP-NOS, bipolar disorder not otherwise specified; BPRS, Brief Psychiatric Rating Scale; CCT, cognitive control training; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression - Severity scale; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptomatology; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-SR, Montgomery-Åsberg Depression Rating Scale - Self-Report; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; PGI-I, Patient Global Impression of Improvement; QIDS-C, Quick Inventory of Depressive Symptomatology - Clinician Rating; QIDS-SR, Quick Inventory of Depressive Symptomatology - Self-Report; SELECT-TDCS, The sertraline versus electrical current therapy for treating depression clinical study; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.

<sup>a</sup> N refers to the number of participants whose data was included at the final stage of analysis.

depression ratings (HRSD, BDI) but increased subjectively-rated positive emotions (according to the PANAS) in 22 participants with refractory MDD ( $n = 20$ ) or BP ( $n = 2$ ) (Palm et al., 2012). Similarly, whilst 10 sessions of sham-controlled twice-daily tDCS did not alleviate symptoms in 23 patients with treatment-resistant MDD (indexed by the HRSD, BDI, and Montgomery-Åsberg Depression Rating Scale [MADRS]), more participants in the active tDCS group met the response and remission criteria immediately, 12 days, and 30 days after treatment (Bennabi et al., 2015).

In a parallel group RCT conducted by Loo et al. (2010), comparable reductions in depression severity (HRSD, MADRS) occurred following 5 sessions of real and sham anodal l-DLPFC tDCS in 35 patients with MDD. Although the authors later recorded a reduction in MADRS scores in 58 MDD/BP patients following 15 sessions of sham-controlled tDCS, this result was clinically modest, the differences did not reach significance on any other mood outcome measures, and an equal number of participants in the active and sham groups met the response and remission criteria (Loo et al., 2012). Nevertheless, a between-group difference in the proportion of responders became apparent after participants ( $n = 52$ ) received an additional 15 sessions of open-label active tDCS: at 1-week and 1-month follow-ups, responder rates were superior in the group that had received active treatment throughout (Loo et al., 2012). Interestingly, 11 participants who showed an inadequate response to, or relapsed following, 3 weeks of active tDCS treatment in this study (Loo et al., 2012) subsequently displayed moderate clinical improvements after 20 further sessions of open-label tDCS in which the cathode was placed extracephalically (over the right upper arm) instead of over the right lateral orbit (Martin et al., 2011). Those who met the criterion for response ( $n = 7$ ), and 19 responders from the original study (Loo et al., 2012), then received 6 months of weekly/fortnightly continuation tDCS and data indicated that the cumulative probability of surviving without relapse was 84% at 3 months and 51% at 6 months (Martin et al., 2013).

In contrast to those described above, a number of studies investigating the effects of tDCS in major depression have used bilateral DLPFC modulation (anodal left/cathodal right). For example, Ferrucci et al. (2009b) administered 10 sessions of twice-daily open-label tDCS to 14 patients with severe, drug-resistant MDD and observed mood improvements (HRSD, BDI, self-report visual analogue scales [VASs]) which persisted for at least 1 month after the end of treatment. Similarly, Dell'Osso et al. (2012) delivered tDCS at the same parameters to 23 poor-responder depressed patients (MDD = 15, BP = 8) and noted a clinical benefit that was maintained for at least 3 months in half of the sample (Dell'Osso et al., 2014). This protocol (10 sessions of twice-daily open-label tDCS) was adopted by three further studies which explored the comparative benefits of tDCS in patients with differing clinical profiles (Brunoni et al., 2013a, 2011b; Ferrucci et al., 2009a). Robust and persisting improvements in depressive symptoms were recorded across a total of 145 individuals with MDD ( $n = 112$ ) or BP ( $n = 33$ ) (Brunoni et al., 2013a, 2011b; Ferrucci et al., 2009a), and whilst the treatment appeared to be equally effective for patients regardless of their diagnosis (Brunoni et al., 2013a, 2011b), a better response was seen in participants with severe MDD than in those with mild/moderate MDD (Ferrucci et al., 2009a). Interactions between tDCS and drug therapy were also reported: whereas benzodiazepine use was associated with a worse outcome, antidepressants generally increased the beneficial effects of tDCS (Brunoni et al., 2013a).

