Safety and Tolerability of Transcranial Direct Current Stimulation (tDCS) on Children and Adolescents

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Prologue

This present study which examines the safety and tolerability of transcranial direct current stimulation (tDCS) in children and adults has been ongoing since September 2014 and I began contributing in September 2016. This study has been conducted as a collaboration between Carleton University's Neuroscience of Imagination Cognition and Emotion Research (NICER) Lab, as well as The Children's Hospital of Eastern Ontario (CHEO) Research Institute Neuropsychiatric Lab. Here I will be discussing my personal contributions to the present study as well as the development from participant recruitment to data collection.

Initially I began volunteering as a research assistant within the research institute (RI) at CHEO. In order to contribute as a research assistant in CHEO's neuropsychiatric lab, I underwent the hiring process as a volunteer where I was issued a badge and attended an orientation session where I was briefed on all compulsory information to begin volunteering. Additionally I was given three mandatory training modules to complete consisting of Tri-Council Policy Statement (TCPS), Good Clinical Practice (GCP) and Health Canada Food and Drug Regulations, Part C Division 5 where I received certificates upon completion. These training modules were a mandatory component to be completed in order to be working at CHEO RI as a volunteer or employee. As a research assistant I took part in the recruitment of participants from the CHEO Outpatient Clinic as well as the general public. The process of recruitment involved distributing information pamphlets while discussing the present study to potentially interested families and collecting their contact information. This recruitment included the children within the clinic as well as parents of the children and other adults within the community. After documenting the recruitment information I would pass it along to the research coordinator (Matthew Buchanan) to be contacted and screened for participation. This recruitment process is

still ongoing and I was able to contribute to this process for eight months. In addition it was also my responsibility to regularly check the lab's voicemail box for any notifications or participation interest and follow up with the research coordinator. Beyond recruiting participants, I was also heavily involved in running participants in either the NICER Lab or the Neuropsychiatric Lab. This process of running participants' tDCS sessions occurred simultaneously with recruitment and research assistants were regularly divided weekly between recruitment and the running of participants. During these eight months I would alternate from recruiting participants a couple of times a week at the outpatient clinic, and running participants tDCS sessions a couple of times a week. This routine continued regularly, leading to a large number of individuals being recruited and screened to be considered for participation. Once the family committed to participating we would schedule a time for them to come into the lab for their tDCS session. At this time, participants were greeted by the research coordinator and assistant (myself), and given consent confirming their intention to participate. tDCS sessions were typically completed within the CHEO lab for children and adolescents, while adults participated in the NICER lab at Carleton University.

I was trained on the proper procedure for setting up tDCS equipment and placing electrodes onto the scalps of participants, although this was mainly conducted by the researcher coordinator. Aside from acting as a witness during these sessions, as a research assistant, it was my responsibility to complete all of likert scale questionnaires with participants before and after each tDCS session as well as following up the week after the sessions. My involvement in this capacity was crucial as I was blinded to the participants tDCS condition, and thus remained unbiased while collecting their questionnaire responses. Finally, I was also tasked with inputting all of the session data into a master Excel file which was regularly updated and organized for the

purpose of conducting data analysis. Ultimately, as this study is ongoing and data collection is continually progressing, for the purpose of my thesis there will be a focus on the data that is currently completed for analysis. Mainly this data will be derived from the adult population as these records are the only completed datasets for discussion. That said, I have included some basic descriptive statistics of the current available data for the children and adolescent groups. This analysis will be completed later in the summer after the recruitment and data collection is complete.

Appendices

Introduction:

Transcranial direct current stimulation (tDCS) is a type of non-invasive brain stimulation that delivers a constant direct low amplitude electrical current via electrodes placed on the scalp (Mennitto, 2012). As tDCS equipment is inexpensive, non-invasive and typically painless, its implementation in neuroscience research has become increasingly apparent, particularly within studies evaluating possible therapeutic effects as an alternative or adjunct treatment option. tDCS typically employs electrical currents ranging from amplitudes of 0mA-2mA, as safety protocols generally restrict the maximum acceptable amplitude for use on human participants to 2mA (Utz et al, 2010). Transcranial direct current stimulation (tDCS) either enhances or depresses cell membrane excitability by using a positive or negative current from an anodal or cathodal electrode, respectively (Krause & Cohen Kadosh, 2013). tDCS differs qualitatively from other brain stimulation techniques such as transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS) such that it does not induce neuronal action potentials. This is because static fields in this amperage range do not yield the rapid depolarization required to produce action potentials in neural membranes. Hence, tDCS might be better considered as a neuromodulatory intervention (Nitsche et al, 2008). Anodal stimulation administered through tDCS results in positive stimulation, thereby increasing excitability of the stimulated neuronal area whereas cathodal stimulation results in decreased neuronal excitability. Additionally, tDCS offers the opportunity to administer a sham stimulation wherein a current is briefly released during the initial phase of stimulation, and is then discontinued for the remainder of the stimulation. These types of stimulation permit variation in the potential effects of tDCS, as cathodal stimulation is often implemented in attempting to decrease excitability in more hyperactive areas of the brain. Anodal stimulation conversely, has been associated with

advancing and promoting potential benefits of neurorehabilitative therapies as depolarization of the resting membrane potential occurs, in turn providing neuronal excitability. Additionally, sham stimulation is commonly administered as a control wherein the participant is unaware that there is no continual current being released. This variation with tDCS permits the opportunity for comparison between stimulation in order to identify and allocate which effects take place with the respective stimulation, and whether a placebo effect is apparent.

