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Tolerability of transcranial Direct Current Stimulation in Childhood-Onset Schizophrenia

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Abstract

Background—In recent years, transcranial direct current stimulation (tDCS) has been used to study and treat many neuropsychiatric conditions. However, information regarding its tolerability in the pediatric population is lacking.

Objective—This study aims to investigate the tolerability aspects of tDCS in the childhood-onset schizophrenia (COS) population.

Methods—Twelve participants with COS completed this inpatient study. Participants were assigned to one of two groups: bilateral anodal dorsolateral prefrontal cortex (DLPFC) stimulation (n= 8) or bilateral cathodal superior temporal gyrus (STG) stimulation (n=5). Patients received either 2 mA of active treatment or sham treatment (with possibility of open active treatment) for 20 minutes, for a total of 10 sessions (2 weeks).

Results—tDCS was well tolerated in the COS population with no serious adverse events occurring during the study.

Conclusions—This is the first study to demonstrate that a 20 minute duration of 2 mA of bilateral anodal and bilateral cathodal DC polarization to the DLPFC and STG was well tolerated in a pediatric population.

Keywords

dorsolateral prefrontal cortex; transcranial direct current stimulation; childhood-onset schizophrenia

Introduction

In recent years, transcranial direct current (DC) polarization (tDCS), along with transcranial magnetic stimulation (TMS), have emerged as methods for modulating or enhancing symptomatic outcome in major neuropsychiatric conditions (Wagner, Valero-Cabre et al.

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2007). Studies on the use of TMS to modulate auditory hallucinations have been largely positive, while efficacy for negative symptoms is equivocal (Stanford, Sharif et al. 2008). However, the use of TMS can be cumbersome given safety issues, high cost and a bulky delivery system (Priori, Hallett et al. 2009). tDCS uses weak direct current (1–2ma) through electrodes placed on the scalp for periods of seconds to hours. Application of current is thought to modulate cortical excitability by imposing a voltage gradient on superficial neurons aligned with the current path (Priori, Berardelli et al. 1998; Nitsche and Paulus 2000). Surface-anodal polarization of the cortex increases the firing rates of spontaneously active cells while surface cathodol-polarization has the opposite effect (Purpura and Shofer 1964). In recent years, tDCS has been utilized as a neuromodulatory technique to study and treat many neuropsychiatric conditions including Parkinson's disease (Boggio, Ferrucci et al. 2006; Fregni, Boggio et al. 2006), rehabilitation for stroke patients (Hummel, Celnik et al. 2005; Boggio, Nunes et al. 2007), depression (Nitsche, Boggio et al. 2009) and working memory in healthy individuals (Marshall, Molle et al. 2005; Koenigs, Ukueberuwa et al. 2009).

While the use of tDCS in adults has increased, information regarding tolerability in children/adolescents is lacking. We could not find a published study that has specifically investigated the tolerability of tDCS in pediatric patients. A clinical trial of cathodal DC polarization in 19 patients with treatment refractory epilepsy did include a few subjects under the age of 18 who appeared to tolerate the procedure without difficulty (Fregni, Thome-Souza et al. 2006). However, this study focused on electroencephalographic effects of tDCS rather than clinical safety variables. There are a handful of studies that have examined the safety of tDCS in the adult population with authors finding no adverse effects related to motor performance, the electroencephalogram, or other gross clinical measures of brain function (Nitsche, Liebetanz et al. 2003; Iyer, Mattu et al. 2005; Poreisz, Boros et al. 2007). In addition, application of tDCS to the brain has been shown not to cause increased blood-brain barrier permeability, as detected by pre and post contrast MRI (Nitsche, Niehaus et al. 2004). A recent study designed to evaluate safety of tDCS in 102 healthy subjects and patients (in 567 tDCS sessions) showed tDCS to be associated with only minor side effects; the most common was mild tingling at the site of stimulation (75%), followed by moderate fatigue (11.8%), nausea (2.9%), and insomnia (0.9%) (Poreisz, Boros et al. 2007). Similarly, a study of 164 adult subjects participating in 4 different tDCS protocols utilizing weak DC current (1–2 mA) found both active and sham treatment groups had a very small percentage of minor adverse effects (0.11% and 0.08 % respectively) mostly consisting of mild headache (Tadini, El-Nazer et al. 2010). Conventional use of the device can produce mild skin irritation and erythema that resolves shortly after cessation of treatment. However, skin burns are possible when high densities are used or electrodes are placed improperly. It is also important to note that current density, rather than absolute amperage, likely determines both the efficacy and risk of tissue damage (Agnew and McCreery 1987; Liebetanz, Koch et al. 2009). Several studies treating subjects with comparable current density have shown no evidence of neuronal damage induced by tDCS as reflected by a lack of increase in neuronal-specific enloase or brain N-acteyl-aspartate (Nitsche and Paulus 2001; Nitsche, Liebetanz et al. 2003; Cogiamanian, Vergari et al. 2008; Rango, Cogiamanian et al. 2008). Given the simplicity, low cost, and ease of administration of tDCS, a study regarding its tolerability in the pediatric population is clearly warranted.