Evidence from a multi-phase trial by Brunoni et al. (2013b) supports the finding that bilateral DLPFC tDCS has greater efficacy when administered with antidepressants. During phase I, 120 patients with MDD were assigned to 1 of 4 groups: sham tDCS/placebo pill (placebo), sham tDCS/sertraline (sertraline-only), active



**Table 3**  
Studies in patients with schizophrenia (in chronological order).

Study	N <sup>a</sup>	Design		Stimulation protocol for experimental condition(s)				Outcomes extracted for this review	Findings	Comments	
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )				Duration, number, and frequency
Homan et al. (2011)	1	Open-label, uncontrolled	(i) tDCS	Right supraorbital area	Wernicke's area	1	35	15 min, 10 sessions (1 per day for 10 consecutive days)	HCS, PANSS, PSYRATS	Reduction in AVH and improvement in other schizophrenic symptoms post-tDCS, maintained for at least 6 weeks.	No mention of DSM/ICD diagnosis.
Brunelin et al. (2012b)	2	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	PANSS, AHRS	Reduction in AH and improvement in other schizophrenic symptoms post-tDCS, maintained for at least 3 months.	
Brunelin et al. (2012a)	30	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS, PANSS	Reduction in AVH (maintained for at least 3 months) and improvement in other schizophrenic symptoms after active versus sham tDCS.	
Palm et al. (2013)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS, SANS, CDSS	Improvement in positive and negative schizophrenic symptoms post-tDCS.	
Rakesh et al. (2013)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS	Complete cessation of AVH post-tDCS.	
Shiozawa et al. (2013b)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Occipital area then TPJ	2	–	20 min, 20 sessions (1 per day for 10 consecutive days, 5 day break, then 1 per day for 10 consecutive days)	PANSS, LHS, AHRS	Transitory increase during tDCS, followed by reduction post-tDCS, in AH and VH, maintained for at least 2 months, and improvement in other schizophrenic symptoms after tDCS.	No mention of DSM/ICD diagnosis.
Shiozawa et al. (2013a)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 10 sessions (1 per day for 10 consecutive days)	BFCRS	Improvement in catatonic symptoms during tDCS treatment course. Patient was asymptomatic at 4-month follow-up.	No mention of DSM/ICD diagnosis.
Bose et al. (2014)	21	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS.	
Jacks et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	PANSS	Improvement in delusions, AH, blunted affect, emotional withdrawal, and general psychopathology PANSS score post-tDCS, but no change in positive or negative PANSS subscale scores.	Participant received an acute course of ECT plus weekly maintenance sessions for several months prior to commencement of tDCS.
Narayanaswamy et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS, SANS	Delayed improvement in negative symptoms and small reduction in AVH, maintained for at least 6 months.	
Nawani et al. (2014a)	5	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS.	
	1		(i) tDCS	Left DLPFC	Left TPJ	2	–		AHRS		

(continued on next page)

Table 3 (continued)

Study	N <sup>a</sup>	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Nawani et al. (2014b)		Open-label, uncontrolled						20 min, 10 sessions (2 per day for 5 consecutive days)		Reduction in AVH post-tDCS.	
Shiozawa et al. (2014c)	1	Open-label, uncontrolled	(i) tDCS	Left TPJ	Right TPJ	2	35	20 min, 10 sessions (1 per day for 10 consecutive days)	PANSS	No improvement in schizophrenic symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Shivakumar et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days) plus 6 intermittent booster sessions over 1 year (2 per day, single day)	PSYRATS (AHS)	Complete cessation of AVH after acute course of tDCS, maintained for 3 months. Booster tDCS sessions controlled 3 subsequent relapses over 1 year. Participant was free of AVH at 1-year follow-up.	
Bose et al. (2015)	1	Open-label, uncontrolled	(i) left-sided tDCS; (ii) right-sided tDCS	(i) Left DLPFC; (ii) right DLPFC	(i) Left TPJ; (ii) right TPJ	2	35	(i) 20 min, 18 sessions (2 per day for 9 consecutive days); (ii) 20 min, 20 sessions (2 per day for 10 consecutive days)	PSYRATS (AHS)	No improvement in schizophrenic symptoms after left-sided tDCS, but reduction in AH after right-sided tDCS.	Electrode positioning was modified due to lack of clinical response.
Brunelin et al. (2015)	16	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (frequency not stated)	AHRS	Reduction in AH post-tDCS.	Patients with a comorbid tobacco use disorder ( <i>n</i> = 10) were less responsive to tDCS.
Gomes et al. (2015)	15	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms after active versus sham tDCS.	At baseline, the tDCS group had higher PANSS scores for the positive scale relative to the sham tDCS group.
Kurimori et al. (2015)	9	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Mondino et al. (2015b)	28	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	AVH frequency	Reduction in AVH after active versus sham tDCS.	No mention of DSM/ICD diagnosis. 15 participants were from Brunelin et al. (2012a). AVH frequency method of assessment not stated.
Praharaj et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	25	20 min, 5 sessions (1 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS, but symptoms returned to baseline levels 6 days after treatment.	No mention of DSM/ICD diagnosis.
Shenoy et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS, with further improvement for at least 1 month.	Participant was pregnant, and received tDCS treatment previously (reference given to conference abstract only).
Shivakumar et al. (2015)	23	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per	PSYRATS (AHS)	Reduction in AH post-tDCS.	Allelic variations in the COMT gene

Table 3 (continued)

Study	N <sup>a</sup>	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Smith et al. (2015)	29	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	5.08	day for 5 consecutive days) 20 min, 5 sessions (1 per day for 5 consecutive days in most cases)	PANSS, PSYRATS	No improvement in schizophrenic symptoms after active versus sham tDCS.	influenced the clinical efficacy of tDCS.