One useful aspect of tDCS is its ability to achieve cortical changes even after the stimulation has ended. The duration of this change depends on the length of stimulation as well as the intensity of stimulation. This phenomena has been demonstrated by Utz et al. (2010), such that the effects of stimulation increase as the duration of stimulation increases or the strength of the current increases. The potential cultivation of therapeutic effects with tDCS may possibly be due to its ability to modify neuronal membrane polarity and, by so doing, its threshold for action potential generation (Nitsche & Paulus, 2001; Liebetanz et al., 2002; Stagg and Nitsche, 2011) Additionally the currents induce a sustainable response in the form of a long-term potentiation (LTP)- or long-term depression (LTD)-like plasticity (Pelletier & Cicchetti, 2014). LTP and LTD are characteristics underlying synaptic plasticity wherein long-lasting increases or decreases in synaptic strength are achieved respectively. Likewise, tDCS stimulation involves the alteration of synaptic transmission ability through modifications of intracellular Cyclic adenosine monophosphate (cAMP) and calcium levels, as well as glial activation (Monai et al, 2016). Furthermore both LTP, LTD, and the effects of tDCS are protein synthesis dependent. It is for these reasons that LTP and LTD are proposed mechanisms of the function of tDCS (Nitsche et al, 2008). Given these potential mechanisms, it is reasonable to consider tDCS as a potential alternative or adjunct treatment option for various mental health or neurological conditions.

There has been a recent upsurge in interest in tDCS as a tool for neuroscience research, as well as, a modality for treatment of various neurological and neuropsychiatric disorders. Some current applications of tDCS include: enhancing mood in depression (Ferrucci et al, 2009), memory and motor control in Parkinson's (Boggio et al, 2006), memory in Alzheimer's Dementia (Boggio et al, 2012), attention in ADHD (Ditye et al, 2012), and reduction in craving (Lapenta et al, 2014), and pain in chronic pain conditions (Fregni et al, 2006). Currently, most of the available literature is in adults; however the focus of our current research is concerned with the implementation of tDCS in neuropsychiatric conditions in children. This poses a challenge to pursue the necessary task of establishing that tDCS is safe and tolerable to use in pediatric populations. This can be done, in part by drawing inferences from the adult populations, though this approach is limited. It would be better to conduct a study directly on children that also uses an adult reference group to directly compare the responses between groups. Let us first further discuss more regarding the applications of tDCS.

Applications of tDCS for mental health and neurological disorders:

In a study observing the effects of stimulation in treatment resistant depression, there was an observed increase in positive emotions after tDCS was used compared with sham tDCS, although no significant changes in depression scores were found (Palm et al, 2012). tDCS can also assist in improving working memory. Using a 3-back letter working memory task, left prefrontal anodal stimulation led to an enhancement of response accuracy (medium effect size; d= 0.35) in normal control adults and in patients with Parkinson's disease. This enhanced accuracy effect was shown to increase with tDCS duration. Additionally, past studies observed that aphasic patients demonstrated enhanced performance on language tasks once tDCS was applied, prompting a further investigation by Naeser et al. In this study a non-fluent aphasic

patient received semantic-phonological treatment in conjunction with bihemispheric tDCS on the dorsolateral prefrontal cortex (DLPFC). The aphasic patient displayed significant improvement in verb naming skills, demonstrating significant and long-lasting effects when implementing this treatment combined with tDCS (Naeser et al, 2010).

In major depression, an imbalance between right and left DLPFC activity appears to be an important causal factor which may be corrected by tDCS (Grimm et al, 2008) (Nitsche et al, 2009). There is also evidence that anorexia is associated with hyperactivity in right-hemisphere frontal regions. Based on this treatment success, tDCS therefore has a promising potential in facilitating inter-hemispheric balance (Hecht, 2010). In children and adolescents, tDCS is expected to have therapeutic potential for the same indications as in adults, however there is currently a scarcity of trials to actually demonstrate this.

An incremental goal of ours is to see tDCS become a therapeutic option to improve working memory in children with Attention Deficit Hyperactivity Disorder (ADHD), especially but not exclusively inattentive subtype. Working memory training has been investigated as an intervention for children with ADHD and has led to significant gains in verbal and visuo-spatial short-term and working memory performance, maintained after 6 months, in children with ADHD treated with psychostimulants (Beck et al, 2010). It can thus be expected that tDCS during working memory training could increase the effect of training. As stimulant medication also improves working memory in children with ADHD and increases the intensity and the duration of the effects of tDCS, it would be reasonable to expect that different combinations of pharmacological and electrical brain stimulation could further enhance the effects of memory training so that their effect could be large, generalized and durable enough to constitute an effective treatment. With that, there is a natural concern for the safety and tolerability of the

technique; particularly if it is to be used as a treatment in children and adolescents. There have been a number of safety trials in adults, however there are only a handful of published studies involving children and adolescents. A recent review on tDCS safety reports that there was no evidence of serious adverse effects or irreversible injury produced by conventional tDCS protocols within a wide range of stimulation parameters from over 33, 000 sessions and over 1000 subjects who received repeated tDCS sessions. But the same review reports that only 5% of all tDCS research has been conducted in children (Bikson et al, 2016). There are a few minor side effects occasionally associated with tDCS including skin irritation, a phosphene at the start of stimulation, nausea, headache, dizziness, and itching under the electrode; additionally experimental tDCS is not advised for use individuals suffering from seizures or migraines (Poreisz et al, 2007). In addition, there is direct support for the safety of tDCS as applied thus far in controlled human trials as mild skin erythema is common during tDCS and is not inherently hazardous and resolves after stimulation (Bikson et al, 2016). tDCS was also not found to produce edema or injurious alterations of the blood–brain barrier or cerebral tissue detectable by MRI. The US FDA considers trials of tDCS as non-significant risk, which requires reporting of "unanticipated" adverse events. As of this date, the FDA "MedWatch" database search returns no reports for "tDCS" or "transcranial Direct Current Stimulation." A similar research status approval is in place from Health Canada and internationally (Bikson et al, 2016). Furthermore there have been 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 (Mattai et al, 2011). To date, nearly all tDCS research has been conducted in adult populations and not in a clinical setting. Hence, minimal literature is available on tDCS in children and adolescents, and even less

is available regarding the safety of tDCS. If tDCS is to become an expansively used technique, as well as a clinical treatment aid, it is imperative to investigate and publish reports on its safety in all ages.

