Title:

Is transcranial direct current stimulation (tDCS) a potential first line treatment for major depression?

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Abstract

Transcranial direct current stimulation (tDCS) is a novel treatment option for major depression which could be provided as a first-line treatment. tDCS is a non-invasive form of transcranial stimulation which changes cortical tissue excitability by applying a weak (0.5-2 mA) direct current via scalp electrodes. Anodal and cathodal stimulation leads to depolarisation and hyperpolarisation, respectively, and cumulative effects are observed with repeated sessions. The montage in depression most often involves anodal stimulation to the left dorsolateral prefrontal cortex. Rates of clinical response, remission, and improvements in depressive symptoms following a course of active tDCS are greater in comparison to a course of placebo sham-controlled tDCS. In particular, the largest treatment effects are evident in first episode and recurrent major depression, while minimal effects have been observed in treatment-resistant depression. The proposed mechanism is neuroplasticity at the cellular and molecular level. Alterations in neural responses have been found at the stimulation site as well as subcortically in prefrontal-amygdala connectivity. A possible mediating effect could be cognitive control in emotion dysregulation. Additional beneficial effects on cognitive impairments have been reported, which would address an important unmet need. The tDCS device is portable and can be used at home. Clinical trials are required to establish the efficacy, feasibility and acceptability of home-based tDCS treatment and mechanisms.

Keywords

transcranial direct current stimulation, tDCS, major depression, neuroplasticity, neuropsychology, biomarkers

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Introduction

Major depression is a common mental health disorder, affecting about 350 million people worldwide with a lifetime prevalence of about 1 in 7 adults, and is predicted to be the leading contributor to the global burden of disease (Kessler and Bromet, 2013; Vos et al., 2015; Whiteford et al., 2013). The disorder is the largest contributor to non-fatal health loss and the most significant precursor for suicide (Vos et al., 2015; World Health Organization [WHO] 2015). There is a significant socio-economic challenge with the cost being about £9 billion in the UK in 2000 (Thomas and Morris, 2003) and expected to be as much as £12 billion by 2026 in England (McCrone et al., 2008).

The most common forms of treatments are antidepressant medication and psychotherapy. However, clinical response to antidepressant medication (Rush et al., 2006) or to psychotherapy (Cuijpers et al., 2014) is less than 50% following a full course of either treatment. Side effects from antidepressant medications are common, such as sexual dysfunction, sleepiness, and weight gain (Cascade et al., 2009; Ferguson, 2001), yet are often under-reported and can lead to discontinuation (Cipriani et al., 2018; Sinyor et al., 2020). Onset of clinically noticeable effects can take several weeks for antidepressant medication as well as psychotherapy, and access to treatment can be limited, in particular for psychotherapy (Cipriani et al., 2018; Pence et al., 2012). Providing another treatment option would be benefit patients who are unable to take current treatments or who prefer an alternative form of treatment. Transcranial direct current stimulation is a novel, non-invasive form of neurostimulation that is a potential first line treatment option for major depression.

The present review evaluates the current evidence for the efficacy and adverse events associated with a course of tDCS treatment in major depression, potential mechanisms, neuropsychological effects, and initial studies of predictive biomarkers of clinical outcome.

What is transcranial direct current stimulation (tDCS)?

The application of electrical stimulation for therapeutic effect has been reported since the first century. Placing a live electric torpedo fish over the scalp, which generates a strong electric current, was found to create a brief stupor and to alleviate pain from headache. In 1804, Aldini reported that applying electric currents to the scalp could improve melancholia (Priori, 2003).

Non-invasive brain stimulation (NIBS) refers to stimulation that can be given without the need of an implant. tDCS applies a weak direct electric current through electrodes placed on the scalp, which modulates neuronal resting membrane potential but does not directly lead to neuronal discharge (Nitsche & Paulus, 2000). Transcranial alternating current stimulation (tACS) is similar to tDCS, but consists of a sinusoidal alternating current which can be provided at a selected frequency to entrain intrinsic oscillation patterns (Matsumoto & Ugawa, 2017), and transcranial random noise stimulation (tRNS) consists of an alternating current with a random frequency and amplitude (Terney et al., 2008).

Transcranial magnetic stimulation (TMS) is another form of non-invasive brain stimulation. TMS uses a magnetic coil to generate a local electric current through electromagnetic induction. This is applied to a focal brain region leading to depolarization or hyperpolarization, neuronal excitation or inhibition, respectively (Hallet, 2000). In clinical practice, repetitive TMS (rTMS) that can be high frequency or low frequency is most common, while theta-burst TMS (TBS) is demonstrating potential efficacy (Mutz et al., 2019).

Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are forms of invasive brain stimulation techniques. In VNS, an electrical stimulation is delivered to the vagus nerve via a stimulator implanted under the skin, and DBS involves the implantation of electrodes in specific areas in the brain.

Electroconvulsive therapy (ECT) is applied through electrodes placed on the scalp, which induce general convulsive activity leading to a seizure and is provided under a general anaesthetic. While it could be considered to be a non-invasive form of brain stimulation, ECT

is usually placed in between categories as it does not require a surgical procedure but is more invasive than tDCS and TMS, leads to a seizure, and is applied under anaesthesia.

All of these methods can be grouped within the umbrella term of transcranial electric stimulation (TES). tDCS has benefits in cost-effectiveness, portability, and a low side effect profile (Tortella et al., 2015).

How doe tDCS affect neuronal activity?

The current is typically in the range 0.5 – 2 mA and is applied through electrodes placed on the scalp with a conductive substance such as a saline solution or gel. The current flows from the anode electrode to the cathode electrode (and electrons flow from the cathode to the anode). The stimulation is non-focal. The surface area of the sponge-electrode used in studies in depression are typically large, approximately 25 – 35 cm^2, and sponge-electrode size can range from 3.5 – 100 cm^2 (Dedoncker et al., 2016; Turi et al., 2014).

The current passes through the skin, subcutaneous tissue and skull with high impedance. It is estimated that 25 – 50 % of the given current reaches through the cerebrospinal fluid (CSF) to gray matter (Rush & Driscoll 1968; Vöröslakos et al., 2018). Factors such as area of stimulation, electrode size, distance between electrodes, as well as individual differences contribute to the final current intensity (Dedoncker et al., 2016; Rush & Driscoll 1968; Turi et al., 2014; Woods et al., 2015).

Anodal stimulation typically leads to depolarisation of the neuronal resting membrane potential and to increased potential firing of cells. Cathodal stimulation tends to inhibit cortical excitability through hyperpolarisation to decreased potential cell firing (Creutzfeldt et al., 1962). tDCS changes neural activity by modulating the resting membrane potential, rather than directly stimulating an action potential. However, factors including orientation of the

neuronal axon to the current and neuron type impact on the activity and directionality (Jefferys, 1981).

Does tDCS affect neuroplasticity?

Neuroplasticity is a general term that refers to our ability to learn as a result of cellular and molecular changes in neurons leading to alterations in regional brain activity or structure. Synaptic plasticity includes synaptogenesis, forming and fitting new synapses together, and non-synaptic plasticity includes neural migration and neurogenesis. In brain imaging, this can be observed by persistent changes in regional neurofunction or neuroanatomy (Zatorre et al., 2012). While neuroplasticity has typically been described in rehabilitation following brain injury, it is also seen as a mechanism for treatments, such as antidepressant medication, psychotherapy, and mindfulness (Davidson & McEwen, 2012; Lomas et al., 2015; Fu et al., 2020).

The neurophysiological effects of tDCS typically last beyond the immediate stimulation period (Nitsche et al., 2003). Long-term potentiation (LTP) describes the sustained increase in synaptic transmission that is the cellular correlate of learning and memory, first described in neuronal cells in the hippocampus (Bliss & Lømo, 1973). Cortical LTP and long-term depression (LTD)-like changes are modulated by glutamatergic and GABAergic neurons (Trepel & Racine, 2000). Anodal tDCS-enhanced excitability in the primary motor cortex is LTP-like, which is dependent on N-methyl-D-aspartate (NMDA) receptor and calcium channel activity (Leibetanz et al., 2002; Monte-Silva et al., 2013). Stimulation strength, duration and direction have a non-linear relationship impact on whether excitatory or inhibitory effects are generated (Batsikadze et al., 2013; Jamil et al., 2017; Monte-Silva et al., 2013).

Anodal tDCS stimulation to the primary motor cortex (M1) results in a significant decrease in gamma-aminobutyric acid (GABA) concentration in the stimulated region as measured by magnetic resonance spectroscopy (MRS), suggesting a mediating effect that is in part due to

reduced GABAergic inhibition, while cathodal tDCS stimulation is associated with a significant decrease in glutamate with a seemingly counterintuitive correlated decrease in GABA, indicating a mediating effect of a reduction in excitatory glutamatergic function. Effects on GABA levels have been observed in the stimulated primary motor cortex as well as in the non-stimulated but functionally connected contralateral motor cortex demonstrating that neurochemical changes are also evident outside of the targeted region during plasticity induction (Bachtier et al., 2018).