AH, auditory hallucinations; AHRS, Auditory Hallucination Rating Scale; AHS, Auditory Hallucinations Subscale; AVH, auditory verbal hallucinations; BFCRS, Bush-Francis Catatonia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; COMT, Catechol-O-methyltransferase; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; HCS, Hallucination Change Scale; ICD, International Classification of Diseases; LHS, Launay Slade Hallucination Scale; PANSS, Positive And Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scales; SANS, Scale for the Assessment of Negative Symptoms; tDCS, transcranial direct current stimulation; TPJ, temporo-parietal junction; VH, visual hallucinations.

<sup>a</sup> N refers to the number of participants whose data was included at the final stage of analysis.

tDCS/placebo pill (tDCS-only), or active tDCS/sertraline (combined treatment) (the tDCS intervention consisted of 10 consecutive weekday sessions followed by 2 extra sessions every other week) (Brunoni et al., 2013b). On the basis of MADRS scores, tDCS-only was more effective than placebo, but the combined treatment was superior to all other groups (Brunoni et al., 2013b). In phase II of the trial, willing non-responders who received sham tDCS in phase I ( $n = 23$ ) underwent 10 sessions of active tDCS and moderate improvements in depressive symptomatology were observed (Valiengo et al., 2013). During phase III, active tDCS responders from phase I and II ( $n = 42$ ) received 24 weeks of maintenance treatment and continued to respond for an average of 11.7 weeks (Valiengo et al., 2013).

Less promising results were obtained by Blumberger et al. (2012), who found that 15 sessions of sham-controlled bilateral DLPFC tDCS did not lower HRSD scores in 24 patients with treatment-resistant MDD. Additionally, Shiozawa et al. (2015) described a patient – with inferred right hemispheric dominance – whose depressive symptoms intensified (according to HRSD scores) following five sessions of anodal left/cathodal right DLPFC tDCS. Brunoni et al. (2014a) showed that in 37 MDD patients, active tDCS (10 sessions) combined with cognitive control therapy (CCT) was not superior to sham tDCS combined with CCT. This is in contrast to a study by Segrave et al. (2014), in which concurrent CCT potentiated antidepressant outcomes (MADRS, BDI) from anodal I-DLPFC tDCS (the cathode was placed over the right lateral orbit). D'Urso et al. (2013) also described the effects of adjunctive tDCS and cognitive therapy: in a patient with refractory MDD, the therapeutic response to 10 sessions of bilateral DLPFC tDCS (indexed by the HRSD) was substantially more enduring when the treatment was coupled with weekly cognitive behavioural therapy (CBT).

To date, two studies using tDCS to treat major depression have targeted an alternative site to the DLPFC. In these open-label trials, improvements in symptoms (indexed by the MADRS) were observed following modulation of the fronto-occipital (Ho et al., 2014) or -temporal regions (Ho et al., 2015) (20 sessions) in a total of 18 patients with MDD.

### 3.3.2. Schizophrenia

Studies examining the clinical effects of tDCS in schizophrenia have mostly employed an electrode montage in which the anode is placed over the I-DLPFC and the cathode is positioned over the left temporoparietal junction (I-TPJ). This set-up appears to have been consistently successful in ameliorating symptoms of the illness; for example, Brunelin et al. (2012a) demonstrated that in 30 patients, 10 sessions of twice-daily sham-controlled tDCS robustly reduced

auditory verbal hallucinations (AVHs; indexed by the Auditory Hallucination Rating Scale [AHRS]) acutely and at 3-month follow-up. Improvements in other schizophrenic symptoms, according to the total Positive and Negative Syndrome Scale (PANSS) score, were also recorded (Brunelin et al., 2012a). Mondino et al. (2015b) administered the same treatment protocol to a group of 28 patients, 15 of whom had previously taken part in the aforementioned study (Brunelin et al., 2012a), and also observed a large decrease in treatment-resistant AVH frequency in the active versus sham tDCS group.

Additional evidence of efficacy for this tDCS montage and protocol (10 twice-daily sessions, anode I-DLPFC/cathode I-TPJ) comes from three further open-label trials in which a total of 60 schizophrenic patients with persistent auditory hallucinations (AHs) presented significant reductions in Psychotic Symptoms Rating Scales (PSYRATS)/AHRS scores following treatment (Bose et al., 2014; Brunelin et al., 2015; Shivakumar et al., 2015). While all participants experienced improvements, being a non-smoker (Brunelin et al., 2015) and carrying a particular variant of a neuroplasticity-related gene (catechol-O-methyltransferase [COMT]) (Shivakumar et al., 2015) were both associated with having a greater therapeutic response. A number of case reports/series describing patients with refractory schizophrenia have also offered support (Brunelin et al., 2012b; Jacks et al., 2014; Narayanaswamy et al., 2014; Nawani et al., 2014a, 2014b; Rakesh et al., 2013; Shenoy et al., 2015; Shivakumar et al., 2014). For instance, Shenoy et al. (2015) recorded near-total improvement of the exacerbation of AVHs during pregnancy, Narayanaswamy et al. (2014) noted a delayed but persistent improvement in negative symptoms, and Rakesh et al. (2013) observed complete cessation of AVHs immediately after the first two tDCS sessions and at post-intervention reassessment. Shivakumar et al. (2014) also witnessed a tDCS-induced termination of AVHs, and subsequently found that application of intermittent booster tDCS (6 sessions) resulted in sustained improvements for a period of one year.