Childhood-onset schizophrenia (COS), defined as onset of psychotic symptoms before the 13th birthday, and diagnosed using unmodified DSM IV criteria, is a rare form that is continuous with its adult counterpart (Giedd, Jeffries et al. 1999; Nicolson and Rapoport 1999). Most cases are treatment refractory and given the severity and persistence of these symptoms, COS can be quite disabling and resistant to pharmacologic treatment (Nicolson and Rapoport 1999). Thus, there is a dire need for non-pharmacologic treatment alternatives

that focus on residual psychosis or persistent cognitive deficits. In this study, our objective was to evaluate the tolerability of bilateral frontal/temporal tDCS at a moderate dose (2mA) and duration (20 minutes) in a pediatric popultion (COS). We predicted that the tDCS would be well tolerated in COS.

Methods

Participants

Twelve children/adolescents with COS completed the inpatient study; the sample included 5 boys and 7 girls, ages (10–17). Participants had no history of significant neurological illness. The guardians of participants provided written informed consent and COS subjects provided written assent before entering the study. This study was approved by the National Institutes of Health Neuroscience Institutional Review Board.

Study Design

Participants were eligible for one of two study options. During week one of hospital admission, patients had a clinical interview, neurocognitive testing including the California Verbal Learning Test (Delis DC 1994; Delis DC 2000) and Wechsler Memory Scale (Wechsler 1997), as well as clinical ratings (Symptom Assessment for Positive Symptoms (SAPS) and Brief Psychiatric Rating Scale for Children (Overall and Pfefferbaum 1982)) to ascertain the severity of cognitive and/or psychotic symptoms despite medication. Patients also had a routine physical exam, routine blood work, 12-lead electrocardiogram (EKG), and a 21-channel electroencephalogram (EEG) performed with a 11/20 International System electrode placement to make sure there were no medical problems precluding them from entering the study. At the end of the week, an investigator not involved with administering or scoring the outcome measures assigned participants to one of two groups: bilateral anodal dorsolateral prefrontal cortex (DLPFC) stimulation (n=8) to improve cognitive difficulties or bilateral cathodal superior temporal gyrus (STG) stimulation (n=5) to improve continued significant hallucinations. Both treatment options had a double blind, sham-controlled design. During weeks 2 and 3, patients received either active treatment or sham treatment, daily on the weekdays (5 sessions) for 20 minutes each in the morning, for a total of 10 sessions (2 weeks). Patients were questioned about side effects during and after treatments. Vital signs, including pulse, blood pressure, temperature and respirations were monitored within the hour before, during and immediately after the treatment, and once again approximately 8 hrs later in the afternoon. Additional daily monitoring including a clinical assessment of mental status as well a mini mental status exam (MMSE) were conducted. Clinical ratings and neurocognitive testing were conducted on a weekly basis by a trained rater who was blinded to the parameters of the study. Patients who were on clozapine continued their blood draws, per their required regimen. No medications were changed during the research phase of the study.