LTP is further dependent on the neurotrophin, brain-derived neurotrophic factor (BDNF), in motor skill learning (Fritsch et al., 2010). Anodal tDCS applied to the primary motor cortex enhanced motor learning as long as activity-dependent BDNF secretion was present, which was evident in animal studies and behaviourally in human participants with the BDNF Val66Met polymorphism.

In neuroimaging studies, effects have been observed as changes in brain function, for example tDCS modulates distinct resting state networks as measured by functional magnetic resonance imaging (fMRI) (Keeser et al., 2011). Active anodal tDCS applied to the left dorsolateral prefrontal cortex has been associated with significant changes in connectivity in the default mode network, self-referential network and frontal-parietal networks in comparison with sham tDCS.

Does tDCS treatment improve depressive symptoms?

Meta-analyses of sham placebo controlled RCTs

In our meta-analysis, we examined the efficacy and acceptability of non-invasive brain stimulation in adults with major depressive disorder or bipolar depression (Mutz et al., 2018). We obtained data from 56 randomised sham-controlled trials which included a total of 131 treatment arms and 66 treatment comparisons, consisting of tDCS, TMS (repetitive TMS, deep

TMS, and synchronised TMS) and theta-burst stimulation (TBS), without co-initiation of another treatment.

3,058 participants (mean age = 45.0 years; 61.7 % female) had been randomly assigned to active treatment (n = 1,598) or sham therapy (n = 1,460). In our main analysis of response rates, defined as a minimum of 50% reduction in symptom scores, at the primary study endpoint, we found evidence of antidepressant efficacy for high frequency rTMS over the left dorsolateral prefrontal cortex (OR = 3.75, 95% CI 2.44 to 5.75), right-sided low frequency rTMS (OR = 7.44, 95% CI 2.06 to 26.83), bilateral rTMS (OR = 3.68, 95% CI 1.66 to 8.13), deep TMS (OR = 1.69, 95% CI 1.003 to 2.85), intermittent TBS (OR = 4.70, 95% CI 1.14 to 19.38) and tDCS (OR = 4.17, 95% CI 2.25 to 7.74). We did not find evidence that continuous TBS, bilateral TBS or synchronised TMS were more efficacious than sham. We also did not find evidence of differences in all-cause discontinuation rates between active and sham treatment for any of the protocols.

tDCS was associated with higher response rates (k = 9, OR = 4.17, 95% CI 2.25 to 7.74), higher remission rates (k = 8, OR = 2.88, 95% CI 1.65 to 5.04), and lower post-treatment depression severity scores (k = 7, Hedge's g = -0.76, 95% CI −1.31 to −0.21) relative to sham therapy. The overall number of patients included in the tDCS trials was n = 456 (n = 246 participants randomised to active treatment and n = 210 participants randomised to receive sham therapy). Sample sizes of the trials varied substantially, ranging from 10 to 151 participants (median = 35 participants, IQR = 30.25). Most trials (80%) recruited only participants with major depressive disorder, although one trial recruited exclusively participants with bipolar depression. tDCS was applied in an outpatient setting, and trials had excluded patients who had reported psychotic symptoms. In 7 out of 10 trials, tDCS was applied as monotherapy; in 1 trial, tDCS was added to stable pharmacotherapy, and in 2 trials, tDCS was given as monotherapy or augmentation treatment.

The number of tDCS treatment sessions ranged from 5 – 22 (median = 10, IQR = 5.75), applied over the course of 1.5 – 10 weeks (median = 2, IQR = 3.63). Treatment duration was 20 minutes in 6 out of 10 trials and 30 minutes in the remaining 4 trials. The anode was applied over F3 (according to the EEG 10/20 coordinate system), generally referred to as left dorsolateral prefrontal cortex, while the cathode/reference electrode was located over F4 (6/10 trials), FP2 (3/10 trials) or F8 (1 trial). tDCS was most frequently applied with a current strength of 2 mA (in 70% of trials), although 3 trials applied tDCS at 1 mA. 70% of trials used an electrode size of 35 cm^2 and three trials used an electrode size of 25 cm^2. Current density ranged from 0.028 – 0.080.

In subgroup analyses, we found evidence that tDCS was associated with higher response rates only in trials which had recruited participants with a non-treatment resistant form of depression or which had recruited patients with either treatment resistant or non-treatment resistant depression. We did not find evidence of differences in all-cause discontinuation rates between active treatment and sham treatment in any of the treatment protocols.