Less positive results were obtained in one case report of a patient presenting with severe, treatment-resistant symptoms who received a higher acute dose of tDCS (20 twice-daily sessions, anode I-DLPFC/cathode I-TPJ) but did not show any clinical gains (Shiozawa et al., 2014c). In addition, although Praharaj et al. (2015) did observe a reduction of AHs in a patient with treatment-resistant schizophrenia following 10 sessions of tDCS, PSYRATS scores returned to baseline levels six days later. Interestingly, Bose et al. (2015) documented a lack of clinical response to 18 twice-daily sessions of anode I-DLPFC/cathode I-TPJ tDCS in a patient with treatment resistant AVHs; however, significant improvements in

**Table 4**  
Studies in patients with substance use disorders.

Study	N <sup>a</sup>	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Boggio et al. (2008b)	13	Alcohol dependence	Randomised, double-blind, sham-controlled, crossover	(i) anode left/ cathode right tDCS; (ii) anode right/ cathode left tDCS; (iii) sham tDCS	(i) Left DLPFC, (ii) Right DLPFC	(i) Right DLPFC, (ii) Left DLPFC	2	35	20 min, 1 session	AUQ	Reduction in alcohol craving after anode left/ cathode right tDCS and anode right/ cathode left tDCS versus sham tDCS. Alcohol craving could not be increased by alcohol cues after active versus sham tDCS.	
Nakamura-Palacios et al. (2012)	49	Alcohol dependence	Randomised, single-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	1	35	10 min, 1 session	OCDS	No reduction in alcohol craving after active versus sham tDCS.	Alcohol craving was not provoked with cues.
da Silva et al. (2013)	13	Alcohol dependence	Randomised, single-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	2	35	20 min, 5 sessions (1 per week for 5 consecutive weeks)	OCDS, verbally assessed relapse rates	Reduction in alcohol craving after active versus sham tDCS, but trend for relapse during treatment in active tDCS group.	
Klauss et al. (2014)	33	Alcohol dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	13 min, 10 sessions (2 per day, with a 20 min interval, for 5 consecutive days)	Verbally assessed relapse rates, OCDS	No reduction in alcohol craving after active versus sham tDCS, but patients in the active tDCS group were more likely to survive for at least 6 months without relapse.	Alcohol craving was not provoked with cues.
Shahbabaie et al. (2014)	30	mAMP dependence	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left supraorbital area	2	35	20 min, 1 session	Self-reported mAMP craving (VAS), CICT	Reduction in mAMP craving at rest, but increase in cue-induced craving, during active versus sham tDCS.	Effects of tDCS were state-dependent.
Conti et al. (2014)	13	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 min, 5 sessions (1 per day for 5 alternate days)	Relapses/ periods of abstinence	No between-group differences in relapse rates during the treatment period. At 3-month follow-up, more participants in the real than in the sham tDCS group maintained abstinence from crack-cocaine.	Only 50% of participants in the sham group completed all treatment sessions (compared to 86% in the real group).
Batista et al. (2015)	36	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 min, 5 sessions (1 per day for 5 alternate days)	Crack-cocaine craving (scale composed of 5 items from the OCDS)	Reduction in crack-cocaine craving after active versus sham tDCS, maintained for at least 1 week.	

AUQ, Alcohol Urge Questionnaire; CICT, Computerised Cue-Induced Craving Assessment Task; DLPFC, dorsolateral prefrontal cortex; mAMP, methamphetamine; OCDS, Obsessive Compulsive Drinking Scale; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.

<sup>a</sup> N refers to the number of participants whose data was included at the final stage of analysis.

symptoms (indexed by the PSYRATS) were subsequently recorded after an additional 20 sessions in which the electrodes were placed at homologous sites on the right side of the brain.

Shiozawa et al. (2013b) conducted a case study of tDCS in patients with long-term, refractory schizophrenia, opting for a unique protocol targeted at the selective improvement of visual hallucinations (VHs) and AHs. Twenty sessions of tDCS were performed in two blocks with a 5-day interval between: for the first 10 sessions, the cathode was placed over the occipital area (to hypothetically

inhibit VHs) and for the remaining 10 sessions over the I-TPJ (to hypothetically inhibit AHs) (Shiozawa et al., 2013b). The anode was positioned over the I-DLPFC throughout (Shiozawa et al., 2013b). Although a transitory increase in hallucinations was observed during the period of stimulation, this was followed by a reduction in VHs and AHs (assessed with the Launay Slade Hallucination Scale [LSHS] and the AHRS, respectively), as well as marked improvements in other positive, negative, and general symptoms (indexed by the PANSS) (Shiozawa et al., 2013b).