Applications of tDCS in children:

Among the currently limited selection of literature concerning the application of tDCS on children, a majority of these studies have observed the safety and tolerability of this technique relative to a variety of illnesses. The advancement on tDCS as a regulated neuromodulation technique has also been loosely explored although there is a vast lack of literature contributing to this progression. A study conducted by Kirton (2017) reviewed the overall climate, prospects and restrictions regarding the advancement of neuromodulation clinical trials in children, with a focus on perinatal stroke. A complementary relationship between perinatal stroke and neuromodulation techniques was examined, initially finding that in perinatal stroke and hemiparetic cerebral palsy, ipsilateral projections from the unlesioned hemisphere to the paretic hand are common. It is suggested that these ipsilateral projections are associated with poorer motor function, larger deficits due to an over-activation of contralesional M1, and may in turn represent maladaptive plastic organization not compatible with typical hand function (Kirton, 2017). It is furthermore suggested that the ipsilateral weak hand represents a potential therapeutic target as decreasing pathological over-activity of non-lesioned M1 may enhance motor learning, which can be modulated through cortical stimulation of the lesioned M1 or inhibition of the unlesioned M1 (Kirton, 2017). Animal studies have additionally demonstrated that daily M1 electrical stimulation can preserve the corticospinal connections normally withdrawn during the early development in cats, complementing evidence towards activity dependent enhancement of

corticospinal connections, specifically in animals. Whether the optimal window for interventional modulation suggested by these animal models takes place in early childhood is unknown, but Kirton (2017) suggests that before brain stimulation can be advanced towards this young age group, modulatory interventions must first be established in older children and should be ideally explored in school age children. As a result, a 4 arm blinded sham-controlled trial of motor cortex tDCS to enhance motor learning in children aged 6-18 was conducted by Kirton. Subjects were asked to repeatedly perform a motor learning task over three days and were randomly assigned to receive 20 minutes of contralateral anodal (1mA), ipsilateral cathodal (1 or 2 mA) or sham tDCS during the first 20 minutes. It was found that learning curves were strongly enhanced with active treatment with effects retained 6 weeks later and additional gains in untrained motor function of both hands (Kirton, 2017). These findings provide evidence of the substance for advancement of further studies of hemiparetic cerebral palsy as well as neuromodulatory techniques in children.

An additional study conducted by Gillick et al. (2014) examined the possibility of constructing a child-specific tDCS dosing parameter, as tDCS has been mainly investigated in adults implementing parameters that may not be suitable for children. This potential standard for safe parameters was examined in participants with history of perinatal stroke, where potential applications are promising. Specifically, studies in non-invasive brain stimulation such as repetitive transcranial magnetic stimulation have recently produced promising results in children with stroke, prompting these further studies utilizing tDCS (Gillick et al, 2014). Computational models were implemented in this study in order to relate brain current flow from past data on healthy adults as well as adults with stroke, to that in a child with stroke and resultant hemiparesis. The pilot study focused on a 10-year old child with a diagnosis of arterial perinatal

ischemic stroke, with the aim of utilizing a stimulation paradigm the produced the same brain intensity as in the adult cortex while targeting the motor cortices of the brain and the interactions between hemispheres. Two candidate montages were explored leveraging computational models to target the primary motor cortex (M1); a supraorbital montage and a bihemispheric montage. The application 0.7mA in the child subject had produced peak electric field comparable to an average adult receiving a 1.0 mA with a comparable distribution of current flow (Gillick et al, 2014). It was ultimately determined that subsequent to all considerations regarding constraints and modeling concerns, for the single session intervention within the study, a current intensity of 0.7mA for 10 consecutive minutes would be the most appropriate establishing tDCS safety and feasibility in children (Gillick et al, 2014).

A study focusing on refractory childhood focal epilepsy was conducted by Auvichayapat et al. (2013) with the aim of obtaining initial data on the safety and efficacy of tDCS in the pediatric focal epilepsy population. thirty-six participants between the ages of 6 and 15 years of age were recruited with the inclusion criteria consisting of a diagnosis of refractory epilepsy, simple partial or complex partial with and without secondary generalization confirmed by EEG and average seizure frequency of more than one per month for 18 months. Patients were randomized to receive either a single session of sham or cathodal 1mA tDCS for 20 minutes with cathode positioned over the seizure focus and anode on the contralateral shoulder. It was determined that all patients tolerated tDCS well and no serious adverse effects occurred (Auvichayapat et al, 2013). Additionally, active tDCS treatment was associated with significant reductions in epileptic discharge frequency immediately and up to 48 hours after tDCS. It was also found that four weeks after treatment, a small decrease in seizure frequency transpired (Auvichayapat et al, 2013).

Mattai et al. (2011) conducted a study to investigate the tolerability aspects of tDCS in the childhood-onset schizophrenia population, focusing on the electroencephalographic effects of tDCS rather than clinical safety variables. Twelve children/adolescents with childhood-onset schizophrenia between the ages of 10 and 17 years were recruited. Participants were assigned to one of two groups consisting of either bilateral anodal dorsolateral prefrontal cortex (DLPFC) stimulation or bilateral cathodal superior temporal gyrus (STG) stimulation. Additionally, participants received either 2mA of active treatment or sham treatment for 20 minutes for a total of 10 sessions. tDCS was found to be well tolerated in the COS population with no serious adverse events occurring during the study (Mattai, 2011). A tingling sensation was found to be the most frequent side effect during active treatment, as well as itching under the electrodes.

The feasibility, tolerability and short term adverse effects of tDCS in children was explored through a study conducted by Andrade et al. (2014) This study was conducted on 14 participants aged 5-12 with various language disorders and aspects including frequency, intensity, adverse effects and perception of improvement reported by parents were collected. Participants underwent 10 sessions of 1mA tDCS for 1 minute followed by 2mA for 30 minutes as an alternative treatment with the anode positioned in the Broca area and cathode in the right supraorbital area. It was found that

> "The main adverse effects reported were acute mood changes (present in 42.9% of the cases) and irritability (35.7%). Tingling and itching had an incidence of 28.6%, mostly in the mild intensity (21.4%). Headache, burning sensation, sleepiness and trouble concentrating were reported by 14.3%, the majority of them being of them mild. There were no reports of after-treatment seizures during the follow-up of these subjects" (Andrade et al, 2014 p.1362).