In a subsequent meta-analysis, we estimated the comparative clinical efficacy and acceptability of non-surgical brain stimulation treatments more broadly, using network meta-analysis (Mutz et al., 2019). We included clinical trials in which adult patients with major depressive disorder or bipolar depression were randomly assigned to ECT, TMS (repetitive, accelerated, priming, deep, and synchronised), TBS, magnetic seizure therapy, tDCS, or sham therapy.

113 trials (262 treatment arms) that randomised n = 6,750 patients (mean age = 47.9 years, 59% women) met our inclusion criteria. The most studied treatment comparisons were high frequency left rTMS and tDCS compared to sham therapy (40 and 11 treatment comparisons, respectively). In our primary analysis of response rates, 10 out of 18 treatment protocols were associated with higher response rates relative to sham therapy: bitemporal ECT (OR = 8.91,

95% CI 2.57 to 30.91), high dose right unilateral ECT (OR = 7.27, 95% CI 1.90 to 27.78), priming TMS (OR = 6.02, 95% CI 2.21 to 16.38), magnetic seizure therapy (OR = 5.55, 95% CI 1.06 to 28.99), bilateral rTMS (OR = 4.92, 95% CI 2.93 to 8.25), bilateral TBS (OR = 4.44, 95% CI 1.47 to 13.41), low frequency right rTMS (OR = 3.65, 95% CI 2.13 to 6.24), intermittent theta-burst stimulation (OR = 3.20, 95% CI 1.45 to 7.08), high frequency left rTMS (OR = 3.17, 95% CI 2.29 to 4.37), and tDCS (OR = 2.65, 95% CI 1.55 to 4.55).

Active tDCS treatment was also associated higher remission rates (OR = 2.18, 95% CI 1.18 to 4.04) and lower post-treatment depression severity scores (SMD = -0.55, 95% CI -0.96 to -0.14) relative to sham treatment. All treatment protocols included in this study were at least as acceptable as sham treatment, estimated from all-cause discontinuation (i.e. discontinuation of treatment for any reason). We did not examine specific undesired and adverse effects in this study, and future research should systematically evaluate specific cognitive and adverse effects associated with these treatment modalities (Kiebs et al., 2019).

There is a suggestion of a synergistic potential of tDCS with antidepressant medication (Brunoni et al., 2013; Shiozawa et al., 2013). Combination of tDCS with an antidepressant medication, sertraline, demonstrated a significantly greater early improvement in depressive symptoms following 2 weeks of treatment in comparison with placebo only, sertraline only, and tDCS only treatment arms. Factor analysis revealed a main effect of tDCS, indicating that this was driving the initial antidepressant effect (Brunoni et al., 2013). Meron et al. (2015) meta-analysis similarly found active tDCS to be superior to sham tDCS in the treatment of depression, ranging from 1 – 4 weeks of treatment. However, an overall benefit of tDCS combined with antidepressant medication was not observed. The observation of an early improvement in depressive symptoms is an important potential advantage of tDCS relative to current treatment options for depression.

Recent clinical trials

Brunoni et al. (2017a) investigated the efficacy of the antidepressant medication, escitalopram (a selective serotonin-reuptake inhibitor), and tDCS, in patients with major depressive disorder. Participants were enrolled into a non-inferiority, parallel, placebo-controlled trial. There was random allocation to one of three treatment arms for 10 weeks: 1) tDCS group: active tDCS and placebo medication (n=91), 2) escitalopram group: sham tDCS and escitalopram (n=94), and 3) placebo group: sham tDCS and placebo medication (n=60). Active anodal tDCS was administered to the left DLPFC at 2 mA for 30 minutes per session, with sessions on five consecutive weekdays in the first three weeks, and one session per week for the remaining seven weeks. Escitalopram was prescribed daily at 10 mg for the first three weeks and then increased to maximum dose of 20 mg daily until week 10. Clinical improvements were highest for escitalopram, followed by tDCS and then placebo. As the improvement in depressive symptoms in the tDCS group was not 50% or less than in the escitalopram group compared to placebo, the findings failed to show non-inferiority of tDCS as compared with escitalopram.

