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Transcranial Electrical Stimulation (tES) for the Treatment of Neuropsychiatric Disorders Across Lifespan

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Abstract. Transcranial electrical stimulation (tES) is a safe, painless, and inexpensive noninvasive brain stimulation (NIBS) technique. tES has been shown to reduce symptoms in a variety of neuropsychiatric conditions such as depression, schizophrenia, anxiety, autism, and craving. There are many factors that can influence the effects of tES, such as current intensity, duration, baseline level of activity, gender, and age. Age is a critical variable, since the human brain undergoes several anatomical and functional changes across the lifespan. Therefore, tES-induced effects may not be the same across the lifespan. In this review we summarize the effects of tES, including tDCS, tACS, and tRNS, on clinical outcomes in several neuropsychiatric conditions, using a framework in which studies are organized according to the age of subjects. The use of tES in neuropsychiatric disorders has yielded promising results with mild, if any, adverse effects. Most of the published studies with tES have been conducted with tDCS in adult population. Future studies should focus on interventions guided by surrogate outcomes of neuroplasticity. A better understanding of neuroplasticity across the lifespan will help optimize current tES stimulation parameters, especially for use with children and elderly populations.

Keywords: Transcranial electrical stimulation, neuropsychiatric disorders, lifespan

Transcranial electrical stimulation (tES) techniques have been widely used for treating a variety of neuropsychiatric conditions. tES has shown promising results in ameliorating symptomatology in subjects that failed to respond to conventional treatments. Studies have shown that the clinical beneficial effects of these techniques are followed by changes at neuronal level, as measured by neuropsychological tools (Fidalgo et al., 2014). Moreover, these changes outlast the period of stimulation for most clinical conditions, showing sustained effects of tES interventions (Goldsworthy, Pitcher, & Ridding, 2014). However, most of the studies were performed in adults, making it difficult to understand the effects of tES across the lifespan.

Across the lifespan, the human brain undergoes several neuroplastic changes at both the neuroanatomical and neurofunctional level. For instance, during healthy aging there are several cognitive changes that occur (Salthouse, 2009), which have been associated with changes at the macrostructural level of the brain, mainly to an increased ventricular volume and brain shrinkage (see Fjell & Walhovd, 2010 for review). The annual reduction in cortical thickness can be up to 1% (Raz et al., 2005). Similarly, while there is a trend for global increase in white matter during childhood and adolescence, the total volume seems to peak around the age of 50, starting then to gradually decrease (Westlye et al., 2009). In the developing brain, on the other hand, there are several mechanisms such as apoptosis, where a programmed neural death is undertaken, limiting the neural overgrowth (Kuan, Roth, Flavell, & Rakic, 2000), ensuring the correct morphology and function

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development (e.g., Fuchs & Steller, 2011). These changes support the notion that plasticity mechanisms are different across the lifespan. For instance, the decrease of white and gray matter in the elderly has an effect of how neural networks respond to electrical stimulation. However, although evidence seems to suggest that plasticity is indeed different across lifespan, it is not clear how different is the response to brain stimulation when comparing the neural response in a younger versus older subject.

tES is a safe, painless, and inexpensive noninvasive brain stimulation (NIBS) technique . It uses a battery-driven current stimulator to apply weak electrical currents directly to the head (Priori, 2003). Depending on the number of sessions and the tES modality, the generated electrical fields are able to neuromodulate ongoing neuronal activity and induce neuroplasticity. There are various systems of classifying tES techniques. We used the one that was recently published (Guleyupoglu, Schestatsky, Edwards, Fregni, & Bikson, 2013). Therefore, we revise studies using direct current stimulation (tDCS), transcranial alternating current stimulation (tACS); transcranial pulsed current stimulation (tPCS), or transcranial random noise stimulation (tRNS).

Short-term effects of tDCS are associated with induced changes in membrane polarization depolarization under anodal tDCS and hyperpolarization under cathodal tDCS – without inducing action potentials in the cortical neurons (Fregni et al., 2014; Nitsche et al., 2008; Tehovnik, 1996; Wagner et al., 2007). Long-term effects of tDCS are likely to be explained by neuroplastic processes of long-term potentiation (LTP) and long-term depression (LTD) (Nitsche, Muller-Dahlhaus, Paulus, & Ziemann, 2012; Nitsche et al., 2008).

Less is known about the mechanisms of action of tACS, tRNS, and tPCS. tACS consists of delivering an oscillatory electrical current to the head in a frequency-specific fashion, causing an interference with ongoing oscillatory brain activity and inducing changes in cortical excitability as measured by electroencephalography (Antal & Paulus, 2013). tRNS is a new technique that consists of applying alternating current at random frequencies to the head, ranging from 0.1 Hz to 640 Hz. Some studies have found that high-frequency tRNS (hf-tRNS; 101–640 Hz) is able to increase motor cortical excitability (by inducing depolarization), as measured by MEP (Motor Evoked Potential) amplitude increase; these changes outlast the duration of the stimulation (Chaieb, Antal, & Paulus, 2011; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). hf-tRNS is also able to improve performance in perceptual learning task when compared to low-frequency tRNS (lf-tRNS; 0.1–100 Hz), placebo stimulation, and active tDCS (anodal and cathodal) (Pirulli, Fertonani, & Miniussi, 2013). tPCS consists of delivering pulsed current at different frequency ranges through surface electrodes placed on the ears. Modeling studies show that tPCS-induced effects can reach cortical and subcortical areas (Datta, Dmochowski, Guleyupoglu, Bikson, & Fregni, 2013). It can interact with endogenous oscillatory activity inducing significant changes in cortical excitability measured by quantitative electroencephalography (Castillo Saavedra et al., 2014; Morales-Quezada et al., 2014).

There are many factors that can influence the effects of tES, such as intensity, duration, baseline level of activity, gender, and age (Krause & Cohen Kadosh, 2014). Age is a critical variable, since the human brain undergoes several anatomic and functional changes across the lifespan. For instance, research has shown that between childhood and adolescence there is a phenomenon called synaptic pruning (Chechik, Meilijson, & Ruppin, 1999), where some synapses are eliminated. Research shows also that the maturation of the frontal lobe is not completed until adulthood (Johnson, Blum, & Giedd, 2009). The adult brain, on the other hand, is quite anatomically stable, with most neuroplasticity processes resulting mainly from new learning experiences, damage, or other types of neuromodulation.

Therefore, the objective of this review is to summarize the available literature about the effects of tES in treating neuropsychiatric conditions using a framework in which studies are classified according to the age of participants. The neuropsychiatric conditions discussed are mood disorders (Major Depression and Bipolar disorder), schizophrenia, anxiety (Anxiety, OCD spectrum, and stress-related disorders), autism spectrum disorders (ADS), and craving disorders (alcohol, smoking, drugs, and food).

Methodology

For this literature review, we performed an electronic search in PubMed database for articles published from January 2000 through January 2015, combining tES (and its variants) with different neuropsychiatric disorders as keywords. Only articles with the keywords of the neuropsychiatric disorder in the title were retrieved and inspected. The references of the retrieved papers were manually inspected. Studies retrieved were summarized according to the neuropsychiatric condition and age category. For the purpose of this review, children and adolescents were defined as being younger than 18 years old, adults as between 18 and 65 years old, and the elderly as over 65 years old. A total of 61 studies were analyzed, including case reports, open-label studies, and Randomized Clinical Trials (RCTs).

Transcranial Electrical Stimulation in Neuropsychiatric Disorders

Mood Disorders

Major Depression Disorder (MDD)

MDD is characterized by persistent low mood, low self-esteem, and loss of interest or pleasure in most daily activities. Functionally, depression is associated with increased right hemisphere activation and decreased left hemispheric activation (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). In addition, depression has been associated with

dysfunctional plasticity (Normann, Schmitz, Furmaier, Doing, & Bach, 2007; Spedding, Neau, & Harsing, 2003). Therefore, tES interventions aim to increase LTP-like plasticity, increase left hemisphere activity, and/or decrease right hemisphere activity (Schonfeldt-Lecuona et al., 2010). There are 13 studies using tDCS and one case report using tRNS in adults with MDD. We also retrieved one case report using tDCS in elderly adults with MDD.

Effects in Adults

Anodal tDCS protocols, which aim to increase activity over the left hemisphere, have successfully shown symptom amelioration in major depression (see Table 1). Anodal tDCS over the left DLPFC for five consecutive days is able to induce significant clinical improvements in newly diagnosed patients (Fregni et al., 2006). Increasing the current intensity (up to 2 mA) and the number of sessions (15) sustains the clinical improvement up to 1 month (Boggio, Rigonatti, et al., 2008; Knotkova et al., 2012; Loo et al., 2012); this effect is comparable to the one found with 20 mg of fluoxetine (Rigonatti et al., 2008).

Bi-frontal tDCS protocols (i.e., anode over the left DLPFC and cathode over the right DLPFC) have also been showing promising results (Brunoni, Ferrucci, et al., 2013; Brunoni et al., 2011; Dell'Osso et al., 2012). A study assessing the effects of bi-frontal tDCS, sertraline, or the combination of both found that tDCS alone improved depression ratings significantly and similarly extension to that of sertraline. Remarkably enough, the combination of tDCS and sertraline was more effective than each intervention alone (Brunoni, Valiengo, et al., 2013).

Nonetheless, there are some trials where anodal tDCS in the left hemisphere (Palm et al., 2012) and bi-frontal tDCS (Blumberger, Tran, Fitzgerald, Hoy, & Daskalakis, 2012) were not effective in reducing depressive symptomatology. Another trial (Loo et al., 2012) showed that anodal tDCS over the left DLPFC was able to significantly improve mood, but with a similar remission rate (i.e., 13%) when compared to sham. The use of weaker currents, reduced number of sessions, or greater depression severity contribute to explain the negative results. Interestingly enough, moving the return electrode to an extra-cephalic position increased the initial treatment response in patients that were resistant to bi-frontal tDCS (Martin et al., 2011). If "continuation tDCS", given weekly during 3 months and then once per fortnight for another 3 months, is performed after the acute daily tDCS, the remission rate seems to be kept at about 80% after 3, and 50% after 6 months (Martin et al., 2013).

So far, there is one case report where transcranial random noise stimulation (tRNS) was able to decrease the depression clinical ratings in a female patient. After 15 sessions of 1 mA tRNS with electrodes positioned at F3 and F8, the patient improved 63% in the Montgomery-Asberg Depression Rating Scale (MADRS), compared with 31% and 25% improvement in the two previous treatments of 15 daily sessions of tDCS using the same electrode montage (Chan et al., 2012).

Effects in Elderly Adults

There is one case report with tDCS in the elderly adult population as a potential treatment for major depression (Shiozawa, da Silva, et al., 2014). A 92-year-old patient was subjected to 10 daily sessions of tDCS (2 mA for 30 min) with the anode electrode placed over the left DLPFC and the cathode electrode over the contralateral deltoid. This resulted in a 17-point decrease in the Hamilton Depression Rating Scale (HAM-D) when comparing to the baseline. This effect was sustained for 3 weeks.