Ultimately it was implied that tDCS is a feasible and tolerable technique in children although it was stated that studies regarding neuroplastic and cognitive changes in children are needed to confirm its safety.

Up to now, there are only a few published studies involving children and adolescents using tDCS. The objective of the present study is to demonstrate that the standardized tDCS protocol used in adults is safe in regards to the acceptability, tolerability, and feasibility of tDCS for use in children and adolescents. Additionally we hypothesize that any prevalent side effects during stimulation will subside after a 1 hour break. The incremental goal of this study will be to investigate tDCS as a potential treatment option for various pathologies in children and adolescents with a focus on neuropsychiatric disorders. We aim to contribute to the current limited selection of literature by providing further support towards the safety and tolerability of tDCS, but additionally providing support towards the functionality of tDCS as an alternative treatment option.

Methods

Participants:

Sixty-four participants (29 aged from 6 years to 18 years, and 35 aged from 18 to 45 years) were recruited from the Children's Hospital of Eastern Ontario MHPSU outpatient clinic (Mood and Anxiety, ADHD teams) and from the inpatient unit, as well from the community. Participants were recruited from both the neurotypical population as well as individuals suffering from various ongoing clinical conditions, with a focus on ADHD. Due to the experimental nature of tDCS any previous history of seizure/epilepsy was as an exclusion criterion. Other exclusion criteria included: participants with a history of migraine/headaches unstable medical condition or

any condition that may increase the risk associated with transcranial stimulation, cardiac condition/recent cardiac surgery, neurological conditions, epilepsy, seizures and/or brain tumor, electronic implant, e.g, cochlear implant, pacemaker, metal braces, metal plates in the head, etcetera.

Materials:

Each session was conducted with German tDCS device neuroConn DC, with currents ranging from 0mA-2mA. Two electrodes were placed on the scalp through sponges soaked in a saline solution which assists in conducting electricity. A large adjustable rubber band was placed around each participant's head in order to hold the electrodes in place on the scalp in one of six locations. An all-purpose random number generator was utilized in randomly selecting the electrode montage for each participant which included the amperage condition, and the electrode site A likert scale (0-5) questionnaire was implemented with each participant before and after every tDCS session, containing questions relating to the known general side effects of tDCS. These questions were also asked a week later to each participant by a research assistant over the phone or in person.

Procedure:

Before committing to the experiment, all participants were screened to ensure that they properly fit within all of the participation criteria. This screening was conducted verbally, in person or by phone by the research coordinator. All child and adolescent participants were grouped according to age (6 to 12; 13 to 17.9 years), and type of recruitment (clinic or general population). Participants were asked to watch a 5 minute video depicting the use of tDCS, after

which they were asked open-ended questions about what they have viewed. Prior to beginning the sessions, consent an assent forms were given to each participant to read over and sign (Appendices A & B).

Each participant underwent two tDCS sessions with a typical protocol using saline soaked sponges. Two ten minute sessions took place for each participant, separated by a break of 1 hour. Each participant was randomly assigned to two electrode placements among the six most frequently used: the motor cortex (M1), the primary somatosensory cortex (S1), the primary visual cortex (V1), the temporal cortex, the dorsolateral prefrontal cortex (DLPFC) and the parietal cortex (Appendix C). Current intensity was randomly selected among four possible values (0, 0.5, 1.0 and 2.0 mA). The currents were ramped up or down over the first and last 30s of stimulation. After the first 10-minute session, the electrodes were moved to another randomized site on the scalp, determined through measurements on the scalp (Appendix D). The electrodes were covered with saline soaked sponges which were held in place on the scalp with the use of a large rubber band placed around the head by the researcher. During the 1-hour break participants were allowed to sit quietly, watch a movie, or play a videogame in the laboratory or in an adjacent room.

Physical assessment of the skin and scalp, and a side effect questionnaire on a likert scale (0-5) were administered before and after each session including questions pertaining to the prior week (Appendices E-H). Each participant was asked to respond to questions about any prevalent side effects and to rate them on the likert scale, as well as the severity of side effects (headache, difficulties in concentrating, acute mood changes, visual perceptual changes, fatigue and discomforting sensations like pain, tingling, itching or burning under the electrodes) . The questions were asked in the laboratory after the electrodes had been removed, follow-up

assessment, directly by a research assistant blind of the amplitude and electrode placement. The likert scale questionnaire was additionally administered in the week following stimulation by a research assistant over the phone (Appendix I). These phone calls were planned in advance with the participants. For children, parents were also asked to report on side effects they may have observed in their children 1 week before the session, immediately before the sessions and 1 week after the session.

Results:

The mean age of participants belonging to the child and adolescent group was 11 years old, with ages ranging from 6 - 17 years. The average current amperage for this demographic within the first session was 0.95mA, with the mean for the second session reaching 1.34mA. Among the child and adolescent group 13 participants had a diagnosis of ADHD, 15 participants belonged to the neurotypical demographic, and 1 participant had some other prevalent clinical diagnosis. For the first session, 6 participants were subject to stimulation at the motor cortex site (Anode C1 left hemisphere, cathode Right fortonopolar cortex), 2 participants received stimulation at the somatosensory cortex (Anode P1 left hemisphere, cathode Right fortonopolar cortex), 12 received stimulation at the DLPFC site (Anode F3 left frontal, cathode Right fortonopolar cortex), 5 received stimulation at the visual cortex site (Anode Oz occipital midline, cathode Cz central midline), 3 received temporal cortex stimulation (Anode T3 left temporal, cathode T4 right temporal), and 1 participant received parietal cortex stimulation (Anode P6-P8 right occipital, cathode Cz central midline). During second session, 0 participants received motor cortex stimulation, 8 participants received somatosensory cortex stimulation, 6 received stimulation at the DLPFC site, 1 participant received visual cortex stimulation, 9 participants received temporal cortex stimulation, and 5 participants received parietal cortex stimulation. As

data collection and analysis is ongoing for the child and adolescent population, the descriptive statistics for this demographic are based on the currently limited available data. As a result, for the purpose of this study, no analysis will be available for the child and adolescent group. Therefore the current analysis will be focusing on the completed data from the adult population.