**Table 5**  
Studies of patients with other psychiatric disorders (obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa).

Study	N <sup>a</sup>	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm <sup>2</sup> )	Duration, number, and frequency			
Volpato et al. (2013)	1	OCD (comorbid MDD and GAD)	Double-blind, sham-controlled	(i) tDCS; (ii) sham tDCS; (iii) rTMS; (iv) sham rTMS	Posterior neck base	Left DLPFC	2	35	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	Y-BOCS, HRSD, HRSA	No improvement in OCD symptoms, but improvement in depression and anxiety, after real versus sham tDCS.	
Shiozawa et al. (2014b)	1	GAD	Open-label, uncontrolled	(i) tDCS	Left deltoid	Right DLPFC	2	25	30 min, 15 sessions (1 per weekday for 3 consecutive weeks)	GAD-7, BAI, HRSA	Improvement in anxiety symptoms during tDCS treatment course. Patient was asymptomatic post-tDCS and at 1-month follow-up.	No mention of DSM/ICD diagnosis.
Khedr et al. (2014)	7	AN	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right arm	2	24 (100 for extracephalic electrode)	25 min, 10 sessions (1 per weekday for 2 consecutive weeks)	EAT, EDI	Improvement in eating disorder symptoms post-tDCS, maintained for at least 1 month. Large variability in responses.	
D'Urso et al. (2015)	1	OCD	Open-label, uncontrolled	(i) anodal tDCS; (ii) cathodal tDCS	(i) pre-SMA; (ii) right deltoid	(i) Right deltoid; (ii) pre-SMA	2	25	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	Y-BOCS	Worsening and improvement of OCD symptoms after anodal and cathodal tDCS, respectively. Overall reduction in symptoms at the end of treatment, maintained for at least 3 months.	The polarity of the electrodes was inverted after 10 sessions due to exacerbation of symptoms.
Mondino et al. (2015a)	1	OCD	Open-label, uncontrolled	(i) tDCS	Right occipital cortex	Left OFC	2	35 (100 for anode)	20 min, 10 sessions (2 per day for 5 consecutive days)	Y-BOCS	Delayed improvement in OCD symptoms, maintained for at least 1 month.	
Narayanaswamy et al. (2015)	2	OCD	Open-label, uncontrolled	(i) tDCS	Left pre-SMA/SMA	Right supraorbital area	2	35	20 min, 20 sessions (2 per day for 10 consecutive days)	Y-BOCS	Improvement in OCD symptoms post-tDCS, maintained for at least 1 month/2 months.	

AN, anorexia nervosa; BAI, Beck Anxiety Inventory; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; EAT, Eating Attitudes Test; EDI, Eating Disorder Inventory; GAD, generalised anxiety disorder; GAD-7, Generalised Anxiety Disorder 7-item scale; HRSA, Hamilton Rating Scale for Anxiety; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; MDD, major depressive disorder; OCD, obsessive compulsive disorder; OFC, orbitofrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; tDCS, transcranial direct current stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

<sup>a</sup> N refers to the number of participants whose data was included at the final stage of analysis.

A number of other electrode montages have also been trialed for the treatment of schizophrenia, and findings have been mixed. For example, Palm et al. (2013) observed considerable improvement in positive and negative symptoms (using several clinical assessment tools) following a 2-week course of anodal tDCS to the I-DLPFC (the cathode was placed over the right supraorbital area) in a patient with refractory schizophrenia. In contrast, 29 patients who received 5 sessions of sham-controlled tDCS at the same parameters experienced no clinical benefits (indexed by the PANSS and the PSYRATS) (Smith et al., 2015). Shiozawa et al. (2013a) described a treatment-resistant patient who achieved complete remission from catatonic symptoms (indexed by the Bush–Francis catatonic scale) in response to 10 sessions of tDCS over the bilateral DLPFC (anodal left/cathodal right). Gomes et al. (2015) later replicated this protocol in an RCT of 15 participants and correspondingly found a reduction in negative symptoms (according to the PANSS) after active versus sham tDCS. Although no effects were reported for positive symptoms, the real tDCS group had higher scores on the positive subscale of the PANSS at baseline. An improvement in negative but not positive symptoms was also demonstrated by 9 further patients following 10 sessions of anodal I-DLPFC tDCS (with the cathode placed extracephalically) (Kurimori et al., 2015). Finally, Homan et al. (2011) showed that 10 sessions of cathodal stimulation over Wernicke's area (the anode was positioned over the right supraorbital area) led to persisting reductions in AVHs and other symptoms (indexed by the Hallucination Change Scale, PANSS, and the PSYRATS) in a patient with treatment-resistant schizophrenia.