Those patients who were randomized to the sham arm were given a choice to receive ‘open’ active treatment. All clinical/research work continued as in weeks 2 and 3. Patients received 10 sessions, on weekdays, 20 minutes each in the morning. After 2 wks of open treatment, these patients enter the stabilization/discharge phase as well as those initially assigned to active treatment. During the last week of admission (week 4 or week 6), subjects also received an EKG, EEG, and a MRI for clinical monitoring. Patients would be withdrawn from the study if any clinically apparent deterioration in neurological or psychological status occurred before or after tDCS.

MRI

Briefly, T1-weighted images with contiguous 1.5-mm slices in the axial plane were obtained using a 3-dimensional spoiled gradient recalled echo sequence in the steady state. Imaging parameters were echo time of 5 milliseconds, repetition time of 24 milliseconds, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations equaled 1, and a 24-cm field of view. Structural scans were obtained before and after active tDCS treatment. Scans were read by a neuroradiologist.

tDCS

Subjects sat in the same chair or on their bed for DC administration and testing. A physician (AM) trained in tDCS delivered current with a Phoresor II Auto Model PM850 through four 25 cm^2 sponge electrodes moistened with tap water or normal saline. The skin under the electrodes was ascertained to be free of congenital or acute abnormalities. The current intensity was set at of 0.08 ma/cm^2 (2mA) at the skin and treatments lasted 20 minutes. The current intensity and duration of treatment used in this study were comparable to those used in many adult studies (Iyer, Mattu et al. 2005; Fregni, Boggio et al. 2006; Floel, Rosser et al. 2008). The active electrodes delivered either anodal TDCS to the left and right DLPFC, targeted as International 10–20 electrode positions F_{p1} and F_{p2} or cathodal TDCS to the left and right STG, targeted as International 10–20 electrode positions T3. In both cases, the reference electrode was placed on the non-dominant forearm. The electrodes were held in place by elastic, self adhesive bandage material. For sham treatment, the current was turned on for 1 minute and then ramped down to 0mA (Gandiga, Hummel et al. 2006).

Statistical Analysis

Fisher's exact test of independence was used to compare the proportion of side effects between the active and sham treatment groups during the blind portion of the study. The p values denoted are two tailed.

Results

Of the 15 patients initially enrolled, 2 withdrew prior to randomization. One subject was randomized to active temporal treatment but withdrew after one week of treatment due to a family issue that required her to return home. The remaining participants (5 males, 7 females) completed the entire study. Table 1 shows subject demographic and central nervous system (CNS) medication data. No subject asked to stop the study, required a change in CNS medications, or needed medical intervention due to adverse effects of tDCS treatment. Table 2 summarizes the side effects during for those patients receiving active stimulation. No subjects reported significant discomfort at the electrode sites. However, four individuals had transient redness that resolved within about an hour after treatment. The only consistent effect of stimulation was tingling (37.5%) or itching (50.0%) under the electrodes. Three individuals complained of fatigue associated with active treatment.

Table 3 summarizes the side effects associated with sham stimulation. Similar to active stimulation, many subjects reported sham treatment to be associated with tingling (20.0%) and itching (40.0%). Two subjects also complained of fatigue associated with sham treatment. Nonetheless, Fisher's exact test for independence comparing side effects between the active treatment and sham treatment groups during the blind phase of the study did not reveal any significant differences in tingling (p=0.596), itching (p=0.852) or fatigue (p=0.560). There were no clinically significant changes in mood, arousal, MMSE, or verbal output during either of the stimulation conditions. In addition, there were no statistically significant differences in adverse effects in either treatment group over time. Furthermore, neither treatment group had significant changes in respiration, blood pressure, or heart rate

during, or EEG, EKG or MRI after, tDCS. The incidence of tingling, itching and fatigue in those receiving open active treatment was comparable to the other treatment groups. Due to the limited number of patients, and at the suggestion of our IRB, presentation of efficacy data was deferred based on power analysis.