The average age within the adult group of participants was 24 years, with ages in this group ranging from 18-45. The mean amperage for the adult population in session 1 was 0.84mA, and mean amperage during session 2 was 1.2mA. Among the adult group, 10 participants had been diagnosed with ADHD, 22 were neurotypical and 3 participants had some other clinical diagnosis. During the first session, 9 participants received motor cortex site stimulation, 6 participants received somatosensory cortex site stimulation, 4 participants received stimulation at the DLPFC site, 5 participants received visual cortex stimulation, 5 received temporal cortex stimulation, and 6 participants received parietal cortex stimulation. During the second session, 4 participants received motor cortex stimulation, 3 participants received somatosensory cortex site stimulation, 6 participants received DLPFC site stimulation, 8 participants received visual cortex stimulation, 9 participants received stimulation at the temporal cortex site, and 5 participants received parietal cortex site stimulation.

A univariate analysis of variance was conducted in the adult population on each question across all participants to determine if there were any statistically significant differences between each experimental condition. This analysis included each question as a dependent variable, time point as a fixed factor, amperage and electrode placement as random factors, and age, sex, and diagnosis as covariates. This analysis revealed absolutely no main effects, and only a single significant interaction ($p < .0001$, between question 10 (itchiness) and time point/ amperage/ electrode placement. This confirms our hypothesis that tDCS is tolerable, at least in the adult

population. By consideration, since our objective was to demonstrate that tDCS is safe and tolerable, it is a positive outcome for us that there were no main effects: indicating that there were no real changes in question response based on any of our conditions, and thus participants are responding no differently regardless of whether it was before or after the session, regardless of how intense the current was, or where the electrodes were placed. Additionally, our interaction found for question 10 (itchiness) tends to support the current literature, as it is the most commonly reported side effect of tDCS.

Figure 1.

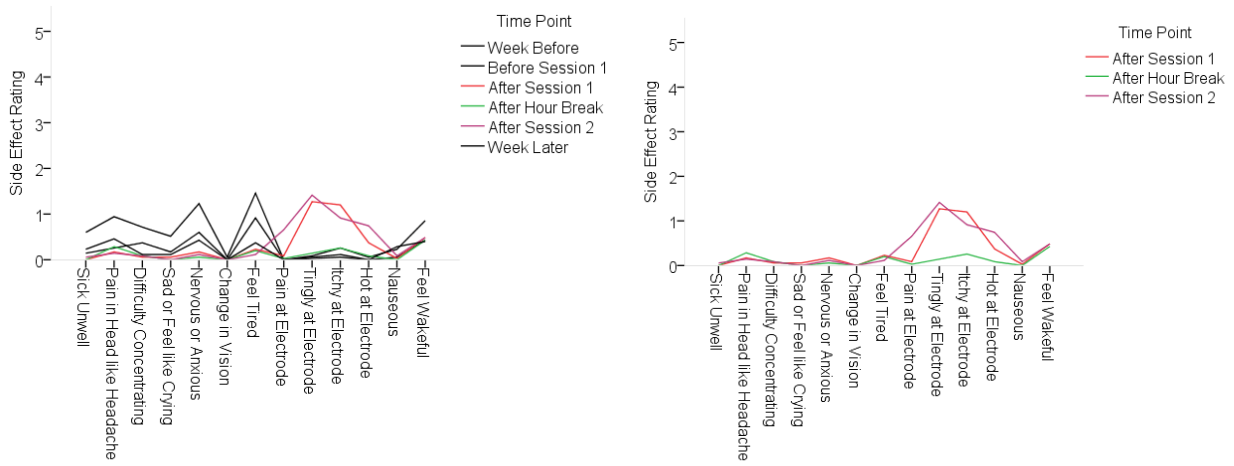

Figure 1. (left) depicts the mean side effect rating for each question by time point. The baseline sessions are depicted in black, (right) shows mean side effect rating for each time point with the baseline conditions removed.

Figure 2.

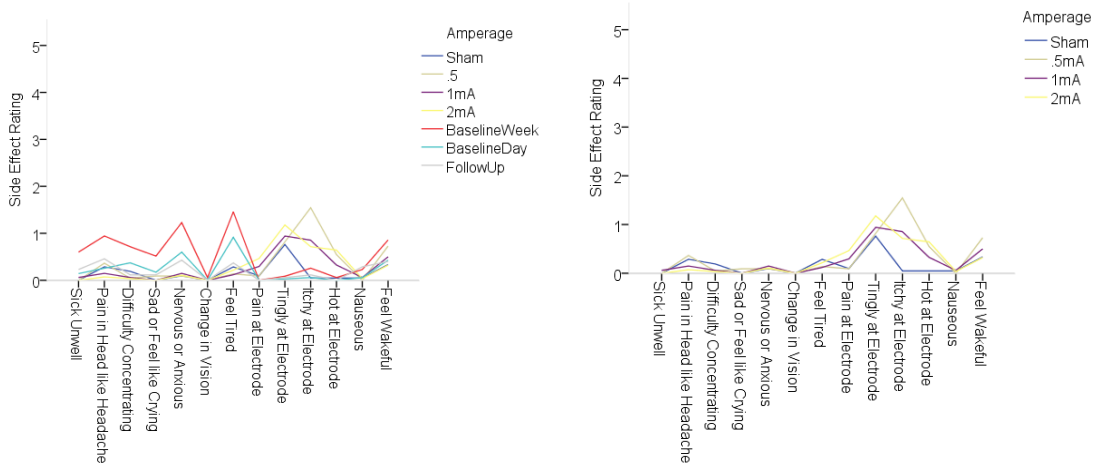

Figure 2. (left) shows mean side effect rating by amperage, (right) shows mean side effect rating by amperage with the baseline conditions removed.