Loo et al. (2018) conducted a two-arm, parallel, randomised, sham-controlled trial to compare the efficacy of tDCS as treatment for unipolar and bipolar depression. All patients were in a current depressive episode and had a diagnosis of recurrent depression, with historic treatment profiles indicating that many had a form of depression approaching treatment resistance. Participants in both unipolar and bipolar samples were randomised to receive either active or sham tDCS for 5 consecutive weekdays over a 4-week period. tDCS was administered for 30 minutes with the anode centered over the left DLPFC. Active tDCS was delivered at 2.5 mA, whilst sham tDCS was set at 0.034 mA for the majority of the session (a current strength thought to be a negligible) with a 10 second ramp up to 1 mA at the start of the session, followed by a 60 second ramp down; this was reversed at the end of the session. However, there was no significant difference in the rates of response or remission in the sham and active tDCS treatment groups. Loo et al. (2018) suggested that the low current of the sham tDCS was sufficient to lead to an improvement in depressive symptoms, however the

clinical history of participants seemed to be approaching a treatment-resistant form of depression, which could have contributed to the low response rates.

What are the adverse effects of tDCS?

Brunoni et al. meta-analysis (2011a) reported that the most common adverse effects are itching (39.3% vs. 32.9%, $p>0.05$) and tingling (22.2% vs. 18.3%, $p>0.05$) followed by headache (14.8% vs. 16.2%, $p>0.05$), burning sensation (8.7% vs. 10%, $p>0.05$) and discomfort (10.4% vs. 13.4%, $p>0.05$) in active tDCS as compared to sham tDCS, respectively. The summary is from 209 studies, consisting of 3,836 participants, in which about 117 studies (56%) had reported side effect symptoms in some form, reflecting also how limited reporting of adverse effects had been in early studies (Brunoni et al., 2011a). Additional side effects also include headache after a tDCS session (11.8%), nausea (2.9%) and insomnia (0.98%) found in a study of 102 patients. Those with a history of migraines appeared to experience this side effect to a significantly higher degree though (55.6%), and could be considered an exclusionary consideration in future studies (Poreisz et al., 2007). Mild skin redness at the site of the electrode, which resolves following stimulation, is commonly reported as an issue that affects blinding in sham placebo-controlled trials (Brunoni et al., 2011a; Guarienti et al., 2014. Ezquerro et al., 2016).

Erythema or redness is likely related to local vasodilatory skin changes rather than damage (Durand et al., 2002). In rare cases, skin lesions have been produced following poor electrode skin contact (Palm et al., 2014; Rodríguez et al., 2014). Diminishing electrode density, such as by increasing the size of the electrode, and reducing electrical resistance, such as by using rubber electrodes covered with sponge and conductive substance, e.g. saline, at the site can improve contact (Woods et al., 2015). MRI studies have not detected oedema or injury in the blood-brain barrier or cerebral tissue following tDCS (Nitsche et al., 2004b). Surface skin

lesions are not attributable to brain injury as electrochemical reactions produced at the skin are not expected to diffuse into the brain (Bikson et al., 2009).

A potentially serious adverse event is treatment-emergent mania or hypomania. From a sample of 231 participants, 14 participants were observed to develop hypomania (n = 11) or mania (n = 3), following either active (n=13) or sham (n=1) tDCS in participants with bipolar depression (n=4) or unipolar depression (n=10) (Brunoni et al., 2017b). Most had also been taking adjunctive medication (n=13), namely antidepressant medication and mood stabilisers, whereby symptoms resolved through withholding treatment for a few days, medication dosage adjustment, additional pharmacotherapy or by themselves (Brunoni et al., 2011a, 2017b).

Charge densities applied in most human clinical studies (range: 171 C/m² - 480 C/m²) are well below the threshold shown to cause tissue damage in rats (above 52,400 C/m²), which is at least 100 times higher (Liebetanz et al., 2009). The threshold might be even higher, as no tissue damage or changes in cerebral temperature were found when cathodal tDCS was applied at a greater charge density (128,571 C/m^2) than the determined threshold (85,714 C/m^2) (Liebetanz et al., 2009; Rueger et al., 2012; Zhang et al., 2019).

Overall, adverse effects have been described as being mild and there have not been any significant differences in discontinuation rates between active and sham tDCS treatment groups due to adverse events, (Aparício et al., 2016; Brunoni et al., 2016; Moffa et al., 2017; Alonzo et al., 2019). Standardised scales though would aid in documenting and reporting adverse effects (Brunoni et al., 2011a).

Ethical concerns include how and who will deliver tDCS, necessity of regulation, particularly in light of a growing ‘do-it-yourself’ community in which there are no current regulatory requirements, and the potential of inducing maladaptive long-term neuroplastic changes.

What are the potential mechanisms of tDCS in depression?