Bipolar Disorder

Manic symptoms in bipolar disorder may be associated with the opposite pattern of prefrontal activation found in MDD – right hypoactivity and left prefrontal hyperactivity; this makes tES an attractive intervention to be tested in clinical trials. So far, there is only one study published on tES for adults with Bipolar disorder (see Table 1). This study was a case report, showing that five consecutive days of 2 mA/20 min anodal tDCS over the right DLPFC was able to induce fast alleviation of acute symptoms (Schestatsky, Janovik, et al., 2013).

Schizophrenia

Schizophrenia is a severe and disabling chronic disorder characterized by hallucinations, delusions, and disorganized speech, behavior, and thinking. The pathophysiology involved in schizophrenia is still largely unknown, however several functional and anatomical brain changes have been reported in the literature (Meyer-Lindenberg & Tost, 2014). Neuroimaging studies have shown that schizophrenia patients with hallucinations exhibit hyperactivity on the left temporo-parietal area (McGuire, Shah, & Murray, 1993), Broca's area (Jardri, Pouchet, Pins, & Thomas, 2011; McGuire et al., 1993), its right homolog (Dierks et al., 1999; Silbersweig et al., 1995), Heschl's gyrus (Dierks et al., 1999), and the superior temporal gyrus (Jardri et al., 2011; Shergill, Brammer, Williams, Murray, & McGuire, 2000). In addition, hypoactivity over the prefrontal cortex has been described and associated with the development of positive symptoms and cognitive function impairments (Lawrie, McIntosh, & Nadeem, 2002; Takeshi, Nemoto, Fumoto, Arita, & Mizuno, 2010).

Young adulthood seems to be the critical stage for the development of schizophrenia. Nonetheless, the childhood-onset is a rare and severe form of schizophrenia (Nicolson & Rapoport, 1999) that seems to be continuous with the adult-onset (David et al., 2011). Neuroimaging studies show it is similar to the neurophysiology seen in adults (Heimer, Harlan, Alheid, Garcia, & de Olmos, 1997; Shergill, Bullmore, Simmons, Murray, & McGuire, 2000; Silbersweig et al., 1995).

So far, there are eight case studies, two open-label studies, and six RCTs assessing the effects of tES in adult patients with schizophrenia (see Table 2). Only one study has been conducted in children with childhood-onset

Table 1. Studies on major depression disorder and bipolar disorder

Author	Condition	No. of subjects (females)	Age group (years old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity/ frequency	Treatment protocol	Main outcomes	Results
Blumberger et al. (2012)	MDD	24 (20)	Adults (18–65)	Sham controlled, double-blind RCT	tDCS	Anodal over F3	Cathodal over F4	35 cm^2	2 mA	20 min/day for 15 consecutive days excluding weekends.	MADRS, HRSD-17, BPRS, BDI	Negative (no significant difference)
Brunoni et al. (2011)	MDD	31 (23)	Adults (30–70)	Open label	tDCS	Anodal over F3	Cathodal over F4	35 cm^2	2 mA	20 min/twice a day for five consecutive days.	HDRS, BDI	Positive
Brunoni, Ferrucci et al. (2013)	MDD	82 (54)	Adults (43–65)	Open label	tDCS	Anodal over F3	Cathodal over F4	35 cm^2	2 mA	20 min/twice a day for five consecutive days.	HDRS, BDI	Positive
Brunoni, Valiengo, et al. (2013)	MDD	120	Adults (18–65)	Placebo controlled, double-blind, factorial RCT	tDCS	Anodal over F3	Cathodal over F4	25 cm^2	2 mA	tDCS – 30 min/day for 10 consecutive days excluding weekends followed by two sessions every other week. Sertraline – 50 mg/day.	MADRS, HDRS	Positive
Chan et al. (2012)	MDD	1 (F)	Adults (35)	Case report	tRNS	Anodal over F3	Cathodal over F8	N/A	2 mA range – 1 mA offset	20 min/day for 4 weeks excluding weekends.	MADRS, QIDS	Positive
Dell'Osso et al. (2012)	MDD	23 (15)	Adults (18–80)	Open label	tDCS	Anodal over F3	Cathodal over F4	32 cm^2	2 mA	20 min/twice a day for five consecutive days.	MADRS, HDRS	Positive
Fregni et al. (2006)	MDD	10	Adults (32–52)	Sham controlled, double-blind RCT	tDCS	Anodal over F3	Cathodal over the right SO	35 cm^2	1 mA	20 min/day for five alternating days.	HDRS, BDI	Positive
Knotkova et al. (2012)	MDD	10 (5)	Adults (38–59)	Open label	tDCS	Anodal over F3	Cathodal over the right SO	36 cm^2	2 mA	20 min/day for 10 consecutive days excluding weekends.	HDRS, MADRS	Positive
Loo et al. (2012)	MDD	64 (28)	Adults (35–61)	Sham controlled, double-blind RCT	tDCS	Anodal over F3	Cathodal over F8	35 cm^2	2 mA	20 min/day for 15 consecutive days excluding weekends.	MADRS, IDS, CGI-S	Positive
Martin et al. (2011)	MDD	11 (8)	Adults (33–59)	Open label	tDCS	Anodal over F3	Cathodal over the right upper arm	35 cm^2	2 mA	20 min/day for 20 consecutive days excluding weekends.	MADRS	Positive
Martin et al. (2013)	MDD	26 (18)	Adults (33-70)	Open label prospective	tDCS	Anodal over F3	Study 1 – Cathodal over F8. Study 2 – Cathodal over the right upper arm	35 cm^2	2 mA	Continuation treatment for 20 min/session weekly for the first 3 months and one per fortnight for the final 3 months.	Surviving without relapse, time to relapse, MADRS	Positive
Palm et al. (2012)	MDD	22 (14)	Adults (36–79)	Sham controlled, double-blind crossover study	tDCS	Anodal over F3	Cathodal over the right SO	35 cm^2	1 mA (10 subjects) 2 mA (12 subjects)	20 sessions (10 active/10 sham) for 20 min/day within 4 weeks. No washout period.	HDRS, BDI, CGI, PANAS	Negative (no significant difference)
Rigonatti et al. (2008)	MDD	42 (28)	Adults (42–56)	Sham controlled, double-blind RCT/open label fluoxetine	tDCS	Anodal over F3	Cathodal over the right SO	35 cm^2	2 mA	20 min/day for 10 consecutive days excluding weekends.	BDI, HDRS	Positive
Schestatsky, Janovik, et al. (2013)	Bipolar Disorder	1 (M)	Adults (41)	Case report	tDCS	Anodal over F4	Cathodal over the left SO	35 cm^2	2 mA	20 min/day for five consecutive days.	YMRA, NOISE	Positive
Shiozawa, da Silva, et al. (2014)	MDD	1 (M)	Elderly (92)	Case report	tDCS	Anodal over F3	Cathodal over the right deltoid	N/A	2 mA	30 min/day for 10 consecutive days excluding weekends.	HAM-D, BAI, MOCA	Positive

MDD = Major Depressive Disorder; F3 = left dorsolateral prefrontal cortex; F4 = right dorsolateral prefrontal cortex; F8 = right fronto-temporal region; SO = Supraorbital region; MADRS = Montgomery-Asberg Depression Rating Scale; HRSD = Hamilton Depression Rating Scale; BPRS = Brief Psychiatric Rating Scale; BDI = Beck Depression Inventory; QIDS = Quick Inventory of Depressive Symptoms; IDS = Inventory of Depressive Symptomatology; CGI-S = Clinical Global Impression – Severity of Illness; CGI = Clinical Global Impression; PANAS = Positive and Negative Affect Scale; BAI = Beck Anxiety Inventory; MOCA = Montreal Cognitive Assessment Scale; YMRA = Young mania rating scale (YMRS); NOSIE = Nurses' Observation Scale for Inpatient Evaluation.

Table 2. Studies on schizophrenia

Author	Condition	No. of subjects (females)	Age group (years old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity/frequency	Treatment protocol	Main outcomes	Results
Bose et al. (2014)	Schizophrenia	21 (12)	Adults (20–45)	Open label	tDCS	Anodal over F3	Cathodal over the midway between T3 and P3 (TPJ)	35 cm^2	2 mA	20 min/session twice a day for five consecutive days.	PSYRATS, SAI, AHS	Positive
Brunelin, Mondino, Gassab, et al. (2012)	Schizophrenia	30 (8)	Adults (30–50)	Sham controlled, double-blind RCT	tDCS	Anodal over F3	Cathodal over the left temporo-parietal cortex	35 cm^2	2 mA	20 min/twice a day for five consecutive days.	AHRS, PANSS	Positive
Brunelin, Mondino, Haesebaert, et al. (2012)	Schizophrenia	2	Adults (46, 29)	Case series	tDCS	Anodal over F3	Cathodal over the left temporo-parietal cortex	N/A	2 mA	20 min/twice a day for five consecutive days.	PANSS, AHRS	Positive
Fitzgerald et al. (2014)	Schizophrenia	24 (9)	Adults (27–51)	Sham controlled, double-blind RCT	tDCS	1. Unilateral tDCS – Anodal over F4 2. Bilateral tDCS – Anodal over the F3 and F4	Cathodal over the right temporo-parietal area	35 cm^2	2 mA	20 min/day for 15 consecutive days excluding weekends.	PANSS, SANS, Calgary Depression Scale	Negative (no significant difference)
Göder et al., 2013	Schizophrenia	14	Adults (25–41)	Sham controlled, double-blind, pseudorandomized trial	so-tDCS	Electrodes were located on F3 and F4 and at the mastoids.		8 mm diameter	Frequency: 0.75 Hz Intensity: as tolerated between 0 and 300 μA	Sleep phase 2–5 blocks of five min sessions of stimulation/1 min interval free of stimulation.	Rey Auditory-Verbal Learning Test	Positive
Haesebaert et al. (2014)	Schizophrenia	1 (F)	Adults (26)	Case report	tRNS	Anodal over F3	Cathodal over the left temporo-parietal junction	35 cm^2	2 mA range – 1 mA offset Frequency: 100–640 Hz	20 min/session twice a day for five consecutive days.	PANSS, AHRS	Positive
Homan et al. (2011)	Schizophrenia	1 (M)	Adults (44)	Case report	tDCS	Cathodal over the left temporo-parietal junction (Wernicke's area)	Anodal over the right SO	35 cm^2	1 mA	15 min/daily for 10 consecutive days.	Arterial spin labeling, Hallucination Change Scale, PANSS, Psychotic Symptom Rating Scale	Positive
Mattai et al. (2011)	Schizophrenia	12 (7)	Children (10–17)	Sham controlled, double-blind RCT	tDCS	Study 1 – Bilateral anodal over Fp1 and Fp2. Study 2 – Bilateral cathodal over T3 and T4	Reference electrode on the nondominant forearm	25 cm^2	2 mA	20 min/day for 10 consecutive days excluding weekends.	Vital sign monitoring, MMSE, EEG, EKG, MRI	Positive
Mondino et al. (2015)	Schizophrenia	28 (16)	Adults (26–58)	Sham controlled, double-blind RCT	tDCS	Anodal over F3	Cathode over the left temporo-parietal junction	35 cm^2	2 mA	20 min/session twice a day for five consecutive days.	PANSS, AVH frequency, source monitoring performances	Positive
Nawani et al. (2014)	Schizophrenia	1(M)	Adults (31)	Case report	tDCS	Anodal over F3	Cathodal over the left temporo-parietal area	35 cm^2	2 mA	20 min/session twice daily for five consecutive days.	PoMS, Attention testing (computerized)	Positive
Palm et al. (2013)	Schizophrenia	1 (M)	Adults (29)	Case report	tRNS	Anodal over F3	Cathodal over the right orbitofrontal region	35 cm^2	2 mA range – 1 mA offset Frequency: 100–640 Hz	20 min/session twice a day for 10 consecutive days.	PANSS, SANS, Calgary Depression Scale	Positive
Rakesh et al. (2013)	Schizophrenia	1 (M)	Adults (24)	Case report	tDCS	Anodal over F3	Cathodal over the left temporo-parietal junction.	35 cm^2	2 mA	20 min/session twice a day for five consecutive days.	AHRS, Insight Rating Scale	Positive
Shiozawa et al. (2013)	Schizophrenia	1 (M)	Adults (31)	Case report	tDCS	Anodal over F3	First 10 sessions – Cathodal on the occipital area. Last 10 sessions – Cathodal on the left temporo-parietal area	35 cm^2	2 mA	20 min/day for 20 consecutive days.	PANSS, Launay-Slade Hallucination Scale and the AHRS	Positive
Shivakumar et al. (2014)	Schizophrenia	1 (F)	Adults (42)	Case report	tDCS	Anodal over F3	Cathodal over the left temporo-parietal junction	35 cm^2	2 mA	Intermittent boosters of two sessions per day of 20 min for a single day as maintenance treatment of hallucinations.	AHS of the PSYRATS	Positive
Vercammen et al. (2011)	Schizophrenia	20 (10)	Adults (19–42)	Case – control, cross over study	tDCS	Anodal over F3	Cathode over the right SO	35 cm^2	2 mA	20 min/session. One active and one sham session on a randomized order and a washout period of 8 day in average.	WAIS-III, WTAR, PANSS	Negative (a subset did improve with tDCS, especially those with greater scores at baseline)