Figure 3.

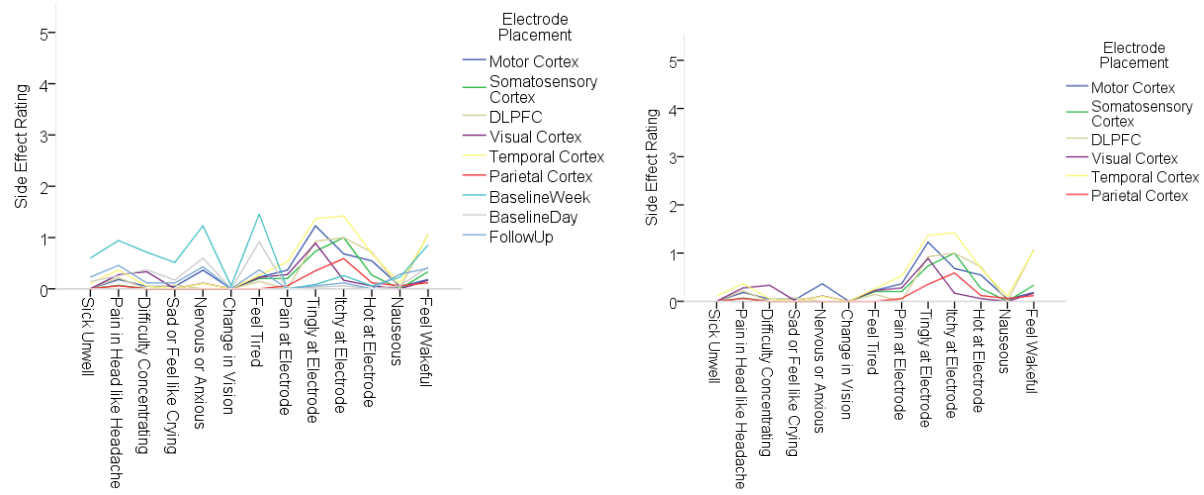

Figure 3. (left) shows the mean side effect rating for each question by electrode location, (right) shows the mean side effect rating for each question by electrode location with the baseline conditions removed.

Overall, one of the most important things to note in the figures is that not a single side effect was rated above 2 (mild) and were below 1 (very mild). This initself demonstrates the

general safety and tolerability of tDCS. Even among the low side effect ratings, these figures illustrate that the highest ratings were given by participants to sensations mainly occuring at the electrode sites including itchiness and tingling. More severe sensations such as pain and a heat sensation at the electrode sites were not as prevalent as itching or tingling, although these sensation are where rating tended to incline and decline from the less common side effects. Ratings of sensations such as a feeling of being sick or unwell, headache, and sadness were virtually non-existant from tDCS. It can also be seen that side effects were much less prevalent and tended to subside when ratings were given after the hour break between sessions. This confirms our hypothesis that the side effects would subside after a break from tDCS. Overall, most side effects were given higher ratings after the second session although itchiness was most commonly reported after the first session.

It is also demonstrated that itchiness was most commonly experienced by participants in general, but reached the highest point when an amperage of 0.5mA was given (although this is still less than mild on average). Tingling and pain at the electrode sites were most prevalant when an amperage of 2mA was given. Participants experienced some minor sensations including hedache, difficulty concentrating and tiredness when given sham stimulation, although the most commonly experienced side effect during sham stimulation was tingling at the electrode sites. Ratings varied mainly for side effects specifically taking place at the electrode sites, as there was no major shift or variation for other side affects. Here it is apparent that the highest ratings were given to side effects when the temporal cortex was stimulated, especially for side effects including pain, itchiness, tingling at the electrode sites but also for nausea and wakefulness. Variation also occured as nervousness and anxiousness was most prevalent when the motor cortex was stimulated. Side effects that commonly recieved higher ratings such as itchiness

appeared to be rated the lowest when the visual cortex was stimulated, and tingling recieved the lowest ratings when the parietal cortex was stimulated. Moreover, there were no serious adverse events, and no drop outs. Overall, this evidence suggests that tDCS is very well tolerated, acceptable, and safe to use.

Conclusion:

The present study has aimed to demonstrate that the standardized tDCS protocol used in adults is safe for use in children and adolescents. As the adult data in this study has been concluded, it has been demonstrated that tDCS is generally safe, acceptable, and tolerable in adults, as expected. Since this study is ongoing in the children and adolescent group, the direction of this study can advance towards implementing this adult data in a between groups comparison with participants <18. As a result the data depicting the safety and tolerability of tDCS in children can be compared directly to the adult group since they were exposed to the exact same protocols and experimental procedures. Additionally, as the child data is currently limited, once collected and compared, we anticipate that the adult findings will be replicated in the child population. This will confirm whether tDCS is safe and tolerable in children. The incremental goal of this study has been to investigate tDCS as a potential treatment option for various pathologies in children and adolescents. As a result, we look forward to the future of this study advancing towards supporting tDCS as an alternative or adjunct treatment option in children once the safety and tolerability is accepted in this population.

Appendix A: Consent Form Under 18

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Information and Consent Form – Under 18

I have been informed about any potential risks of this study and I give consent for my child to participate in this study entitled "Transcranial Direct Current Stimulation: A safety study in children and adolescents".

I have received a copy of this consent form.

I agree that my child will participate in two 10-minute sessions during which an electric current will be delivered through two small electrodes attached to their head. I understand that part of this current is reaching their brain.

I give consent to the researchers in this project to obtain information from the questionnaire relevant to this study.

