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Abstract

Transcranial direct current stimulation is a noninvasive brain stimulation technique that has been studied for the treatment of neuropsychiatric disorders in adults, with minimal side effects. The objective of this study is to report the feasibility, tolerability, and the short-term adverse effects of transcranial direct current stimulation in children from 5 to 12 years of age. It is a naturalistic study of 14 children who underwent 10 sessions of transcranial direct current stimulation as an alternative, off-label, and open-label treatment for various languages disorders. Frequency, intensity, adverse effects, and perception of improvement reported by parents were collected. The main side effects detected were tingling (28.6%) and itching (28.6%), acute mood changes (42.9%), and irritability (35.7%). Transcranial direct current stimulation is a feasible and tolerable technique in children, although studies regarding plastic and cognitive changes in children are needed to confirm its safety. In conclusion, this is a naturalistic report in which we considered transcranial direct current stimulation as feasible in children.

Keywords

tDCS, brain stimulation, language disorders

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Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that has been studied extensively for the treatment of several neuropsychiatric disorders in adults, such as major depression, stroke, movement disorders, and chronic pain.[1-5] Initial trials in adults have shown its efficacy and safety. These initial results together with its low cost and ease of use make transcranial direct current stimulation a desirable technique also to be used in children.[6]

There are limited data in human trials in children. One of the reasons for this is the concern over the vulnerability of the pediatric population and the bioethic aspects of offering a new technique that has not been studied on this specific population. Nevertheless, the results obtained in adults warrant further testing in children. In fact, because of accelerated plasticity of the initial years of life,[7-10] transcranial direct current stimulation can be useful to guide and promote plasticity.[7] On the other hand, there is a concern that transcranial direct current stimulation effects might have a larger impact on this population[10] as it can promote undesirable plasticity or, because of the thinner skull of pediatric population, cause electric currents to have a larger magnitude in this population.

Furthermore, because researchers in this area need to be aware of initial results in children, we report the open-label, off-label clinical, and naturalistic use of transcranial direct current stimulation in 16 children aged from 5 to 12 years old in Salvador, Brazil. Again, there is a potential benefit for this population making these data critical for

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Table 1. Patients' Characteristics.

Patient	Gender	Age (y)	Language disorder	Comorbidities	MRI	PGI-I
1	M	5	ELD	ADHD	Left frontal lobe lesion	1
2	M	7	PDD-NOS + ELD		Unavailable	1
3	F	7	PDD-NOS + PLI		Normal MRI	1
4	M	7	ELD + global dyspraxia		Normal MRI	2
5	M	12	ELD + global dyspraxia	Mild mental retardation	Frontal lobe atrophy	4
6	F	7	Expressive/receptive language disorder + PDD-NOS		Normal MRI	1
7	M	9	Asperger syndrome + ELD		Unavailable	3
8	M	9	ELD	Mild mental retardation	Normal MRI	2
9	M	5	ELD + global dyspraxia	Mild mental retardation	Left-sided perisylvian atrophy	3
10	M	10	ELD + global dyspraxia	Mild mental retardation	Dysgenesis of the corpus callosum	1
11	M	5	Asperger syndrome + ELD			3
12	M	5	ELD			1
13	F	11	PDD-NOS		Normal MRI	4
14	F	7	Expressive/receptive language disorder			1

Abbreviations: ADHD, attention deficit and hyperactive disorder; ELD, expressive language disorder; MRI, magnetic resonance imaging; PDD-NOS, pervasive development disorder not otherwise specified; PGI-I, Patient Global Impression of Improvement; PLI, pragmatic language impairment.

scientists in this field to plan and design further controlled clinical trials with pediatric population.

Methods

Overview

This study consists of a clinical study of children who underwent transcranial direct current stimulation as an off-label treatment at a reference rehabilitation center in Salvador, Brazil. It was a pilot study for tolerability and adverse effects for a future randomized controlled trial, approved by the institutional review board of Hospital Santo Antônio.

Participants

The patients included in this study were 14 children, aged 5 to 12 years, who were all affected by various language disorders. All patients were being observed in this tertiary rehabilitation center. Given the off-label nature of this treatment, patients' parents were requested for an informed consent after explaining the experimental character of such intervention and potential risks. Patients and parents were also asked to report if any adverse effects occurred.

In all children, the cephalic perimeter was equal or superior to 52 cm, the electroencephalogram (EEG) showed no alterations, and there were no reports of seizures, metabolic or immune-allergic diseases, or other underlying conditions. All patients were right-handed. Patients' characteristics (including clinical characteristics) are summarized in Table 1. We attempted to include all patients who received treatment in this clinical center; however, some subjects could not be reached in 5 consecutive days; therefore, we could not collect assessment data on these particular patients.

Intervention

The stimulation was performed with 7 × 5 cm (35 cm^2) electrodes in saline-soaked sponges and were held in place by elastic bandages (we used the device Striat [Ibramed, Amparo-SP, Brazil] as approved by the Brazilian Health Agency, ANVISA). The anode was positioned in the Broca area (mid-left inferior frontal gyrus as defined according to landmark scalp references) and the cathode in the right supraorbital area. In patient number 3, in which the objective was to improve the pragmatic component of speech, we placed the electrodes in the opposite hemisphere (however, in the same location). Subjects received a 1 mA current during the first minute, followed by a 2 mA current for 30 minutes with a current intensity of 0.057 mA/cm^2. During the stimulation, subjects were asked to perform activities of social interaction and speech. Parents were present in all sessions.