PSYRATS = The Psychotic Symptom Rating Scales; SAI = Schedule for Assessment of Insight; AHS = Auditory hallucinations Score; AHRS = Auditory Hallucination Rating Scale; PANSS = Positive and Negative Syndrome Scale; MMSE = Mini-Mental State Examination; EEG = Electroencephalogram; EKG = Electrocardiogram; MRI = Magnetic Resonance Imaging; AVH = Auditory Verbal Hallucination; PoMS = Profile of Mood State; WAIS-III = Wechsler Adult Intelligence Scale III; WTAR = Wechsler test of Adult Reading; F3 = Left dorsolateral prefrontal cortex; F4 = Right dorsolateral prefrontal cortex, Fp1 = Left fronto-parietal cortex; Fp2 = Right fronto-parietal cortex; T3 = Left temporal cortex; T4 = Right temporal cortex; SO = Supraorbital region; M = Male; F = Female.

schizophrenia. Most of them used tDCS, while only two of them investigated tRNS effects in schizophrenia.

Effects in Children/Adolescents

Only one study in this category was published so far, which aimed to investigate the tolerability of tDCS in childhood-onset schizophrenia (Mattai et al., 2011). In this study, 13 children were assigned randomly to receive either bilateral anodal DLPFC tDCS (n = 8) or bilateral cathodal superior temporal gyrus (STG) tDCS (n = 5). Although no significant clinical improvements were reported, tDCS within the applied parameters seemed to be well tolerated in children.

Effects in Adults

tES has been tested using two main approaches. One is increasing cortical excitability in the abnormally depressed frontal areas in order to improve the cognitive function and negative symptoms. The other is inhibiting the hyperactivity on the temporo-parietal areas, which is thought to be related with positive symptoms such as hallucinations.

Most of the studies using both strategies have shown promising results. Several case reports, open-label studies, and RCTs investigating tDCS effects in order to decrease negative symptoms in schizophrenia have mainly used anodal stimulation over the DLPFC. This intervention with sessions ranging from 1 to 10 was able to improve cognitive functioning, namely working memory, verbal fluency, learning, and insight facilitation (Bose et al., 2014; Vercammen et al., 2011).

With the aim of improving positive symptoms, several cathodal tDCS protocols over the fronto-temporal area have been conducted and shown both monotherapy and add-on therapy of tDCS significantly decreased auditory and verbal hallucinations (Brunelin, Mondino, Gassab, et al., 2012; Brunelin, Mondino, Haesebaert, et al., 2012; Homan et al., 2011; Mondino, Haesebaert, Poulet, Suaud-Chagny, & Brunelin, 2015; Nawani et al., 2014; Rakesh et al., 2013; Shiozawa, da Silva, Cordeiro, Fregni, & Brunoni, 2013; Shivakumar et al., 2014).

Despite the promising results of tDCS in Schizophrenia, there are also negative findings. In two small RCTs testing the effects of anodal tDCS over DLPFC and cathodal stimulation over the temporo-parietal junction, both unilaterally and bilaterally, no effects were found in either hallucinations or negative symptoms (Fitzgerald, McQueen, Daskalakis, & Hoy, 2014). One possible explanation for these negative results is that tDCS was administered once daily, in contrast to other studies where tDCS was administered twice daily. Also, in this negative study, the population was noticeably heterogeneous, which could have also contributed to the failure of the therapy (Fitzgerald et al., 2014).

One study used intermittent tDCS (as current intensity varies over time) in schizophrenic patients (Göder et al., 2013). Sinusoidal currents at the same frequency of slow sleep oscillations, when delivered during non-rapid eye movement sleep, were able to improve mood and the retention of verbal materials in 14 patients. tRNS has also been recently studied for the management of schizophrenia. So far, two case reports were published. In one anodal tRNS over the DLPFC, it was shown to substantially improve positive symptoms and paranoia (Haesebaert, Mondino, Saoud, Poulet, & Brunelin, 2014); while on the other, anodal tRNS over DLPFC significantly decreased the negative symptoms (Palm, Hasan, Keeser, Falkai, & Padberg, 2013).

Anxiety: Generalized Anxiety Disorder (GAD)

Cathodal tDCS protocols, which aim to decrease activity over the right DLPFC, have successfully shown symptom amelioration in GAD. There are only four studies using tES in adults with GAD: one using tDCS and three other with tPCS (see Table 3).

Effects in the Adults

A case report showed that cathodal tDCS over the right DLPFC, applied during 15 sessions, substantially improved anxiety symptoms in a female subject with severe refractory GAD. Interestingly, 1 month after the tDCS intervention the subject was reported to be asymptomatic with several significant clinical improvements (Shiozawa, Leiva, et al., 2014)

tPCS has also shown significant effects in adults with GAD. Three studies using daily tPCS reduced both anxiety and comorbid, depressive symptoms in adults with GAD. Daily tPCS at a frequency of 0.5 Hz 60 min for 6 weeks had significant clinical effects in patients with anxiety and concomitant depression (Bystritsky, Kerwin, & Feusner, 2008). In the same line, daily 60 min of tPCS delivered at a frequency of 0.5 Hz, during 5 weeks, in 115 subjects, was able to reduce both anxiety and comorbid, depressive symptoms in adults with GAD (Barclay & Barclay, 2014). tPCS was also able to reduce anxiety levels and withdrawal responses in undergoing thyroidectomy as compared to placebo stimulation (Lee et al., 2013).

Obsessive-Compulsive (OCD) Spectrum Disorders

Obsessive-Compulsive Disorder (OCD)

OCD is a neuropsychiatric disorder, characterized by the presence of repetitive, upsetting, and unwanted thoughts and/or images and behavior and/or mental rituals. Cortico-striato-thalamo-cortical (CSTC) loops are implicated in the pathophysiology of OCD (Goncalves et al., 2011).

Effects in Adults

There are two case studies published using tDCS in adults with OCD. Anodal tDCS applied twice a day,

Table 3. Studies in anxiety disorders

Author	Condition	No. of subjects (females)	Age group (years old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity/frequency	Treatment protocol	Main outcomes	Results
Barclay and Barclay (2014)	GAD	115 (78)	Adults (28–56)	Sham controlled, double-blind RCT	tPCS	Clipped electrodes on both earlobes		N/A	Frequency: 0.5 Hz Intensity: minimum of 100 μA	1 hr/day for 5 weeks.	HAM-A, HAM-D	Positive
Bystritsky et al. (2008)	GAD	12 (9)	Adults (29–58)	Open label	tPCS	Clipped electrodes on both earlobes		N/A	Frequency: 0.5 Hz Intensity: as tolerated between 10 and 500 μA	60 min/day for 6 weeks.	HAM-A, CGI-S, CGI-I, HAM-D	Positive
Carvalho et al. (2014)	Tourette Syndrome	1 (M)	Adolescent (16)	Case report	tDCS	Cathodal over the left pre-SMA	Anodal extra-cephalic on the right deltoid muscle	25 cm^2	1.425 mA	30 min/daily for 1-consecutive day excluding weekends.	YGTSS, fMRI signals	Positive
Lee et al. (2013)	Preoperative anxiety	50 (50)	Adults (35–60)	Sham controlled, double-blind RCT	tPCS	Clipped electrodes on both earlobes		N/A	Frequency: 0.5 Hz Intensity: 100 μA	20 min/session. One session on the night before surgery and another one on the morning of surgery.	Anxiety Scores, Pain Scores, ACTH and Cortisol levels, withdrawal response to Rocuronium	Positive
Narayanaswamy et al. (2014)	OCD	2 (1)	Adults (39, 24)	Case series	tDCS	Anodal over the left pre-SMA/SMA	Cathodal over the right SO	35 cm^2	2 mA	20 min/twice daily for 10 consecutive days.	YBOCS, HAM-A, HAM-D, fMRI BOLT signal	Positive
Prehn-Kristensen et al. (2014)	ADHD	ADHD: 12 (0)	Children (10–14)	Sham controlled, double-blind, case control crossover study	so-tDCS	Electrodes were located on F4 and F3 and at the mastoids.		8 mm diameter	Frequency: 0.75 Hz Intensity: as tolerated between 0 and 250 μA	Sleep phase 2–5 blocks of 5 min sessions of stimulation/1 min interval free of stimulation.	"Concentration or Memory" Task, Wechsler Intelligence Scale for Children, Polysomnography EEG	Positive
Saunders et al. (2014)	PTSD	4 (0)	Adults (55–65)	Pilot study	tDCS	Anodal over F3	Cathodal over the right SO	35 cm^2	1 mA	20 min/session once a week for five consecutive weeks.	Cognitive and emotional assessments; P3 ERP	Positive
Shiozawa et al. (2014)	GAD	1 (F)	Adults (58)	Case report	tDCS	Cathodal over F4	Anodal extra-cephalic over the contralateral deltoid	25 cm^2	2 mA	30 min/day for 15 consecutive days excluding weekends.	GAD 7 item scale, Beck Anxiety Inventory, HAM-A, HAM-D	Positive
Volpato et al. (2013)	OCD	1 (M)	Adults (35)	Case report	tDCS	Cathodal over F3	Anodal over the posterior neck base	35 cm^2	2 mA	20 min/day for 10 consecutive days excluding weekends.	fMRI, YBOCS, HAM-A, HAM-D	Negative (no effect on OC symptoms, only in depression and anxiety)