I have legal custody of my child and consent to allow my child to participate in this project.

_____	_____	_____
Child's last name (please print)	**Child's first name (please print)**	**Subject ID**

Gender of my child: □ Male

□ Female

Decision for my child: □ Yes, I wish my child to participate in this study.

□ No, I do not wish my child to take part in this study.

Decision for parent: □ Yes, I agree to be present during the sessions and thus participate in this study.

□ No, I do not wish to participate in this study.

I would like to be informed of the results: □ Yes

□ No

Consent form Signatures

By signing this consent form I agree that:

- I am voluntarily agreeing to participate in this research study;
- I understand the information within this consent form;
- All of the risks and benefits of participation have been explained to me;
- All of my questions have been answered;
- I allow access to my medical records and/or personal information as described in this consent form, and;
- I do not give up my legal rights by signing this form.

Signature of Participant	Name of Participant	Date

Witness to Participant's Signature	Name of Witness	Date

Signature of Person Obtaining Informed Consent	Name of Person Obtaining Informed Consent	Date

Signature of Participant's Substitute Decision Maker	Name of Participant's Substitute Decision Maker	Date

If the consent discussion has been conducted in a language other than English, please indicate:

Language

Signature of Translator	Name of Translator	Date

Appendix B: Consent Form Age 18+

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Information and Consent Form – 18+

I have been informed about any potential risks of this study and I give consent to participate in this study entitled "Transcranial Direct Current Stimulation: A safety study in children and adolescents".

I have received a copy of this consent form.

I agree that I will participate in two 10-minute sessions during which an electric current will be delivered through two small electrodes attached to my head. I understand that part of this current is reaching my brain.

I give consent to the researchers in this project to obtain information from the questionnaire relevant to this study.

I consent to participate in this project.

_____	_____	_____
Last name (please print)	**First name (please print)**	**Subject ID**

Gender:

□ Male

□ Female

Decision:

□ Yes, I wish to participate in this study.

□ No, I do not wish to take part in this study.

I would like to be informed of the results: □ Yes □ No

Consent form Signatures

By signing this consent form I agree that:

- I am voluntarily agreeing to participate in this research study;
- I understand the information within this consent form;
- All of the risks and benefits of participation have been explained to me;
- All of my questions have been answered;
- I allow access to my medical records and/or personal information as described in this consent form, and;
- I do not give up my legal rights by signing this form.

Signature of Participant	Name of Participant	Date
Witness to Participant's Signature	Name of Witness	Date
Signature of Person Obtaining Informed Consent	Name of Person Obtaining Informed Consent	Date

If the consent discussion has been conducted in a language other than English, please indicate:

Language

Signature of Translator	Name of Translator	Date

Appendix C: Common Electrode Placements

Brain region	Active electrode	Reference electrode
Motor cortex (M1)	C1 left hemisphere	Right frontopolar cortex (above the eyebrow)
Somatosensory cortex (S1)	P1 left hemiphere	Right frontopolar cortex (above the eyebrow)
Dorsolateral prefrontal cortex (DLPFC)	F3 left frontal	Right frontopolar cortex (above the eyebrow)
Visual cortex (V1)	Oz occipital midline	Cz central midline
Temporal cortex	T3 left temporal	T4 right temporal
Parietal cortex	P6-P8 right occipital	Cz central midline

Figure 1. Six most frequently used electrode placements.

Appendix D: Electrode Placement (Scalp)

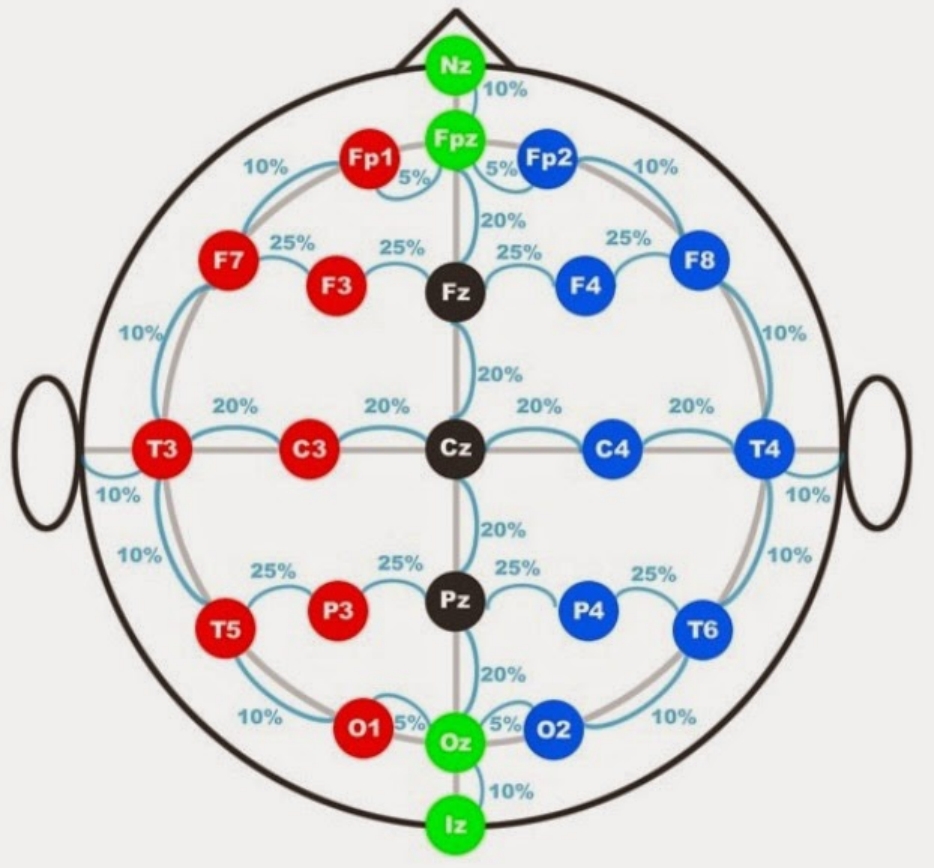

Figure 2. Electrode placement positions on scalp (Kuchibhotla, 2015)