Discussion

This pilot study, based on analyses of 125 tDCS sessions, is the first to demonstrate that tDCS is easily tolerated in adolescents. The most frequent side effect during active treatment was tingling (n=6, 46.1 %) or itching (n=7, 53.8%) at the electrode sites. Several patients complained of fatigue (n= 4, 30.7%). However, this could be related to medication regimens that frequently include the atypical antipsychotic clozapine. As noted previously, no subjects asked to stop the study due to concerns about side effects. The incidence of side effects during sham stimulation were comparable to active stimulation suggesting these effects may be associated with the onset of tDCS rather than duration. Our findings are in accordance with other studies of tDCS in adults in regards to the incidence of these side effects (Iyer, Mattu et al. 2005; Poreisz, Boros et al. 2007).

However, it is important to note the data are not directly comparable across studies due to differences in study populations, current strength, durations of treatment and electrode placement of the reference electrode. Like adults (Iyer, Mattu et al. 2005; Fregni, Boggio et al. 2006; Gandiga, Hummel et al. 2006), pediatric patients had trouble differentiating sham from real stimulation. In fact, four subjects did not feel anything during active stimulation while two patients reported tingling during sham stimulation.

There was no clinical/symptomatic decompensation or worsening of psychotic/cognitive symptoms in relation to tDCS. However, as noted previously, tDCS may have the potential to modulate the excitability of cortical neurons on a long-term basis, so the effects of prolonged or repeated exposure should be evaluated on a longitudinal basis.

Our study's use of an extracephalic reference electrode also appears to be tolerated in the pediatric population. Given the potential for unwanted excitability changes under reference electrodes in the brain, the use of extracephalic electrodes has increased in recent years (Cogiamanian, Vergari et al. 2008; Priori, Mameli et al. 2008; Koenigs, Ukueberuwa et al. 2009). However, a recent study of 12 healthy subjects by Moliadze et al found that inter-electrode distance is negatively related to the duration and magnitude of induced after-effects (Moliadze, Antal et al. 2010). Therefore, the effect of extracranial reference electrodes the efficacy of tDCS needs to be further evaluated.

This study has potential limitations regarding our tolerability data that warrant discussion. The sample size may have been underpowered to detect a difference in side effects between groups. Second, antipsychotic medication may have altered cortical excitability in our cohort, thereby preventing the functional effects of tDCS. This is supported by a previous study in which sulpiride, a dopamine antagonist, prevented the reestablishment of the excitability changes induced by tDCS (Nitsche, Lampe et al. 2006). However, the effects of antipsychotics, in particular clozapine, on cortical excitability pre and post tDCS are unknown. Third, given the cognitive deficits often see in COS, patients may have had difficulty differentiating side effects such as tingling, itching and pain. They may have also had trust in a new therapeutic method resulting in self-reported minimization of side effects. Finally, there were limitations in the sensitivity of our measures (i.e., MMSE, EEG, ECG, MRI) that may have prevented us from detecting subtle side effects of the treatment. After our pilot study is complete, we plan to use more sensitive measures (e.g., diffusion weighted MRI) to make these determinations. In light of its favorable tolerability profile, portability

and being fairly inexpensive, the use of tDCS may offer a new valuable tool to modulate brain activity of a specific cortical region in a controlled manner. Future work will continue to investigate this as an adjunctive tool in the treatment of COS.

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Table 1

List of Medications for Study Participants

Participant/Number tDCS of Sessions			
Prefrontal Arm	**Sex**	**Age (yrs)**	**CNS Medications/Dosage**
1 (10)	F	17.4	Clozapine 275 mg PO qhs
2 (10)	M	17.1	Clozapine 200 mg PO qhs
3 (10)-open	F	15.8	Clozapine 100 mg PO qam, Clozapine 200 mg PO qhs, Citalopram 20 mg PO qam
4 (10)	M	13.5	Clozapine 200 mg PO BID, Gabapentin 300 mg PO BID
5 (10)-open	M	17.0	Clozapine 150 mg PO BID
6 (10)	F	10.5	Clozapine 100 mg PO qam, Clozapine 300 mg PO qhs, Citalopram 30 mg PO qam
7 (10)	M	17.0	Clozapine 100 mg PO qam, Clozapine 400 mg PO qhs Aripiprazole 7.5 mg PO qam
8 (10)-open	M	14.2	Clozapine 150 mg PO qam, Clozapine 200 mg PO qhs
Temporal Arm			
1 (10)	F	15.7	Clozapine 200 mg PO qam, Clozapine 400 mg PO qhs , Risperidone 1 mg PO qhs
2 (10)-open	F	13.5	Clozapine 100 mg PO qam, Clozapine 200 mg PO qhs, Citalopram 10 mg PO qam
3 (10)	F	13.3	Clozapine 250 mg PO BID, Aripiprazole 5 mg PO qam
4 (10)-open	M	17.2	Clozapine 100 mg PO qam, Clozapine 400 mg PO qhs, Aripiprazole 5 mg PO qam, Haloperidol 1 mg Po qhs,
5 (5)	F	17.6	Clozapine 100 mg PO qam, Clozapine 300 mg PO qhs, Lithium Carbonate 450 mg PO qday