GAD = Generalized Anxiety Disorder; OCD = Obsessive-Compulsive Disorder; ADHD = Attention Deficit and Hyperactivity Disorder; PTSD = Post-traumatic Stress Disorder; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; CGI-I = The Clinical Global Impressions Scale (Improvement Index); CGI-S = The Clinical Global Impressions Scale (Severity Index); YGTSS = Yale Global Tic Severity Scale; fMRI = Functional Magnetic Resonance Imaging; ACTH = Adrenocorticotropic Hormone; EEG = Electroencephalogram; YBOCS = Yale-Brown Obsessive Compulsive Scale; SAM = Supplementary Motor Area; F3 = Left Dorsolateral Prefrontal Cortex; F4 = Right Dorsolateral Prefrontal Cortex; SO = Supraorbital region; OC = Obsessive-Compulsive; M = Male; F = Female; P3 ERP = P300 Event Related Potential.

during 10 days, over the pre- and supplementary motor area (pre-SMA/SMA) leads to significant clinical improvements in obsessions, compulsions, depressive and anxiety symptoms in two selective serotonin reuptake inhibitor-resistant (SSRI) OCD patients (Narayanaswamy et al., 2014). In another case study, tDCS had no effects on obsessive-compulsive symptoms, however it reduced anxiety and depression levels (Volpato et al., 2013).

Tourette Syndrome

TS is characterized by the presence of rapid, stereotyped movements and vocalizations (i.e., tics) (Vicario et al., 2010). Neuroimaging data shows that tics severity is associated with increased activation over motor pathways and reduced activation over the control areas of the cortico-striato-thalamo-cortical circuits (Wang et al., 2011). The temporal pattern of tic generation suggests that cortical precedes subcortical activation, with the SMA playing a key role in tics generation (Neuner et al., 2014).

Effects in Adolescents

There is only one case report testing the feasibility of this approach in an adolescent with TS. This study shows that delivering 10 daily sessions of cathodal tDCS over the pre-SMA is able to decrease tic severity, which can be sustained up to 6 months (Carvalho et al., 2014). No studies have been published so far in adults or elderly adults.

Post-Traumatic Stress Disorder (PTSD)

PTSD is a neuropsychiatric disorder that is developed after exposure to life-threatening situations. A recent meta-analysis showed that when exposed to negative stimulus, PTSD patients exhibit an amygdala and mid-ACC hyperactivation, accompanied by decreased activation over the lateral and medial prefrontal cortex (Hayes, Hayes, & Mikedis, 2012). For PTSD, there is only one pilot study.

Effects in Adults

In a pilot study involving four subjects, anodal tDCS over the left DLPFC in combination with working memory (WM) training induced significant clinical improvements in patients with PTSD and poor WM (Saunders et al., 2014).

Attention-Deficit and Hyperactivity Disorder (ADHD)

ADHD is a disabling brain condition, highly prevalent in childhood and continuing throughout adolescence into adulthood (Sharma & Couture, 2014). It is characterized by difficulties in sustained focus, attention, inhibition control, and/or hyperactivity. Neuroimaging data shows that these symptoms are related to abnormal cortical activity in frontal, parietal, and cingulate regions (Bush, 2011). Given the chronic nature of this disorder and limited effects of pharmacological agents, tES is an attractive option to be tested. In fact, only one study was published so far using tES in children with ADHD.

Effects in Children/Adolescents

So far, only one study has been published using tES in children with ADHD (see Table 3). Transcranial oscillating direct current stimulation applied bilaterally to the DLPFC at 0.75 Hz during slow wave sleep was able to increase slow wave power and boost memory performance in 12 children with ADHD to a level similar to that of healthy controls (Prehn-Kristensen et al., 2014). It is worthy to note that the patients were regularly taking methylphenidate but were asked to discontinue their treatment for the study sessions.

Autism Spectrum Disorders (ASD)

ASD are characterized by severe social communication deficits with repetitive behaviors or restrictive interests (Anagnostou & Taylor, 2011). Neuroimaging data suggests changes in connectivity. Cortical-cortical connectivity is decreased, while subcortical-cortical connectivity is increased, thus suggesting an ineffective system with abnormal signal-to-noise ratio (Minshew & Keller, 2010). There are also evidences of abnormal cortical excitability and plasticity. More specifically, an altered synapse development in regions related to language and social skills in the frontal and prefrontal cortices has been thought to create an imbalance of excitation and inhibition, leading to an inappropriate hyperactivity of the brain (Rubenstein & Merzenich, 2003). Furthermore, several studies have identified a reduction in the GABAergic activity in these regions in patients with autism (Oberman, Pascual-Leone, & Rotenberg, 2014).

There is limited data on the therapeutic effects of tES on autism. There are three published studies: one open label in children, one RCT in children, and one case study in adults (see Table 4).

Effects in Children/Adolescents

In an open-label study, anodal tDCS over the Broca's area was able to improve language acquisition in 10 autistic children with minimal verbal language (Schneider & Hopp, 2011). A recent study, conducted in 2014 with 20 autistic children, showed that five consecutive daily sessions of anodal tDCS applied over the DLPFC were able to significantly decrease symptomatology on several standardized scales (Amatachaya & Auvichayapat, 2014). These effects outlasted tDCS for 7 days.

Table 4. Studies in autism spectrum disorders

Author	Condition	No. of subjects (females)	Age group (years old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity	Treatment protocol	Main outcomes	Results
Amatachaya and Auvichayapat (2014)	ASD	20 (0)	Children (5–8)	Sham controlled, double-blind crossover study	tDCS	Anodal over F3	Cathodal over the right shoulder	35 cm^2	1 mA	20 min/day for five consecutive days.	CARS, ATEC, CGAS	Positive
D'Urso et al. (2014)	ASD	1 (M)	Adults (26)	Case report	tDCS	Cathodal over F3	Anodal extra-cephalic over the right deltoid	25 cm^2	1.5 mA	20 min/day for 10 consecutive days excluding weekends.	ABC score	Positive
Schneider and Hopp (2011)	ASD	10 (2)	Children/adolescents (6–14)	Open label	tDCS	Anodal over F3	Cathodal over the right SO	25 cm^2	2 mA	30 min of stimulation.	Syntax testing	Positive

ASD = Autism Spectrum Disorders; CARS = Childhood Autism Rating Scale; ATEC = Autism Treatment Evaluation Checklist; CGAS = Children's Global Assessment Scale; M = Male; ABC Score = Aberrant Behavior Checklist; F3 = Left Dorsolateral Prefrontal Cortex; SO = Supraorbital Region.

Effects in Adults

Only one case study to date has been published reporting the use of electrical stimulation in the adult population. A refractory adult with autistic disorder received 10 sessions of cathodal tDCS over the DLPFC. The patient manifested an overall clinical improvement in his behavior that was still present 3 months after the stimulation had ended (D'Urso et al., 2014).

Craving Disorders

Addictive disorders are characterized by abuse or dependence of a behavior or substance (e.g., tobacco). These disorders are thought to involve the brain reward network, where prefrontal regions play an important role in inhibitory control mechanisms (Bechara, 2005). Bi-frontal tDCS has been commonly used in addictive disorders because it is thought to modulate general decision-making process (Fecteau et al., 2007; Leite, Carvalho, Fregni, Boggio, & Goncalves, 2013). In fact, using tES for craving modulation has been one of the first applications tested in psychiatry. There have been five studies testing tES for food craving and 13 studies in drug craving (see Table 5). All of these studies were conducted in adults.

Alcohol Craving/Addiction

Five studies were conducted assessing the effects of tDCS on alcohol craving. Positive acute effects following right anodal/left cathodal and left cathodal/right anodal tDCS have been reported in alcohol craving (Boggio, Sultani, et al., 2008), as well as relapse reduction following consecutive sessions of tDCS (Klauss et al., 2014). This relapse prevention was also found when only the left DLFPC was stimulated (da Silva et al., 2013; Nakamura-Palacios et al., 2012). However, a recent study with heavy drinkers found no effects of stimulating the inferior frontal gyrus (den Uyl, Gladwin, & Wiers, 2014).

Smoking Craving

Six studies have been published assessing the effects of tDCS on tobacco craving. Bi-frontal tDCS is also effective in reducing the number of smoked cigarettes (Fregni, Liguori, et al., 2008), and when five consecutive sessions of bi-frontal tDCS (anodal left/cathodal right or cathodal left/anodal right) are applied, craving reductions were also observed (Boggio et al., 2009; Fecteau et al., 2014). Interestingly enough, it seems that if the anode is placed over the left DLPFC and the cathode over the contralateral supraorbital area, only mood (but no craving) is improved in overnight abstinent tobacco-dependent smokers (Xu, Fregni, Brody, & Rahman, 2013). Another study, using cathodal tDCS bilaterally over the frontal-parietal-temporal association area (FPT), was also able to significantly reduce daily cigarette consumption (Meng, Liu, Yu, & Ma, 2014).