Neuroplasticity

Growing evidence implicates impaired neuroplasticity in major depression (Fossati et al., 2004; Pittenger & Duman, 2008; Player et al., 2013). Current treatments are associated with neuroplastic changes in the brain (Arnone et al., 2012; Joshi et al., 2016; Tendolkar et al., 2013; Fu et al., 2020). tDCS can enhance neuroplasticity (Stagg et al., 2018), however there has been limited direct evidence as to whether this mechanism contributes to the improvement in depressive symptoms following tDCS.

The glutamatergic system, in particular NMDA receptors, have an important role in LTP, and impairments in glutamatergic neurotransmission are evident in major depression (Valentine & Sanacora, 2009). LTP is the neural basis for memory (Bliss & Collingridge, 1993). Learning and memory impairments in depression may reflect impaired neuroplasticity (Pittenger & Duman, 2008), and LTP is instrumental to recovery in depression, in which upregulation of biomarkers such as BDNF are associated with increased long-term potentiation and neuroplasticity (Martinowich et al., 2007, Brunoni et al., 2008). As a potential mechanism by which tDCS contributes to recovery from depression, effects in the glutamatergic system and BDNF measures would be expected.

Widespread functional and structural abnormalities are observed in major depression (Wise et al., 2018). In particular, bilateral reductions in hippocampal volume are one of the most common findings (Cole et al., 2011; Schmaal et al., 2016). Located within the limbic system in the medial temporal lobe, the hippocampus plays a central role in learning and memory. It is a plastic brain structure, in which excitatory amino acids neurotransmitters and NMDA receptors are involved in the damaging effects of stress and trauma effects on function and structure (McEwen, 1999). Neuroplastic changes in the hippocampus are associated with changes in mood, and hippocampal grey matter volume is state dependent (Arnone et al., 2012). Clinical efficacy of antidepressant medication is proposed to be mediated through

neural plasticity (Castrén & Hen, 2013; Santarelli et al., 2003; Warner-Schmidt & Duman, 2006; Fu et al., 2020). Treatment with antidepressant drugs can stimulate neurogenesis in the hippocampus and restore grey matter to a volume similar to that in both healthy participants and patients in remission (Arnone et al., 2012; Warner-Schmidt & Duman, 2006). At the cellular level, animal models show increased postsynaptic spine density and enhanced synaptic plasticity following treatment with fluoxetine (Ampuero et al., 2010). Increases BDNF serum levels, indicating increased neuroplasticity, are observed following treatment with antidepressant medication which are associated with improvements in depressive symptoms (Brunoni et al., 2008; Duman & Monteggia, 2006).

Clinical studies of the treatment resistant form of major depression have reported increases in hippocampal connectivity and volume following ECT treatment (Abbott et al., 2014; Gbyl & Videbech, 2018; Joshi et al., 2016; Nordanskog et al., 2010; Sartorius et al., 2016; Tendolkar et al., 2013). ECT treatment modulates alterations in white matter microstructure in pathways connecting frontal and limbic areas in major depression (Lyden et al., 2014). In animal models, ECT has been found to stimulate neurogenesis in frontal regions (Inta et al., 2013). Moreover, an increase in a range of plasticity-associated transcripts, including BDNF, have been found after ECT (Conti et al., 2006). However, Brunoni et al. (2008) meta-analysis found that BDNF levels did not tend to increase following a course of ECT or TMS, suggesting that this may be due to an BDNF increase prior to brain stimulation as a majority of patients receiving these treatments had already been taking antidepressant medication.

Relative to healthy participants, patients in a current depressive episode show reduced paired-associative stimulation (PAS)-induced neuroplasticity in the motor cortex (Player et al., 2013; 2014) implicating reduced neuroplasticity in major depression. Anodal tDCS to the left dorsolateral prefrontal cortex has been associated with increased PAS-induced neuroplasticity in the motor cortex of currently depressed patients in comparison to sham tDCS (Player et al., 2014), suggesting that tDCS induces neuroplasticity. This effect was evident in a greater

proportion of patients who had received a longer course of tDCS with a minimum of 20 sessions (Player et al., 2014).

The prefrontal-limbic dysregulation model of emotion processing of major depression involves a dorsal component, which includes the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, hippocampus and middle frontal regions, implicated in attentional and cognitive qualities of the disorder, such as cognitive regulation when responding to emotional cues, and a ventral component, which includes the amygdala, subgenual anterior cingulate, anterior insula, orbitofrontal and ventrolateral prefrontal regions, that are involved in the production of emotional states (Mayberg, 1993; Phillips et al., 2003). The rostral anterior cingulate cortex is an important region in connecting these components, in which cognitive and emotion processing systems depend on coordinated interactions between these two systems, which are impaired in major depression (Mayberg, 1993; Costafreda et al., 2013).