### 3.3.3. Substance use disorders

The literature on the clinical utility of tDCS for treating SUDs consists of a small number of RCTs which have generated mixed results. Boggio et al. (2008b) were the first to publish data here: in a group of 13 participants with alcohol dependence, one session of tDCS to the bilateral DLPFC (either anodal left/cathodal right or anodal right/cathodal left) was shown to decrease alcohol craving (indexed by the Alcohol Urge Questionnaire [AUQ]) relative to sham stimulation. Interestingly, Klauss et al. (2014) found that a higher dose of bilateral DLPFC tDCS (10 twice-daily sessions) did not diminish craving (assessed with the Obsessive Compulsive Drinking Scale [OCDS]) but reduced relapse probability in 33 alcohol dependent individuals (Klauss et al., 2014). A dissociation between levels of craving and the likelihood of relapse to alcohol use was also reported by da Silva et al. (2013): 13 alcoholics received 5 weekly sessions of sham-controlled unilateral DLPFC stimulation (anode over the I-DLPFC, cathode over the right supradeltoid area) and, although the treatment suppressed cravings (indexed by the OCDS), there was an unexpected trend for more relapses in the active versus sham tDCS group. The same electrode montage was adopted in a single-session trial involving 49 alcohol-dependent patients in which no anti-craving effects were observed (Nakamura-Palacios et al., 2012).

Three studies examining the therapeutic potential of tDCS in individuals addicted to substances other than alcohol have been conducted. In the first, Shahbabaie et al. (2014) provided evidence suggesting that tDCS has a state-dependent effect on craving in methamphetamine (mAMP) users. Thirty patients underwent one session of sham-controlled anodal tDCS over the right DLPFC (r-DLPFC) (the cathode was placed over the left supraorbital area) and, while active tDCS acutely reduced craving at rest, it increased craving during mAMP-related cue exposure. In the second, Conti et al. (2014) administered 5 sessions of real or sham bilateral DLPFC stimulation (anodal right/cathode left) to 13 crack-cocaine addicted individuals and observed a higher percentage of abstinence at 3-month follow-up in those assigned to the real tDCS

group. This study was later replicated using a larger group of patients ( $n = 36$ ), whose crack-cocaine cravings were suppressed for at least one week by active versus sham tDCS (Batista et al., 2015).

### 3.3.4. Other psychiatric disorders

Limited data exist on the clinical efficacy of tDCS in other psychiatric disorders; however, some promising results have been reported. For example, Shiozawa et al. (2014b) described the case of a patient with treatment-resistant GAD who underwent a three-week course of cathodal r-DLPFC tDCS (the anode was placed over the left deltoid) and was asymptomatic both acutely and at one-month follow-up. Additionally, Khedr et al. (2014) showed that 10 sessions of anodal stimulation over the I-DLPFC (the cathode was positioned over the right arm) relieved eating disorder symptoms in 5 of 7 AN patients and, furthermore, 4 participants maintained these improvements for at least 1 month after the end of treatment.

Mondino et al. (2015a) demonstrated that 10 sessions of twice-daily cathodal tDCS over the left OFC (the anode was positioned over the right occipital cortex) induced delayed but lasting reductions in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores in a patient with treatment-resistant OCD. Sustained symptom improvements were also recorded in two patients with drug-resistant OCD, following 20 sessions of twice-daily anodal tDCS over the left pre-SMA/SMA (the cathode was placed over the right supraorbital area) (Narayanaswamy et al., 2015). Interestingly, D'Urso et al. (2015) found that a two-week course of anodal tDCS over the same region (with the cathode placed extracephalically) exacerbated a patient's OCD symptoms. The electrodes were then inverted for a further 10 sessions, which reduced Y-BOC scores (beyond baseline levels) for at least 3 months post-treatment (D'Urso et al., 2015). Lastly, Volpato et al. (2013) administered 10 sessions of cathodal I-DLPFC tDCS (with the anode placed over the posterior neck base) to a patient with severe and enduring OCD and, although the intervention had no effect on OCD-specific symptoms (indexed by the Y-BOCS), it improved the patient's comorbid anxiety and depression (assessed with the Hamilton Rating Scale for Anxiety [HRSA] and the HRSD, respectively).

## 4. Discussion

### 4.1. Clinical efficacy

This review provides evidence that tDCS has the potential to ameliorate symptoms associated with several major psychiatric disorders. Most notably, data from a number of RCTs suggest that tDCS interventions comprised of multiple sessions can induce enduring therapeutic effects in patients with depressive disorders and schizophrenia. Further indication of clinical utility in these conditions has come from numerous open-label trials and case reports, often involving patients who have experienced dramatic improvements and, in some instances, achieved full remission following treatment with tDCS. Although research in other mental disorders is somewhat limited, several RCTs support the prospective application of tDCS in SUDs, and emerging data from a small number of patients indicate that tDCS can induce significant clinical gains in people with OCD, GAD, and AN.