Table 5. Studies in drug craving disorders

Author	Condition	No. of subjects (Females)	Age group (Years Old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity/frequency	Treatment protocol	Main outcomes	Results
Boggio, Sultani, et al. (2008)	Alcohol craving	13 (2)	Adults (35–47)	Sham controlled, double-blind crossover study	tDCS	1. Anodal over F3 2. Anodal over F4	1. Cathodal over F4 2. Cathodal over F3	35 cm^2	2 mA	20 min/session for three sessions, one of each condition in a randomized order – 48 hr washout period.	SOCRATES Scale, SADD questionnaire, AUQ, VAS for mood	Positive
Boggio et al. (2009)	Smoking craving	27 (15)	Adults (18–34)	Sham controlled, double-blind, randomized crossover study	tDCS	Anodal over F3	Cathodal over F4	Anode: 35 cm^2 Cathode: 100 cm^2	2 mA	20 min/daily for five consecutive days for each condition in a randomized order.	VAS for mood and smoking craving, FTND, cigarette smoking diary	Positive
Boggio et al. (2010)	Marijuana craving	25 (10)	Adults (20–26)	Sham controlled, double-blind RCT	tDCS	1. Anodal F3 2. Anodal F3	1. Cathodal over F4 2. Cathodal over F3	35 cm^2	2 mA	15 min/session for one session only.	VAS for craving, Risk task	Positive
da Silva et al. (2013)	Alcohol craving	13 (0)	Adults (29–59)	Sham controlled, double-blind RTC	tDCS	Anodal over F3	Cathodal over the right supra-deltoid area.	35 cm^2	2 mA	20 min/weekly stimulation sessions for five consecutive weeks.	FAB, MMSE, OCDS, HAM-D, HAM-A, EEG, ERPs	Positive
den Uyl et al. (2014)	Alcohol craving	41 (26)	Adults (19–24)	Sham controlled, double-blind RCT	tDCS	1. Anodal over F3 2. Anodal over the right inferior gyrus	Cathodal over the contralateral SO	35 cm^2	1 mA	10 min/session, for a single session.	AIT, AAAQ, AUDIT	Positive
Fecteau et al. (2014)	Smoking craving	12 (7)	Adults (21–64)	Sham controlled, double-blind, randomized crossover study	tDCS	1. Anodal F3 2. Anodal F4	1. Cathodal over F4 2. Cathodal over F3	35 cm^2	2 mA	30 min/ daily for a single session of each type in a randomized order, washout period of 3 months.	Cigarette diary, time between awakening and first cigarette, FTND, BIS, BDI	Positive
Fregni, Liguori et al. (2008)	Smoking craving	24 (11)	Adults (17–32)	Sham controlled, double-blind, randomized crossover study	tDCS	1. Anodal over F3 2. Anodal over F4	1. Cathodal over F4 2. Cathodal over F3	Anode: 35 cm^2 Cathode: 100 cm^2	2 mA	20 min/session for a single session of each condition in a randomized order – 48 hr washout period.	VAS for mood and smoking craving, FTND	Positive
Klauss et al. (2014)	Alcohol craving	33 (1)	Adults (36–55)	Sham controlled, double-blind RCT	tDCS	Cathodal over F3	Anodal over F4	35 cm^2	2 mA	13 min/twice daily with an interval of 20 min for five consecutive days.	Alcohol use relapse, FAB, MMSE, OCDS, HAM-D	Positive
Meng et al. (2014)	Smoking craving	30 (0)	Adults (16–30)	Sham controlled, double-blind RCT	tDCS	1. Cathodal over the right FPT 2. two cathodes over each FPT	1. Anodal over the left FPT 2. two anodes over the occipital lobes bilaterally	6.5 cm diameter	1 mA	20 min/session for one session only.	Eye tracking, cigarette consumption, questionnaires about smoking sensations	Positive
Nakamura-Palacios et al. (2012)	Alcohol craving	49 (4)	Adults (39–58)	Sham controlled, double-blind crossover study	tDCS	Anodal over F3	Cathodal over the right supra-deltoid area.	35 cm^2	1 mA	10 min/session for 2 sessions, one of each condition in a randomized order – 7 day washout period	FAB, OCDS, MMSE, ERPs	Positive
Shahbabaie et al. (2014)	Methamphetamine craving	30 (0)	Adults (20–45)	Sham controlled, double-blind, randomized crossover study	tDCS	Anodal over F4	Cathodal over the left SO	35 cm^2	2 mA	20 min/session for a single session of each type in a randomized order. Washout period of 72 hr.	PANAS, VAS for craving, Computerized cue-induced craving assessment task	Positive
Xu et al. (2013)	Smoking craving	24 (3)	Adults (28–59)	Sham controlled, double-blind, randomized, crossover study	tDCS	Anodal over F3	Cathodal over the right SO	35 cm^2	2 mA	20 min/daily for a single session of each type in a randomized order, washout period of 48 hr	POMS, UTS, Attention testing (computerized)	Positive

SADD = Alcohol Dependence Data Questionnaire; AUQ = Alcohol Urge Questionnaire; VAS = Visual Analog Scale; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; OCDS = Obsessive-Compulsive Drinking Scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; EEG = Electroencephalogram; ERPs = Event Related Potentials; AIT = Alcohol Implicit Association Test; AAAQ = The Approach and Avoidance of Alcohol Questionnaire; AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test for Nicotine Dependence; PoMS = Profile of Mood State; BIS = Barratt Impulsiveness Scale; BDI = Beck Depression Inventory; PANAS = Positive and Negative Affect Schedule; F3 = Left Dorsolateral Prefrontal Cortex; F4 = Right Dorsolateral Prefrontal Cortex; FPT = Fronto-Parietal-Temporal; SO = Supraorbital region.

Marijuana and Methamphetamine Craving

Right anodal/left cathodal bi-frontal tDCS is also associated with diminished craving in chronic marijuana users (Boggio et al., 2010); and when the anode is placed over the right DLPFC and the cathode over the contralateral supraorbital region, craving is also reduced in the rest condition for methamphetamine users (Shahbabaie et al., 2014). But if a craving inducing task was performed, anodal tDCS actually increases craving revealing the state dependency effects (Shahbabaie et al., 2014).

Food Craving

Binge eating and food craving are important eating disorders with rapidly growing incidence. Food craving has been defined as the "irresistible urge to eat" and is directly related with overweight and obesity, turning it into a big public health concern. The pathophysiology behind this problem has been widely studied and has been found to be similar to that of addiction and drug craving, suggesting a shared nature and a similar possible treatment approach (Pelchat, 2009).

Similar to other craving behaviors, food-craving behavior has been attributed to specific changes in inhibitory circuits in lateral prefrontal areas. Some abnormalities in dopaminergic pathways are also thought to lead to a deficient cortical inhibitory control (Goldstein & Volkow, 2011).

Effects in Adults

Five studies have been conducted assessing the effects of tDCS on food craving and overeating (see Table 6). Bi-frontal tDCS was able to reduce food-craving behavior and the consumption of food (Fregni, Orsati, et al., 2008). Several groups have replicated these results, more specifically when the anode is located over the right DLPFC and the cathode over the left DLPFC (Goldman et al., 2011; Kekic et al., 2014; Lapenta, Sierve, de Macedo, Fregni, & Boggio, 2014). Interestingly, the reduction of craving has been more prominent for sweet food and carbohydrates (Goldman et al., 2011). In an interesting study, the combination of anodal tDCS over the left DLPFC with aerobic exercises was able to decrease the urge to eat and increased satiety more than tDCS and exercise alone (Montenegro et al., 2012).

Eating Disorders

In addition to food-craving modulation in a healthy subject, studies have also been conducted in Anorexia and Bulimia Nervosa. These conditions are severe psychiatric conditions that represent a life-threating problem to patients. Neuroimaging data using taste/reward conditioning task suggest that brain-related dopaminergic activity is physiologically hypersensitive in Anorexia Nervosa (AN) and hyporesponsive in Bulimia Nervosa (BN) (Frank, 2015).

Effects in Adults

Different NIBS techniques have been proposed as possible adjuvant therapies for eating disorders, however only one study has been performed using tES so far. Khedr, Elfetoh, Ali, and Noamany (2014) performed an open-label study in seven adults suffering from AN. These patients received a daily session of anodal tDCS over the left DLPFC for 10 consecutive days. Three subjects showed significant improvements after the intervention sessions and 1 month later, as assessed by three scales – The Eating Attitude Test (EAT), The Eating Disorder Inventory (EDI), and the Beck Depression Inventory (BDI). Two patients showed improvements only right after the intervention and only one showed improvements in mood as assessed by the BDI.

Discussion

Transcranial electrical stimulation (tES), similar to other noninvasive brain stimulation techniques (NIBS), has been showing promising results as potential therapeutic interventions for mood disorders, schizophrenia, and craving in adults.

Most of the studies so far have focused on adults. There are promising results for Depression, schizophrenia, Generalized Anxiety Disorder, Obsessive-compulsive disorder Post-traumatic Stress disorder, Autism, and craving disorders. But most of the studies reviewed seem to be lacking long-term assessments of tES efficacy. Studies on depression are an exception, where we have several studies with larger number of sessions, and extended follow-ups (Boggio, Rigonatti, et al., 2008; Brunoni, Ferrucci, et al., 2013; Brunoni, Valiengo, et al., 2013; Brunoni et al., 2011).

There is still limited data about the effects of tDCS on children, which hinders the assessment of tES efficacy for this specific population. Potentially, one of the major concerns for using tES in children is safety. Krishnan, Santos, Peterson, and Ehinger (2015) reviewed safety concerns in 48 studies using NIBS in pediatric population with different neuropsychological conditions (with a total of 513 children/adolescents). Most of the side effects reported in the literature are mild and transient. Therefore, if the standard parameters of stimulation are correctly followed, these techniques are quite safe for use in children.

There is very limited data available on the effects of tES on the elderly for the treatment of neuropsychiatric conditions. There was one case report of tDCS in a 92-year-old patient with major depression. Due to the complex nature of depression and age, future systematic studies are needed in order to truly assess the results found in that study. Also it is important to note that tDCS on the aging brain could have a different impact than the one found in children and adults (Shiozawa, da Silva, et al., 2014). For instance, Fertonani, Brambilla, Cotelli, and Miniussi (2014) showed that anodal tDCS over the left DLPFC only improved naming task performance if it were applied during the actual task performance. While in younger adults the tDCS-dependent effects were identical regardless of the timing of tDCS