Prefrontal-limbic dysregulation in major depression is characterised by decreased activity in prefrontal cortical regions and reduced inhibition in the amygdala (Ressler & Mayberg, 2008; Savitz & Drevets, 2009; Costafreda et al., 2013; Fidalgo et al., 2014). The amygdala shows increased responsivity to negative stimuli (Fu et al., 2004, 2008; Siegle et al., 2007; Arnone et al., 2012; Hamilton et al., 2012). Following treatment with antidepressant medication (Drevets, 2001; Fu et al., 2004, Arnone et al., 2012), rTMS (Kito et al., 2008; Ding et al., 2014; Luborzewski et al., 2006) as well as cognitive behavioural therapy (Fu et al, 2008), normalisation in amygdala activity has been observed.

Ironside et al. (2018) observed a direct relationship between prefrontal cortical and amygdala responses in participants with trait anxiety. Following anodal tDCS stimulation over the left dorsolateral prefrontal cortex, amygdala “hyper” responsivity was reduced to a similar level to that in participants with low anxiety. Behavioural data revealed that following active tDCS, accuracy on an attentional load task was improved, reflecting that fearful distractor faces had

reduced attentional capture and suggesting that the fear response associated with amygdala hyperactivity was reduced. Additionally, Nord et al. (2019) reported that dorsolateral prefrontal cortical activity was increased during an emotion processing task following active tDCS stimulation combined with CBT, which was not observed in patients who had received sham tDCS and CBT, although there were not any significant changes in amygdala activity following tDCS. Anodal tDCS is associated with increased activation at the stimulation site, typically left dorsolateral prefrontal cortex in major depression which in turn could regulate prefrontal cortical-amygdala function.

Although, functional connectivity changes following tDCS treatment in major depression have not yet been reported, a recent TMS study observed increased global connectivity following active rTMS but not sham treatment, which were more in line with connectivity in healthy controls, in particular significant changes were noted in connectivity between amygdalae and contralateral dorsolateral prefrontal cortex (Eshel et al., 2020).

While the relationship between BDNF levels and tDCS treatment have so far not demonstrated significant effects, sample sizes have been small (Loo et al., 2018; Palm et al., 2013; Player et al., 2014). As LTP is mediated by activity-dependent BDNF secretion (Fritsch et al., 2010) and BDNF levels correlate with amygdala responses in major depression (Lorenzetti et al., 2020), there is a potential relationship of BDNF with prefrontal-amygdala responses in the clinical efficacy of tDCS treatment.

Neuropsychology

Anodal tDCS shows a beneficial effect on stress-related emotional reactivity, strengthening cognitive processes which modulate negative emotional states in response to stress reactions and attenuating acute stress reactivity (Smits et al., 2020). Improved recognition in an emotional face recognition task, most notably for positive faces with anodal tDCS in healthy participants (Nitsche et al., 2012), support left dorsolateral prefrontal cortical stimulation in

major depression. Anodal tDCS stimulation to the left dorsolateral prefrontal cortex increased valence ratings of negative affective images, which were perceived as being less negative, as compared to sham and cathodal stimulation (Peña-Gómez et al., 2011). Ratings of unpleasantness while viewing aversive emotional pictures were significantly decreased following anodal tDCS relative to sham tDCS of the left dorsolateral prefrontal cortex (Maeoka et al., 2012). Significant decreases in EEG alpha band power and increases in beta band power accompanied the subjective responses, reflecting modulation of affective processing networks through increased local cortical activity (Maeoka et al., 2012).

Specific biases in processing affectively negative stimuli and information are evident in major depression, including difficulties in attentional disengagement from negative stimuli and impaired cognitive control in processing negative stimuli (Mitterschiffthaler et al., 2008; Foland-Ross and Gotlib, 2012). Vanderhasselt et al., (2013) assessed the effects of tDCS on cognitive control by using a cued emotional conflict task (CECT). Participants responded to a happy or sad face by selecting the same or opposite emotion, depending on the cue they were given. In 'opposite' trials, cognitive control enables one to respond with the incongruent emotion to the presented emotional stimuli. A three-way interaction between cue, emotion and group was found in healthy participants. tDCS improved reaction times during trials that require an inhibition in responses to happy but not sad faces. Vanderhasselt et al. (2014) subsequently observed that participants with major depression demonstrated a greater response time to 'opposite-sad' than to 'opposite-happy' cue-emotion combination trials, in that response time was slower when addressed with a conflict that was negatively valenced than that of the positive conflict. This suggests patients had difficulty in overriding a habitual response to negative stimuli. Further, the contrast of 'opposite' was associated with greater activity in right middle frontal gyrus and bilateral precuneus. In comparison to cue-emotion 'actual-sad', 'opposite-sad' also led to a stronger bilateral activation of dorsal anterior cingulate cortex, reflecting enhanced conflict-detection or a compensatory process. Both depression