Despite evidence that tDCS offers exciting possibilities for treatment development in psychiatry, symptom improvements have been modest or absent in a considerable number of studies. Furthermore, a small number of publications have reported a tDCS-induced exacerbation of symptoms. Multiple factors are likely to contribute to the variability of response in tDCS studies, and these are discussed in turn below.

#### 4.2. Patient characteristics

A number of interindividual biological, psychological, and lifestyle factors appear to influence the clinical efficacy of tDCS. First, differences in genotype have been linked to altered tDCS responding, possibly via impact on anatomical and neurophysiological states. [Shivakumar et al. \(2015\)](#), for example, showed that a polymorphism at the neuroplasticity-related COMT gene moderated the therapeutic effects of tDCS in a group of patients with schizophrenia. Second, the psychological state of participants at the time of stimulation seems to play a role: in SUD, prefrontal tDCS has been found to intensify cravings if those receiving it are in the presence of drug-related cues ([Shahbabaie et al., 2014](#)). Third, nicotine smoking has been associated with reduced clinical efficacy of tDCS in patients with schizophrenia ([Brunelin et al., 2015](#)). This may explain the negative results reported by [Smith et al. \(2015\)](#), since all participants in this study were regular smokers. Fourth, illness severity has been identified as a predictor of response to tDCS: [Ferrucci et al. \(2009a\)](#) observed a greater therapeutic effect for severe MDD than for mild/moderate MDD.

It has been proposed that degree of treatment-resistance may also influence clinical outcomes of tDCS ([Brunoni and Fregni, 2011](#); [Mondino et al., 2014](#)), although this factor has not been explicitly investigated and studies of patients with treatment-resistant disorders have produced both negative (e.g., [Bennabi et al., 2015](#); [Blumberger et al., 2012](#); [Palm et al., 2012](#)) and positive (e.g., [Dell'Osso et al., 2012](#); [Ferrucci et al., 2009b](#); [Palm et al., 2013](#)) results. Nevertheless, close attention must be paid to the definition of treatment-resistance because, in some instances, studies with negative results ([Blumberger et al., 2012](#); [Palm et al., 2012](#)) have used more stringent refractoriness criteria than those with positive ones ([Dell'Osso et al., 2012](#)).

#### 4.3. Concomitant therapy

The medication status of patients varied significantly both within and between studies included in this review. In some cases, tDCS was administered as an “add-on” therapy to a stable dose of medication (e.g., [Bose et al., 2014](#)), while other studies excluded participants taking any neuropsychotropic drugs (e.g., [Boggio et al., 2008b](#)), included a mix of medicated and non-medicated patients (e.g., [Loo et al., 2010](#)), or failed to address concomitant pharmacotherapy at all (e.g., [da Silva et al., 2013](#)). Evidence indicates that particular psychoactive substances can interact with the effects of tDCS; specifically, benzodiazepines have been reported to hinder therapeutic effects, whereas antidepressants have been associated with enhanced outcomes ([Brunoni et al., 2013a, 2013b](#)). Crucially, three studies which found tDCS to be clinically ineffective permitted benzodiazepine use during the trial (26–33% of patients were taking benzodiazepines) ([Bennabi et al., 2015](#); [Blumberger et al., 2012](#); [Brunoni et al., 2014a](#)), and one study which found tDCS to be effective tolerated antidepressant but not benzodiazepine use (52% of patients were taking antidepressants) ([Segrave et al., 2014](#)). Nonetheless, [Boggio et al. \(2008a\)](#) used opposing eligibility criteria – allowing benzodiazepine but not antidepressant use – and still observed positive effects. Cognitive-based therapies can also influence clinical outcomes from tDCS ([D'Urso et al., 2013](#); [Segrave et al., 2014](#)); however, information regarding the use of concurrent non-pharmacological treatments was seldom provided.

#### 4.4. Parameters of stimulation

tDCS interventions varied extensively between the reviewed studies according to a range of parameters, such as electrode size

and positioning, current amplitude, duration of stimulation, and number and frequency of sessions (see [Tables 2–5](#)). Considerable heterogeneity was even present among studies attempting to treat the same psychiatric disorder. Unsurprisingly, results from several investigations suggested that the number of sessions administered, the placement of the reference electrode, and the anode/cathode polarity moderate the therapeutic effects of tDCS ([Bose et al., 2015](#); [D'Urso et al., 2015](#); [Loo et al., 2012, 2010](#); [Martin et al., 2011](#)). Most notably, [D'Urso et al. \(2015\)](#) demonstrated that 10 sessions of anodal tDCS applied to the pre-SMA led to an exacerbation of symptoms in a patient with OCD; however, when the polarity of the electrodes was inverted (for a further 10 sessions of tDCS), significant and persisting improvements beyond baseline levels were observed.