Appendix E: Self & Parent-Reports to be administered in the week before the session

Overall, in the week, did your child appear to be, or complain of any of the following? (And if yes, to what degree and how often?)	0 none/ good	1 very mild	2 Mild	3 moder ate/fair	4 Severe	5 very severe/ poor	N days/ week	N hours/ day
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision? (e.g., blurry, phosphenes)								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Were there any changes to your child's routine in the last few days? Was there anything different or out of the ordinary about the last few days?								
Additional information:								

Overall, in the last week, did you experience any of the following? (If yes, to what degree and how often?)	0 none/ good	1 very mild	2 Mild	3 moder ate/fair	4 Severe	5 very severe/ poor	N days/ week	N hours/ day
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision? (e.g., blurry, phosphenes)								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Was anything different in your life in the last few days (e.g. changes in your schedule or routine)? If yes, what?								
Additional information:								

Appendix F: Self & Parent-Reports to be administered immediately before the first session

Overall, in the last 24 hours, did your child appear to be, or complain of any of the following? (And if yes, to what degree and how often?)	**0 none/ good**	**1 very mild**	**2 Mild**	**3 moderate/fair**	**4 Severe**	**5 very severe/ poor**	**N hours/ day**	**Still present ?**
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision? (e.g., blurry, phosphenes)								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Were there any changes to your child's routine in the last few days? Was there anything different or out of the ordinary about the last few days?								
Additional information:								

Overall, in the last 24 hours, did you experience any of the following? (If yes, to what degree and how often?)	0 none/ good	1 very mild	2 Mild	3 moderate/fair	4 Severe	5 very severe/ poor	N hours/ day	Still present ?
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision? (e.g., blurry, phosphenes)								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Was anything different in your life in the last few days (e.g. changes in your schedule or routine)? If yes, what?								
Additional information:								

Appendix G: Self-Report administered immediately after each session

During the session, did you experience any of the following? (If yes, to what degree and at the beginning or over the whole session?)	0 none/ good	1 very mild	2 mild	3 moderate/fair	4 severe	5 very severe/ poor	Beginning only	Over the whole session
)id you feel sick or unwell?								
)id you feel any pain in your head, like a eadache?								
)id you have difficulty concentrating?								
)id you feel sad, or did you feel like crying?								
)id you feel nervous or scared at all?								
)id you notice anything different in your ision? (For example, did things look blurry, hosphenes?)								
)id you feel tired?								
)id you feel any pain under or around the lectrodes? (Researcher will point to lectrode site)								
)id you feel any tingling at the electrode site, ke needles or pin pricks?								
)oes your head feel itchy anywhere, like you ave a bug bite? If yes, where?---------- ----------								
)oes your head feel hot or like it's burning at ll? If yes, where?---------- ----------								
)id you feel nauseous, like throwing up?								
)id you feel more awake?								
)id the headband feel too tight?								
s there anything else you want to tell us?								
Researcher may note any changes in he skin at the electrode site):								

Appendix H: Self-Report to be administered immediately before the second session

Overall, in the last hour, did you experience any of the following? (If yes, to what degree for how long?)	0 none/ good	1 very mild	2 mild	3 moderate/fair	4 severe	5 very severe/ poor	Beginning only	Over the whole session
Did you feel sick or unwell?								
Did you feel any pain in your head, like a headache?								
Did you have difficulty concentrating?								
Did you feel sad, or did you feel like crying?								
Did you feel nervous or scared at all?								
Did you notice anything different in your vision? (For example, did things look blurry, phosphenes?)								
Did you feel tired?								
Did you feel any pain under or around the electrodes? (Researcher will point to electrode site)								
Did you feel any tingling at the electrode site, like needles or pin pricks?								
Does your head feel itchy anywhere, like you have a bug bite? If yes, where?----------								
Does your head feel hot or like it's burning at all? If yes, where?----------								
Did you feel nauseous, like throwing up?								
Did you feel more awake?								
Did the headband feel too tight?								
Is there anything else you want to tell us?								
(Researcher may note any changes in the skin at the electrode site):								

Appendix I: Self & Parent-Report to be administered to the parents in the week after the session

Overall, since the session, have you noticed or has your child complained of any of the following? (And if yes, to what degree and how often?)	0 none/ good	1 very mild	2 Mild	3 moder ate/fair	4 Severe	5 very severe/ poor	N days/ week	N hours/ day
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision (phosphenes)?								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Were there any changes to your child's routine in the last few days? Was there anything different or out of the ordinary about the last few days?								
Additional information:								

Overall, since the session, did you experience any of the following? (If yes, to what degree and how often?)	0 none/ good	1 very mild	2 Mild	3 moder ate/fair	4 Severe	5 very severe/ poor	N days/ week	N hours/ day
Feeling sick or unwell?								
Having headaches?								
Having trouble concentrating at school or on homework?								
Being tearful, prone to cry, or sad?								
Being unusually nervous or anxious?								
Having changes in vision (phosphenes)?								
Being more tired than usual?								
Having pain on their scalp?								
Feeling tingling on their scalp?								
Having an itchy scalp?								
Feeling a burning or hot sensation on their scalp?								
Being nauseous?								
Having trouble sleeping?								
Is there anything else you want to tell us?								
Was anything different in your life in the last few days (e.g. changes in your schedule or routine)? If yes, what?								
Additional information:								

Appendix J: Research Logs

Researcher Log Session 1

Participant ID:

Date of Session:

Electrode Site:

Level of Current:

Participant Gender:

Participant D.O.B.: ***Age =***

Type of Recruitment:

No changes on the skin noted

Changes at Electrode Site (if any; describe if applicable):

Symptom	***Description***
Redness	
Dryness	
Skin blanches when pressure is applied	
Blistering	
Child indicates pain at site	

Additional changes	

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