and healthy control groups had greater response times for ‘actual-sad’ than ‘actual-happy’ trials (Vanderhassalt et al., 2014). This behavioural data support both the negative bias and reduced cognitive control in major depression, as the response was selectively slower when participants were asked to press an incongruent answer (opposite) as a response to negative stimuli (sad face).

Increased accuracy in an affective go-no go task (Boggio et al., 2007) as well as increases response rates for negative vs. neutral and positive vs. neutral words in an emotional Stroop task (Brunoni et al., 2014) have been found following tDCS. Salehinejad et al. (2017) reported improvements in working memory and attention along with improvements in depressive symptoms in participants with major depression who received 10 consecutive daily anodal tDCS sessions over the left dorsolateral prefrontal cortex as compared to participants who received sham tDCS sessions. The ability of tDCS to improve emotion processing (Peña-Gómez et al., 2011) and affective cognitive control (Boggio et al., 2007; Brunoni et al., 2014; Vanderhassalt et al., 2014) in major depression, which is associated with improved depressive symptoms, support improved prefontal-limbic regulation following tDCS treatment.

An area of unmet need is how to improve the cognitive impairments in major depression that contribute to psychosocial impairments. Impairments in executive functions, attention, memory and psychomotor speed are common in major depression, which can be seen during an acute depressive episode and can persist into recovery and remission phases (Paelecke-Habermann et al., 2005; Hammar and Ardal, 2009; Shilyansky et al., 2016).

Preliminary evidence suggests that tDCS could uniquely improve cognitive impairments in major depression (Loo et al., 2012; Moreno et al., 2015; Oliveira et al., 2013). Improvement in acute working memory after a single session of tDCS has been reported, with (Loo et al., 2012) and without (Moreno et al., 2015; Oliveira et al., 2013) concurrent antidepressant medication. tDCS over the dorsolateral prefrontal cortex was associated with both improved

discriminability and response criterion in a working memory n-back task, suggesting an increase of signal-to-noise ratio that enables responses to be fine-tuned (Oliveira et al., 2013). tDCS not only modulates affective processing but also impairments in executive functions in major depression, which might be evident following one session and also following a course of tDCS treatment. Whether the improvements endure in the long term require further investigation.

Is there potential for biomarkers to improve tDCS response?

Biomarkers are objective biological measures that indicate the underlying pathogenesis of disease, including normal biological processes, that aid in the classification of a disease and risk factors (Mayeux, 2004). The measurements could be biological media, such as physiological or biochemical measures, or brain imaging measures, which link to changes neural structure or function.

Predictive biomarkers may aid in clinical decision making for tDCS for the forms of depression most likely respond and those less likely to respond well to current tDCS montage, such as treatment resistant depression. As a predictor of clinical outcome, increased activity in the left dorsolateral prefrontal cortex at baseline (Nord et al., 2019) and volume (Bulubas et al., 2019) have been associated with improved treatment responses to tDCS. Common and distinct predictors to tDCS treatment in comparison with antidepressant medication and psychotherapy treatments (Pizzagalli, 2011; Fu et al., 2013) are continuing areas of investigation.

Summary

A course of active tDCS treatment demonstrates greater clinical efficacy as measured by rate of response, remission, and continuous symptom ratings in comparison to a course of placebo sham tDCS treatment. However, lack of inferiority to a course of treatment with antidepressant

medication has not yet been established. The mechanism is proposed to be through neuroplasticity with effects observed at the neuronal level. Evidence of neuroplastic effects mediating clinical outcome in major depression has been limited to date. Identifying predictive biomarkers is important to understanding disease pathophysiology and would aid in clinical decision making. tDCS is a potential treatment for individual with major depression who are unable to or prefer not to take current first line treatments. With high levels of acceptability, portability, and cost-effectiveness, tDCS is a potential first line treatment for major depression.

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