#### 4.5. Study design

This review incorporated studies of varying design. Interestingly, the majority of studies with negative results were RCTs (e.g., [Blumberger et al., 2012](#); [Klauss et al., 2014](#); [Loo et al., 2012](#); [Nakamura-Palacios et al., 2012](#); [Palm et al., 2012](#); [Smith et al., 2015](#)), which raises the possibility of a placebo effect. Indeed, sham tDCS frequently exerts some degree of influence over outcomes; however, the improvements observed in open-label investigations are unlikely to be the result of placebo mechanisms alone since many of the patients involved in these studies were treatment-resistant, and refractoriness is associated with lower placebo responding ([Brunoni et al., 2009](#)). It should also be noted that publication bias – in which research with unfavourable results has a lower probability of being published – is more likely to affect open-label, uncontrolled studies than RCTs ([Easterbrook et al., 1991](#)). Thus, the higher proportion of RCTs with negative results may be, at least in part, an artefact of such bias.

#### 4.6. Safety issues and ethical considerations

Administration of tDCS interventions that comply with recommended safety regulations (current: <2.5 mA, duration: 20–60 min per session, frequency: ≤ twice per day, application: with electrodes that minimise skin burns) ([Fregni et al., 2015](#)) has presented minimal risk across a wide range of participants. Only mild and transient side-effects – such as itching, tingling, and headache – have been reported ([Brunoni et al., 2011a](#)), leading to the conclusion that tDCS is a relatively safe procedure. However, the absence of serious adverse events is not irrefutable evidence that the technique is unequivocally benign, and a number of ethical and safety issues remain ([Fitz and Reiner, 2015](#); [Kadosh et al., 2012](#); [Widdows and Davis, 2014](#)).

Firstly, [Brunoni et al. \(2011a\)](#) argue that adverse events are being neglected in tDCS research, possibly due to a subjective belief that the technique raises negligible safety concerns. In their systematic review of 209 tDCS clinical trials, 92 studies did not report the presence and/or absence of adverse effects, which the authors interpret as evidence of selective reporting bias ([Brunoni and Fregni, 2011](#)). Secondly, despite knowledge that stimulation of one particular cortical site can alter activation and connectivity in regions distal to the electrodes, the nature of the functional networks associated with the target brain areas seems to have little influence in the design of tDCS experiments ([Wokke et al., 2014](#)). Data suggest that cognitive enhancement mediated by tDCS can occur at the expense of other cognitive functions ([Iuculano and Cohen Kadosh, 2013](#)), yet the potential for collateral behavioural impairments arising from the use of tDCS in psychiatric research has been largely overlooked. Our incomplete

understanding of the neural bases of mental disorders and the resultant lack of any standardised stimulation guidelines pose risks for the occurrence of unintended and undesirable effects. Thirdly, [Widdows and Davis \(2014\)](#) point out that qualitative differences in anatomy are sometimes seen in people with mental illness compared to healthy controls; for example, patients with eating disorders have shown low levels of subcutaneous adipose tissue around the head and altered cortical folding. These factors are likely to have an impact on the effects of tDCS-induced electrical currents, therefore extra caution ought to be exercised in such patient groups ([Widdows and Davis, 2014](#)). Lastly, tDCS has recently garnered considerable ‘neuro-hype’ in the media as a portable, painless, inexpensive, and safe therapeutic device. This positive portrayal has the potential to shape the public’s risk-benefit perceptions, promote a therapeutic misconception, and have an impact on the uptake of this technology ([Dubljević et al., 2014](#)). Without some degree of ‘neuromodesty’ ([Morse, 2012](#)), desperate and vulnerable mentally ill patients may overestimate the benefits and underestimate the risks of tDCS.

## 5. Conclusions and future directions

Research into the clinical efficacy of tDCS in psychiatric disorders has grown exponentially over the past decade. We have systematically reviewed the literature and have provided an objective and analytical account of its current state. Overall, data from studies appraised in this review suggest that tDCS has the potential to induce clinically relevant behavioural changes in often difficult-to-treat patient populations, and could thus represent a valuable tool for intervention in a range of mental disorders. Nevertheless, the use of tDCS for treating psychiatric disorders is still in its infancy, and further evidence of its efficacy from large-scale, multi-centred RCTs is required if the transition of this therapy from the laboratory to the clinic is to be considered. Indeed, the approval of repetitive transcranial magnetic stimulation (a related non-invasive neuromodulation technique) as a second-line treatment for major depression in several countries was preceded by extensive sham-controlled investigations ([Dell’Osso and Altamura, 2014](#)). It is also essential that steps are taken to resolve the discrepancies in clinical findings; for example, sample variability should be controlled and reproducible stimulation parameters should be defined in terms of optimising therapeutic response for different clinical applications. A better understanding of the neural responses to tDCS will accelerate progress here, and is likely to arise through combined tDCS-neuroimaging experiments ([Venkatakrisnan and Sandrini, 2012](#)) and computational neurostimulation approaches ([de Berker et al., 2013](#)). Finally, all investigators conducting research with tDCS should be mindful of the various safety and ethical issues associated with the use of this neuromodulation technique.

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