Table 6. Studies in food craving and overeating

Author	Condition	No. of subjects (females)	Age group (years old)	Study design	Technique	Active electrode	Reference electrode	Active electrode size	Intensity/frequency	Treatment protocol	Main outcomes	Results
Fregni, Orsati, et al. (2008)	Food craving and overeating	23 (21)	Adults (18–30)	Sham controlled, double-blind, randomized crossover study	tDCS	1. Anodal over F3 2.Anodal over F4	1. Cathodal over F4 2. Cathodal over F3	35 cm^2	2 mA	20 min/session for a single session of each type in a randomized order. Washout period of 48 hr.	VAS for mood and food craving, eye tracking	Positive
Goldman et al. (2011)	Food craving and overeating	19 (13)	Adults (21–45)	Sham controlled, double-blind, randomized crossover study	tDCS	Anodal over F4	Cathodal over F3	35 cm^2	2 mA	20 min/session for a single session of each type in a randomized order.	FCI, CESD-10, CVAS for craving after exposure to food photos with the IAPS	Positive
Kekic et al. (2014)	Food craving and overeating	17 (17)	Adults (19–34)	Sham-controlled, double-blind, randomized crossover study	tDCS	Anodal over F4	Cathodal over F3	25 cm^2	2 mA	20 min/session for a single session of each type in a randomized order.	Food craving Questionnaire – Trait, VAS for hunger, food challenge task, FCQ-State, saliva sample, TD Task	Positive
Khedr et al. (2014)	Anorexia nervosa	7 (6)	Adults (13–30)	Open label	tDCS	Anodal over the F3	Cathodal over the SO	24 cm	2 mA	25 min/day for 10 consecutive days excluding weekends.	EAT, EDI, BDI	Positive
Lapenta et al. (2014)	Food craving and overeating	9 (9)	Adults (20–27)	Sham-controlled, double-blind, randomized crossover study	tDCS	Anodal over F4	Cathodal over F3	35 cm^2	2 mA	20 min/session for a single session of each type in a randomized order. Washout period for 1 week.	ERPs Go/No-Go task, eye tracking, VAS for food craving	Positive
Montenegro et al. (2012)	Food craving and overeating	9 (4)	Adults (20–32)	Sham-controlled, double-blind, randomized crossover study	tDCS	Anodal over F3	Cathodal over right SO	35 cm^2	2 mA	20 min/session for a single session of each type in a randomized order. Washout period of 48–120 hr.	VAS for hunger and craving, maximal cardiorespiratory exercise test,	Positive

VAS = Visual Analog Scale; FCI = Food Craving Inventory; CESD-10 = Center for Epidemiological Studies Depression Scale; CVAS = Craving Visual Analog Scale; IAPS = International Affective Picture System; FCQ = Food Craving Questionnaire; TD = Temporal Discounting; ERPs = Event Related Potentials; EAT = Eating Attitude Test; EDI = Eating Disorder Inventory; BDI = Beck Depression Inventory; F3 = Left Dorsolateral Prefrontal Cortex; F4 = Right Dorsolateral Prefrontal Cortex; SO = Supraorbital region.

administration (i.e., prior or during task performance). Additionally, Fujiyama et al. (2014) showed that although anodal tDCS was able to increase cortical excitability in younger and older adults, older adults exhibited a delayed plastic response. These are clear evidences that more studies are still needed to help us understand the true impact of tES in the aging brain.

The available data so far does not allow drawing definite conclusions about the effects of tES across lifespan. Namely, on how the neurophysiological changes across lifespan are effect modifiers to tES. Especially, during "critical periods" which are thought to be more sensitive to environmental influences and stimulation than other periods (Takesian & Hensch, 2013). Although, there is available evidence to support that the mechanisms of plasticity in cortical areas decrease progressively with aging (Freitas et al., 2011), there is also data to support that brain's plasticity is not immutable after a consolidation process in early life. On the contrary, across development, brain plasticity seems to be diminished by brake-like factors which can be overturned (Takesian & Hensch, 2013).

Therefore, the optimization of tES interventions must rely on a better integration between neuroplasticity changes due to normal and abnormal development and stimulation parameters. These interventions should be guided by surrogate outcomes of neuroplasticity. For instance, by coupling tES interventions with TMS measurements, such as the paired-associative stimulation (PAS), it is possible to mimic the long-term depression and potentiation protocols used in animal models (Chen & Udupa, 2009) and therefore assess neuroplasticity effects. Also tES may be coupled with EEG so as to assess in real time neuroplasticity changes and therefore guide the intervention. Recent have proposed the use of closed-loop system as a method to optimize tES parameters (Schestatsky, Morales-Quezada, & Fregni, 2013). Finally, recent research with near-infrared spectroscopy (NIRS) may also be useful for monitoring and adjustment of tES parameters (Dutta, Jacob, Chowdhury, Das, & Nitsche, 2015).

It is possible that these efforts could be hindered by safety concerns, especially in children and elderly. However, most of the studies across lifespan conducted so far report no or mild adverse effects, thus demonstrating that tES has a satisfactory safety profile, even when applied during several consecutive days.

Although the ease-of-use, portability, and safety profile make tES (and especially tDCS) ideal to combine with other therapies, most of the studies so far have been using tES alone. The combination of tES with other therapies is highly recommended, as synergistic effects could arise from them (Brunoni, Valiengo, et al., 2013).

The use of tES in neuropsychiatric disorders has yielded promising results. It is usually well tolerated and produces significant clinical outcomes where conventional approaches fail to do so. Future studies should focus on interventions guided by surrogate outcomes of neuroplasticity. Better understanding of plasticity across the lifespan will help in the optimization of the current tES stimulation parameters, especially for use with children and elderly populations.

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References

Amatachaya, A., & Auvichayapat, N. (2014). Effect of anodal transcranial direct current stimulation on autism: A randomized double-blind crossover trial. *Behavioural Neurology, 2014*, 173073. doi: 10.1155/2014/173073

Anagnostou, E., & Taylor, M. J. (2011). Review of neuroimaging in autism spectrum disorders: What have we learned and where we go from here. *Molecular Autism, 2*, 4. doi: 10.1186/2040-2392-2-4

Antal, A., & Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in Human Neuroscience, 7*, 317. doi: 10.3389/fnhum.2013.00317

Barclay, T. H., & Barclay, R. D. (2014). A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. *Journal of Affective Disorders, 164*, 171–177. doi:10.1016/j.jad.2014.04.029

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience, 8*, 1458–1463. doi: 10.1038/nn1584

Blumberger, D. M., Tran, L. C., Fitzgerald, P. B., Hoy, K. E., & Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. *Frontiers in Psychiatry, 3*, 74. doi: 10.3389/fpsyt.2012.00074

Boggio, P. S., Liguori, P., Sultani, N., Rezende, L., Fecteau, S., & Fregni, F. (2009). Cumulative priming effects of cortical stimulation on smoking cue-induced craving. *Neuroscience Letters, 463*, 82–86. doi: 10.1016/j.neulet.2009.07.041

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11*, 249–254. doi: 10.1017/s1461145707007833

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., … Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug and Alcohol Dependence, 92*, 55–60. doi: 10.1016/j.drugalcdep.2007.06.011

Boggio, P. S., Zaghi, S., Villani, A. B., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). *Drug and Alcohol Dependence, 112*, 220–225. doi: 10.1016/j.drugalcdep.2010.06.019

Bose, A., Shivakumar, V., Narayanaswamy, J. C., Nawani, H., Subramaniam, A., Agarwal, S. M., … Venkatasubramanian, G. (2014). Insight facilitation with add-on tDCS in schizophrenia. *Schizophrenia Research, 156*, 63–65. doi: 10.1016/j.schres.2014.03.029

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M. F., … Poulet, E. (2012). Examining transcranial direct-current stimulation (tDCS) as a treatment

for hallucinations in schizophrenia. *The American Journal of Psychiatry, 169*, 719–724. doi: 10.1176/appi.ajp.2012.11071091

Brunelin, J., Mondino, M., Haesebaert, F., Saoud, M., Suaud-Chagny, M. F., & Poulet, E. (2012). Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. *Brain Stimulation, 5*, 431–432. doi: 10.1016/j.brs.2011.03.010

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P. S., Fregni, F., … Priori, A. (2013). Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study. *European Psychiatry: The Journal of the Association of European Psychiatrists, 28*, 356–361. doi: 10.1016/j.eurpsy.2012.09.001

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Boggio, P. S., … Priori, A. (2011). Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35*, 96–101. doi: 10.1016/j.pnpbp.2010.09.010

Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., … Fregni, F. (2013). The sertraline vs. electrical current therapy for treating depression clinical study: Results from a factorial, randomized, controlled trial. *JAMA Psychiatry, 70*, 383–391. doi: 10.1001/2013.jamapsychiatry.32

Bush, G. (2011). Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 69*, 1160–1167. doi: 10.1016/j.biopsych.2011.01.022

Bystritsky, A., Kerwin, L., & Feusner, J. (2008). A pilot study of cranial electrotherapy stimulation for generalized anxiety disorder. *The Journal of Clinical Psychiatry, 69*, 412–417.

Carvalho, S., Goncalves, O. F., Soares, J. M., Sampaio, A., Macedo, F., Fregni, F., & Leite, J. (2014). Sustained effects of a neural-based intervention in a refractory case of Tourette syndrome. *Brain Stimulation, 8*, 657–659. doi: 10.1016/j.brs.2014.12.008

Castillo Saavedra, L., Morales-Quezada, L., Doruk, D., Rozinsky, J., Coutinho, L., Faria, P., … Fregni, F. (2014). QEEG indexed frontal connectivity effects of transcranial pulsed current stimulation (tPCS): A sham-controlled mechanistic trial. *Neuroscience Letters, 577*, 61–65. doi: 10.1016/j.neulet.2014.06.021

Chaieb, L., Antal, A., & Paulus, W. (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. *Restorative Neurology and Neuroscience, 29*, 167–175. doi: 10.3233/rnn-2011-0589

Chan, H. N., Alonzo, A., Martin, D. M., Player, M., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2012). Treatment of major depressive disorder by transcranial random noise stimulation: Case report of a novel treatment. *Biological Psychiatry, 72*, e9–e10. doi: 10.1016/j.biopsych.2012.02.009

Chechik, G., Meilijson, I., & Ruppin, E. (1999). Neuronal regulation: A mechanism for synaptic pruning during brain maturation. *Neural Computation, 11*, 2061–2080.

Chen, R., & Udupa, K. (2009). Measurement and modulation of plasticity of the motor system in humans using transcranial magnetic stimulation. *Motor Control, 13*, 442–453.

da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., Fregni, F., … Nakamura-Palacios, E. M. (2013). Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *Journal of Physiology, Paris, 107*, 493–502. doi: 10.1016/j.jphysparis.2013.07.003

Datta, A., Dmochowski, J. P., Guleyupoglu, B., Bikson, M., & Fregni, F. (2013). Cranial electrotherapy stimulation and transcranial pulsed current stimulation: A computer based high-resolution modeling study. *NeuroImage, 65*, 280–287. doi: 10.1016/j.neuroimage.2012.09.062

David, C. N., Greenstein, D., Clasen, L., Gochman, P., Miller, R., Tossell, J. W., … Rapoport, J. L. (2011). Childhood onset schizophrenia: High rate of visual hallucinations. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*, 681–686.e683. doi: 10.1016/j.jaac.2011.03.020

Dell'Osso, B., Zanoni, S., Ferrucci, R., Vergari, M., Castellano, F., D'Urso, N., … Altamura, A. C. (2012). Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. *European Psychiatry: The Journal of the Association of European Psychiatrists, 27*, 513–517. doi: 10.1016/j.eurpsy.2011.02.008

den Uyl, T. E., Gladwin, T. E., & Wiers, R. W. (2014). Transcranial direct current stimulation, implicit alcohol associations and craving. *Biological Psychology, 105*, 37–42. doi: 10.1016/j.biopsycho.2014.12.004

Dierks, T., Linden, D. E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., & Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22*, 615–621.