qhs-at bedtime, qam-every morning, BID-twice daily

Table 2

Subject demographics and side effects of tDCS during active stimulation (blind and open treatment)

Participant/Number tDCS of Sessions Prefrontal Arm	Sex	Age (yrs)	Tingling	Pain	Itching	Fatigue	Mental Status Changes	EEG Changes	MRI Changes	EKG Changes	MMSE**
1 (10)	F	17.4	N	N	N	N	N	N	N	N	21 (2)
2 (10)	M	17.1	N	N	N	N	N	N	N	N	26 (1)
3 (10)-open	F	15.8	Y	N	Y	Y	N	N	N	N	24(1)
4 (10)	M	13.5	Y	N	Y	Y	N	N	N	N	18 (2)
5 (10)-open	M	17.0	N	N	N	N	N	N	N	N	27 (0)
6 (10)	F	10.5	Y	N	Y	N	N	N	N	N	23 (−1)
7 (10)	M	17.0	N	N	N	N	N	N	N	N	22 (2)
8 (10)-open	M	14.2	N	N	Y	N	N	N	N	N	25 (1)
Temporal Arm											
1 (10)	F	15.7	Y	N	Y	N	N	N	N	N	24 (2)
2 (10)-open	F	13.5	Y	N	N	Y	N	N	N	N	22 (3)
3 (10)	F	13.3	N	N	N	N	N	N	N	N	22 (−1)
4 (10)-open	M	17.2	Y	N	Y	Y	N	N	N	N	23 (−1)
5* (5)	F	17.6	N	N	Y	Y	N	N	N	N	26 (−1)
Totals	**7 F**	**15.4**	**6**	**0**	**7**	**4**	**0**	**0**	**0**	**0**	**23.30**
125 tDCS sessions	**(53.8%)**	**(2.21)**	**(46.1%)**	**(0%)**	**(53.8%)**	**(30.7%)**	**(0%)**	**(0%)**	**(0%)**	**(0%)**	**(0.77)**

Y-Yes
N-No

*Participant completed only one week of active treatment

**Baseline MMSE score is noted. Change after blind or open active treatment is noted in parentheses.

Table 3

Subject demographics and side effects of tDCS during sham treatment

Participant/Number tDCS of Sessions Prefrontal Arm	Sex	Age (yrs)	Tingling	Pain	Itching	Fatigue	Mental Status Changes	EEG Changes	MRI Changes	EKG Changes	MMSE* (Changes)
1 (10)	F	15.8	N	N	N	Y	N	N	N	N	24 (0)
2 (10)	M	17.0	N	N	N	N	N	N	N	N	27 (1)
3 (10)	M	14.2	N	N	N	N	N	N	N	N	25 (0)
Temporal Arm											
1 (10)	F	13.5	N	N	Y	Y	N	N	N	N	22 (2)
2 (10)	M	17.2	Y	N	Y	N	N	N	N	N	23 (−1)
Totals	**2 F**	**15.5**	**1**	**0**	**2**	**2**	**0**	**0**	**0**	**0**	**24.2**
50 tDCS sessions	**(40.0%)**	**(1.65)**	**(20.0%)**	**(0%)**	**(40.0%)**	**(40.0%)**	**(0%)**	**(0%)**	**(0%)**	**(0%)**	**(0.4)**

Y-Yes
N-No

*Baseline MMSE score is noted. Change after sham treatment is noted in parentheses.