D'Urso, G., Ferrucci, R., Bruzzese, D., Pascotto, A., Priori, A., Altamura, C. A., … Bravaccio, C. (2014). Transcranial direct current stimulation for autistic disorder. *Biological Psychiatry, 76*, e5–e6. doi: 10.1016/j.biopsych.2013.11.009

Dutta, A., Jacob, A., Chowdhury, S. R., Das, A., & Nitsche, M. A. (2015). EEG-NIRS based assessment of neurovascular coupling during anodal transcranial direct current stimulation-a stroke case series. *Journal of Medical Systems, 39*, 1–9.

Fecteau, S., Agosta, S., Hone-Blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., & Pascual-Leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: A preliminary study. *Drug and Alcohol Dependence, 140*, 78–84. doi: 10.1016/j.drugalcdep.2014.03.036

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Theoret, H., Boggio, P. S., & Fregni, F. (2007). Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 27*, 6212–6218. doi: 10.1523/jneurosci.0314-07.2007

Fertonani, A., Brambilla, M., Cotelli, M., & Miniussi, C. (2014). The timing of cognitive plasticity in physiological aging: A tDCS study of naming. *Frontiers in Aging Neuroscience, 6*, 131. doi: 10.3389/fnagi.2014.00131

Fidalgo, T. M., Morales-Quezada, J. L., Muzy, G. S., Chiavetta, N. M., Mendonca, M. E., Santana, M. V., … Fregni, F. (2014). Biological markers in noninvasive brain stimulation trials in major depressive disorder: A systematic review. *The Journal of ECT, 30*, 47–61. doi: 10.1097/YCT.0b013e31828b34d8

Fitzgerald, P. B., McQueen, S., Daskalakis, Z. J., & Hoy, K. E. (2014). A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. *Brain Stimulation, 7*, 813–816. doi: 10.1016/j.brs.2014.08.002

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences, 21*, 187–222.

Frank, G. K. (2015). Advances from neuroimaging studies in eating disorders. *CNS Spectrums, 20*, 391–400. doi: 10.1017/s1092852915000012

Fregni, F., Boggio, P. S., Nitsche, M. A., Marcolin, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006). Treatment of major depression with transcranial direct current

stimulation. *Bipolar Disorders, 8*, 203–204. doi: 10.1111/j.1399-5618.2006.00291.x

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: A randomized, sham-controlled study. *The Journal of Clinical Psychiatry, 69*, 32–40.

Fregni, F., Nitsche, M., Loo, C., Brunoni, A., Marangolo, P., Leite, J., … Paik, N. (2014). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): Review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs, 32*, 22–35.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., Nitsche, M. A., … Boggio, P. S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 51*, 34–41. doi: 10.1016/j.appet.2007.09.016.

Freitas, C., Perez, J., Knobel, M., Tormos, J. M., Oberman, L., Eldaief, M., … Pascual-Leone, A. (2011). Changes in cortical plasticity across the lifespan. *Frontiers in Aging Neuroscience, 3*, 5. doi: 10.3389/fnagi.2011.00005

Fuchs, Y., & Steller, H. (2011). Programmed cell death in animal development and disease. *Cell, 147*, 742–758.

Fujiyama, H., Hyde, J., Hinder, M. R., Kim, S. J., McCormack, G. H., Vickers, J. C., & Summers, J. J. (2014). Delayed plastic responses to anodal tDCS in older adults. *Frontiers in Aging Neuroscience, 6*, 115. doi: 10.3389/fnagi.2014.00115

Göder, R., Baier, P. C., Beith, B., Baecker, C., Seeck-Hirschner, M., Junghanns, K., & Marshall, L. (2013). Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. *Schizophrenia Research, 1*, 153–154.

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K., … George, M. S. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite, 56*, 741–746. doi: 10.1016/j.appet.2011.02.013

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*, 652–669.

Goldsworthy, M. R., Pitcher, J. B., & Ridding, M. C. (2014). Spaced noninvasive brain stimulation: Prospects for inducing long-lasting human cortical plasticity. *Neurorehabilitation and Neural Repair, 29*, 714–721. doi: 10.1177/1545968314562649

Goncalves, O. F., Carvalho, S., Leite, J., Pocinho, F., Relvas, J., & Fregni, F. (2011). Obsessive Compulsive Disorder as a functional interhemispheric imbalance at the thalamic level. *Medical Hypotheses, 77*, 445–447. doi: 10.1016/j.mehy.2011.06.004

Guleyupoglu, B., Schestatsky, P., Edwards, D., Fregni, F., & Bikson, M. (2013). Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. *Journal of Neuroscience Methods, 219*, 297–311. doi: 10.1016/j.jneumeth.2013.07.016

Haesebaert, F., Mondino, M., Saoud, M., Poulet, E., & Brunelin, J. (2014). Efficacy and safety of fronto-temporal transcranial random noise stimulation (tRNS) in drug-free patients with schizophrenia: A case study. *Schizophrenia Research, 159*, 251–252. doi: 10.1016/j.schres.2014.07.043

Hayes, J. P., Hayes, S. M., & Mikedis, A. M. (2012). Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders, 2*, 9. doi: 10.1186/2045-5380-2-9

Heimer, L., Harlan, R. E., Alheid, G. F., Garcia, M. M., & de Olmos, J. (1997). Substantia innominata: A notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. *Neuroscience, 76*, 957–1006.

Homan, P., Kindler, J., Federspiel, A., Flury, R., Hubl, D., Hauf, M., & Dierks, T. (2011). Muting the voice: A case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. *The American Journal of Psychiatry, 168*, 853–854. doi: 10.1176/appi.ajp.2011.11030496

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: A coordinate-based meta-analysis. *The American Journal of Psychiatry, 168*, 73–81. doi: 10.1176/appi.ajp.2010.09101522

Johnson, S. B., Blum, R. W., & Giedd, J. N. (2009). Adolescent maturity and the brain: The promise and pitfalls of neuroscience research in adolescent health policy. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine, 45*, 216–221. doi: 10.1016/j.jadohealth.2009.05.016

Kekic, M., McClelland, J., Campbell, I., Nestler, S., Rubia, K., David, A. S., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. *Appetite, 78*, 55–62. doi: 10.1016/j.appet.2014.03.010

Khedr, E. M., Elfetoh, N. A., Ali, A. M., & Noamany, M. (2014). Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: A pilot study. *Restorative Neurology and Neuroscience, 32*, 789–797. doi: 10.3233/rnn-140392

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., de Almeida Correia Santos, G., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 17*, 1793–1803. doi: 10.1017/s1461145714000984

Knotkova, H., Rosedale, M., Strauss, S. M., Horne, J., Soto, E., Cruciani, R. A., … Malamud, D. (2012). Using transcranial direct current stimulation to treat depression in HIV-infected persons: The outcomes of a feasibility study. *Frontiers in Psychiatry, 3*, 59. doi: 10.3389/fpsyt.2012.00059

Krause, B., & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience, 8*, 25. doi: 10.3389/fnsys.2014.00025

Krishnan, C., Santos, L., Peterson, M. D., & Ehinger, M. (2015). Safety of noninvasive brain stimulation in children and adolescents. *Brain Stimulation, 8*, 76–87. doi: 10.1016/j.brs.2014.10.012

Kuan, C. Y., Roth, K. A., Flavell, R. A., & Rakic, P. (2000). Mechanisms of programmed cell death in the developing brain. *Trends in Neurosciences, 23*, 291–297.

Lapenta, O. M., Sierve, K. D., de Macedo, E. C., Fregni, F., & Boggio, P. S. (2014). Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. *Appetite, 83*, 42–48. doi: 10.1016/j.appet.2014.08.005

Lawrie, S., McIntosh, A., & Nadeem, Z. (2002). Schizophrenia. *Clinical Evidence, 8*, 1019–1049.

Lee, S. H., Kim, W. Y., Lee, C. H., Min, T. J., Lee, Y. S., Kim, J. H., & Park, Y. C. (2013). Effects of cranial electrotherapy

stimulation on preoperative anxiety, pain and endocrine response. *The Journal of International Medical Research, 41*, 1788–1795. doi: 10.1177/0300060513500749

Leite, J., Carvalho, S., Fregni, F., Boggio, P. S., & Goncalves, O. F. (2013). The effects of cross-hemispheric dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS) on task switching. *Brain Stimulation, 6*, 660–667. doi: 10.1016/j.brs.2012.10.006

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *The British Journal of Psychiatry: The Journal of Mental Science, 200*, 52–59. doi: 10.1192/bjp.bp.111.097634

Martin, D. M., Alonzo, A., Ho, K. A., Player, M., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2013). Continuation transcranial direct current stimulation for the prevention of relapse in major depression. *Journal of Affective Disorders, 144*, 274–278.

Martin, D. M., Alonzo, A., Mitchell, P. B., Sachdev, P., Galvez, V., & Loo, C. K. (2011). Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: An open-label pilot study. *Journal of Affective Disorders, 134*, 459–463. doi: 10.1016/j.jad.2011.05.018

Mattai, A., Miller, R., Weisinger, B., Greenstein, D., Bakalar, J., Tossell, J., … Gogtay, N. (2011). Tolerability of transcranial direct current stimulation in childhood-onset schizophrenia. *Brain Stimulation, 4*, 275–280. doi: 10.1016/j.brs.2011.01.001

McGuire, P. K., Shah, G. M., & Murray, R. M. (1993). Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet, 342*, 703–706.

Meng, Z., Liu, C., Yu, C., & Ma, Y. (2014). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. *Journal of Psychiatric Research, 54*, 19–25. doi: 10.1016/j.jpsychires.2014.03.007

Meyer-Lindenberg, A., & Tost, H. (2014). Neuroimaging and plasticity in schizophrenia. *Restorative Neurology and Neuroscience, 32*, 119–127. doi: 10.3233/rnn-139014

Minshew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. *Current Opinion in Neurology, 23*, 124–130. doi: 10.1097/WCO.0b013e32833782d4

Mondino, M., Haesebaert, F., Poulet, E., Suaud-Chagny, M. F., & Brunelin, J. (2015). Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. *Schizophrenia Research, 161*, 515–516. doi: 10.1016/j.schres.2014.10.054

Montenegro, R. A., Okano, A. H., Cunha, F. A., Gurgel, J. L., Fontes, E. B., & Farinatti, P. T. (2012). Prefrontal cortex transcranial direct current stimulation associated with aerobic exercise change aspects of appetite sensation in overweight adults. *Appetite, 58*, 333–338. doi: 10.1016/j.appet.2011.11.008

Morales-Quezada, L., Cosmo, C., Carvalho, S., Leite, J., Castillo-Saavedra, L., Rozisky, J. R., & Fregni, F. (2014). Cognitive effects and autonomic responses to transcranial pulsed current stimulation. *Experimental Brain Research, 233*, 701–709. doi: 10.1007/s00221-014-4147-y

Nakamura-Palacios, E. M., de Almeida Benevides, M. C., da Penha Zago-Gomes, M., de Oliveira, R. W., de Vasconcellos, V. F., de Castro, L. N., … Fregni, F. (2012). Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 15*, 601–616. doi: 10.1017/s1461145711001040

Narayanaswamy, J. C., Jose, D., Chhabra, H., Agarwal, S. M., Shrinivasa, B., Hegde, A., … Reddy, Y. C. (2014). Successful application of add-on Transcranial Direct Current Stimulation (tDCS) for treatment of SSRI resistant OCD. *Brain Stimulation, 8*, 655–657. doi: 10.1016/j.brs.2014.12.003

Nawani, H., Kalmady, S. V., Bose, A., Shivakumar, V., Rakesh, G., Subramaniam, A., … Venkatasubramanian, G. (2014). Neural basis of tDCS effects on auditory verbal hallucinations in schizophrenia: A case report evidence for cortical neuroplasticity modulation. *The Journal of ECT, 30*, e2–e4. doi: 10.1097/YCT.0b013e3182a35492

Neuner, I., Werner, C. J., Arrubla, J., Stocker, T., Ehlen, C., Wegener, H. P., … Shah, N. J. (2014). Imaging the where and when of tic generation and resting state networks in adult Tourette patients. *Frontiers in Human Neuroscience, 8*, 362. doi: 10.3389/fnhum.2014.00362

Nicolson, R., & Rapoport, J. L. (1999). Childhood-onset schizophrenia: Rare but worth studying. *Biological Psychiatry, 46*, 1418–1428.

Nitsche, M. A., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2009). Treatment of depression with transcranial direct current stimulation (tDCS): A review. *Experimental Neurology, 219*, 14–19. doi: 10.1016/j.expneurol.2009.03.038

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., … Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation, 1*, 206–223. doi: 10.1016/j.brs. 2008.06.004

Nitsche, M. A., Muller-Dahlhaus, F., Paulus, W., & Ziemann, U. (2012). The pharmacology of neuroplasticity induced by non-invasive brain stimulation: Building models for the clinical use of CNS active drugs. *The Journal of Physiology, 590*, 4641–4662. doi: 10.1113/jphysiol.2012.232975

Normann, C., Schmitz, D., Furmaier, A., Doing, C., & Bach, M. (2007). Long-term plasticity of visually evoked potentials in humans is altered in major depression. *Biological Psychiatry, 62*, 373–380. doi: 10.1016/j.biopsych.2006.10.006

Oberman, L. M., Pascual-Leone, A., & Rotenberg, A. (2014). Modulation of corticospinal excitability by transcranial magnetic stimulation in children and adolescents with autism spectrum disorder. *Frontiers in Human Neuroscience, 8*, 627. doi: 10.3389/fnhum.2014.00627

Palm, U., Hasan, A., Keeser, D., Falkai, P., & Padberg, F. (2013). Transcranial random noise stimulation for the treatment of negative symptoms in schizophrenia. *Schizophrenia Research, 146*, 372–373. doi: 10.1016/j.schres.2013.03.003

Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., … Padberg, F. (2012). Transcranial direct current stimulation in treatment resistant depression: A randomized double-blind, placebo-controlled study. *Brain Stimulation, 5*, 242–251. doi: 10.1016/j.brs.2011.08.005

Pelchat, M. L. (2009). Food addiction in humans. *The Journal of Nutrition, 139*, 620–622. doi: 10.3945/jn.108.097816

Pirulli, C., Fertonani, A., & Miniussi, C. (2013). The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. *Brain Stimulation, 6*, 683–689. doi: 10.1016/j.brs.2012.12.005

Prehn-Kristensen, A., Munz, M., Goder, R., Wilhelm, I., Korr, K., Vahl, W., … Baving, L. (2014). Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain Stimulation, 7*, 793–799. doi: 10.1016/j.brs.2014.07.036

Priori, A. (2003). Brain polarization in humans: A reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 114*, 589–595.

Rakesh, G., Shivakumar, V., Subramaniam, A., Nawani, H., Amaresha, A. C., Narayanaswamy, J. C., & Venkatasubramanian, G. (2013). Monotherapy with tDCS for Schizophrenia: A case report. *Brain Stimulation, 6*, 708–709. doi:10.1016/j.brs.2013.01.007

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex, 15*, 1676–1689.

Rigonatti, S. P., Boggio, P. S., Myczkowski, M. L., Otta, E., Fiquer, J. T., Ribeiro, R. B., … Fregni, F. (2008). Transcranial direct stimulation and fluoxetine for the treatment of depression. *European psychiatry: The Journal of the Association of European Psychiatrists, 23*, 74–76. doi: 10.1016/j.eurpsy.2007.09.006

Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior, 2*, 255–267.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*, 507–514.

Saunders, N., Downham, R., Turman, B., Kropotov, J., Clark, R., Yumash, R., & Szatmary, A. (2014). Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. *Neurocase, 21*, 271–278. doi: 10.1080/13554794.2014.890727

Schestatsky, P., Janovik, N., Lobato, M. I., Belmonte-de-Abreu, P., Schestatsky, S., Shiozawa, P., & Fregni, F. (2013). Rapid therapeutic response to anodal tDCS of right dorsolateral prefrontal cortex in acute mania. *Brain Stimulation, 6*, 701–703. doi: 10.1016/j.brs.2012.10.008

Schestatsky, P., Morales-Quezada, L., & Fregni, F. (2013). Simultaneous EEG monitoring during transcranial direct current stimulation. *Journal of Visualized Experiments: JoVE, 76*, e50426. doi: 10.3791/50426

Schneider, H. D., & Hopp, J. P. (2011). The use of the Bilingual Aphasia test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. *Clinical Linguistics & Phonetics, 25*, 640–654. doi: 10.3109/02699206.2011.570852

Schonfeldt-Lecuona, C., Lefaucheur, J. P., Cardenas-Morales, L., Wolf, R. C., Kammer, T., & Herwig, U. (2010). The value of neuronavigated rTMS for the treatment of depression. *Neurophysiologie Clinique = Clinical Neurophysiology, 40*, 37–43. doi: 10.1016/j.neucli.2009.06.004

Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., … Ekhtiari, H. (2014). State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 17*, 1591–1598. doi: 10.1017/s1461145714000686

Sharma, A., & Couture, J. (2014). A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). *The Annals of Pharmacotherapy, 48*, 209–225. doi: 10.1177/1060028013510699

Shergill, S. S., Brammer, M. J., Williams, S. C., Murray, R. M., & McGuire, P. K. (2000). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry, 57*, 1033–1038.

Shergill, S. S., Bullmore, E., Simmons, A., Murray, R., & McGuire, P. (2000). Functional anatomy of auditory verbal imagery in schizophrenic patients with auditory hallucinations. *The American Journal of Psychiatry, 157*, 1691–1693.

Shiozawa, P., da Silva, M. E., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2013). Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: A case study. *Brain Stimulation, 6*, 831–833. doi: 10.1016/j.brs.2013.03.003

Shiozawa, P., da Silva, M. E., Dias, D. R., Chaves, A. C., de Oliveira Diniz, B. S., & Cordeiro, Q. (2014). Transcranial direct current stimulation for depression in a 92-year-old patient: A case study. *Psychogeriatrics: The Official Journal of the Japanese Psychogeriatric Society, 14*, 269–270. doi: 10.1111/psyg.12100

Shiozawa, P., Leiva, A. P., Castro, C. D., da Silva, M. E., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2014). Transcranial direct current stimulation for generalized anxiety disorder: A case study. *Biological Psychiatry, 75*, e17–e18. doi: 10.1016/j.biopsych.2013.07.014

Shivakumar, V., Narayanaswamy, J. C., Agarwal, S. M., Bose, A., Subramaniam, A., & Venkatasubramanian, G. (2014). Targeted, intermittent booster tDCS: A novel add-on application for maintenance treatment in a schizophrenia patient with refractory auditory verbal hallucinations. *Asian Journal of Psychiatry, 11*, 79–80. doi: 10.1016/j.ajp.2014.05.012

Silbersweig, D. A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., … Frackowiak, J. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176–179. doi: 10.1038/378176a0

Spedding, M., Neau, I., & Harsing, L. (2003). Brain plasticity and pathology in psychiatric disease: Sites of action for potential therapy. *Current Opinion in Pharmacology, 3*, 33–40.

Takeshi, K., Nemoto, T., Fumoto, M., Arita, H., & Mizuno, M. (2010). Reduced prefrontal cortex activation during divergent thinking in schizophrenia: A multi-channel NIRS study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34*, 1327–1332. doi: 10.1016/j.pnpbp.2010.07.021

Takesian, A. E., & Hensch, T. K. (2013). Balancing plasticity/stability across brain development. *Progress in Brain Research, 207*, 3–34.

Tehovnik, E. J. (1996). Electrical stimulation of neural tissue to evoke behavioral responses. *Journal of Neuroscience Methods, 65*, 1–17.

Terney, D., Chaieb, L., Moliadze, V., Antal, A., & Paulus, W. (2008). Increasing human brain excitability by transcranial high-frequency random noise stimulation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 28*, 14147–14155. doi: 10.1523/jneurosci.4248-08.2008

Vercammen, A., Rushby, J. A., Loo, C., Short, B., Weickert, C. S., & Weickert, T. W. (2011). Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. *Schizophrenia Research, 131*, 198–205. doi: 10.1016/j.schres.2011.06.021

Vicario, C. M., Martino, D., Spata, F., Defazio, G., Giacche, R., Martino, V., … Cardona, F. (2010). Time processing in children with Tourette's syndrome. *Brain and Cognition, 73*, 28–34. doi: 10.1016/j.bandc.2010.01.008

Volpato, C., Piccione, F., Cavinato, M., Duzzi, D., Schiff, S., Foscolo, L., & Venneri, A. (2013). Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. *Neurocase, 19*, 360–370. doi: 10.1080/13554794.2012.667131

Wagner, T., Fregni, F., Fecteau, S., Grodzinsky, A., Zahn, M., & Pascual-Leone, A. (2007). Transcranial direct current stimulation: A computer-based human model study. *NeuroImage, 35*, 1113–1124. doi: 10.1016/j.neuroimage.2007.01.027

Wang, Z., Maia, T. V., Marsh, R., Colibazzi, T., Gerber, A., & Peterson, B. S. (2011). The neural circuits that generate tics in Tourette's syndrome. *The American Journal of Psychiatry, 168*, 1326–1337. doi: 10.1176/appi.ajp.2011.09111692

Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., … Fjell, A. M. (2009).

Life-span changes of the human brain white matter: Diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex, 20*, 2055–2068.

Xu, J., Fregni, F., Brody, A. L., & Rahman, A. S. (2013). Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. *Frontiers in Psychiatry, 4*, 112. doi: 10.3389/fpsyt.2013.00112

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