The stimulation was delivered throughout 10 sessions, during 2 groups of 5 consecutive weekdays, separated by a 2-day interval. These sessions took place between January and November 2012.

Outcome Measures

Because our goal was to assess feasibility of this treatment, we used the following assessments:

Adverse effects: These were defined as any adverse effect reported by the patient after being given a standard questionnaire proposed by Brunoni et al.[6] It lists the adverse effects reported in most transcranial direct current stimulation studies and quantitatively assesses their intensities and the patients' perception of causality between the intervention and the adverse effect. In order to standardize the assessment, we asked parents who were present during the stimulation to complete this assessment. We also asked questions in an open-ended manner in order to detect any additional adverse effects or impressions about the technique.

Patient Global Impression of Improvement: The Patient Global Impression of Improvement is a 1-question subjective scale that evaluates and ordinates the patients' perception of change after a particular event, translating it into natural numbers. Its values are 1 (very much better), 2 (much better), 3 (slightly better), 4 (no change), 5 (slightly worse), 6 (much worse), and 7 (very much worse). Although its ability to accurately detect improvement is somewhat limited, it does provide further information regarding adverse effects and long-term tolerability. The Patient Global Impression of

Improvement was collected prospectively, through a telephone-based interview, with the parent or adult responsible for the child reporting their impressions on the child's reaction to the stimulation.

Relevant medical record data: All patients underwent a complete medical examination in our institution, prior to and after the transcranial direct current stimulation. Abnormalities in physical examination, along with relevant patient complaints, were collected retrospectively, through medical records.

Data Analysis

Patient characteristics are presented through their absolute values, percentages, central tendency, and dispersion measures or integrally reported through tables, lists, and charts. As this is a descriptive study, no hypothesis testing was performed in the collected data.

Table 2. Adverse Effects Incidence.

Adverse effect	Incidence (%)	Mild (%)	Moderate (%)	Severe (%)
Headache	14.3	14.3	0.0	0.0
Neck pain	0.0	0.0	0.0	0.0
Scalp pain	7.1	7.1	0.0	0.0
Tingling	28.6	21.4	7.1	0.0
Itching	28.6	21.4	7.1	0.0
Burning sensation	14.3	14.3	0.0	0.0
Local redness	7.1	7.1	0.0	0.0
Sleepiness	14.3	0.0	14.3	0.0
Trouble concentrating	14.3	7.1	7.1	0.0
Acute mood changes	42.9	21.4	14.3	7.1
Irritability	35.7	7.1	14.3	14.3

Results

Patients' characteristics are summarized in Table 1. The mean age was 7.57 ($\pm$2.31 [$\pm$standard deviation]). The majority of subjects were male (81.2%), with expressive language disorder (78.5%), global dyspraxia (25%), pervasive development disorder not otherwise specified (25%), and Asperger syndrome (18.7%), either alone or combined. More than one-third (37.5%) patients also presented mild mental retardation and attention-deficit hyperactivity disorder (ADHD) as comorbidities. Most of the patients underwent magnetic resonance imaging (MRI) prior to stimulation. Patient Global Impression of Improvement values ranged from 4 (no change) to 1 (very much better).

The main adverse effects reported were acute mood changes (present in 42.9% of the cases) and irritability (35.7%; see Table 2). 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.

Regarding the potential relationship between transcranial direct current stimulation and the observed adverse effects, we noted that burning sensation, scalp pain, and redness complaints were considered by the parents as definitively related to the intervention in all cases. Headache, sleepiness, and trouble concentrating were also considered to be possibly or probably related to stimulation in 50% of the cases. Other psychological symptoms, such as acute mood change and irritability, were not reported as being related to stimulation in 66.7% and 40% of the patients, respectively.

Discussion

We found that transcranial direct current stimulation is a feasible technique in pediatric patients, which demonstrated mild and short-term adverse effects. In accordance with previous findings in adults,[6] common side effects observed were tingling, itching, and burning sensation, most of which were considered as "mild" or "moderate" (in 28.6%, 28.6%, and 14.3% of subjects, respectively). Interestingly, significant adverse effects not usually reported, such as acute mood change, irritability, and trouble concentrating, were observed. However, as the study population consisted mostly of children with autism spectrum disorders and ADHD, these observations could be part of the disease's natural course or parents could have been more aware of these symptoms after the stimulation visits. The perceived correlation between these alterations and transcranial direct current stimulation was lower when compared to the usual adverse effects of itching and tingling. The only sham-controlled transcranial direct current stimulation study exclusive to the pediatric population has also reported fatigue and tingling in 40% of sham patients, whereas headache, irritability, and acute mood changes were not asked about or spontaneously reported.[11]

Other brain stimulation techniques so far tested in children, such as transcranial magnetic stimulation and theta-burst stimulation, have also been associated with minimal and short-term side effects, including mild headache and tension.[11-13] On the other hand, pharmacologic studies in autistic children have shown several side effects, such as irritability (12%) and social outburst (13.8%), with medium doses of methylphenidate.[14] Being a nonpharmacologic tool, transcranial direct current stimulation can be an especially appealing option in chronic diseases and refractory cases, when high drugs levels can be toxic to young patients after long-term use.

Neuronal plastic changes are known to be age related: early in development, there is an overproduction of spines (dendritic arborization), followed by a prolonged pruning.[10] During this period, the nervous tissue might be more easily reorganized, possibly accounting for the beneficial results observed in the noninvasive brain stimulation studies in infants. Although this enhanced plasticity can help to sustain a larger therapeutic benefit in children, it can also be riskier. Increased plasticity can act as a detrimental factor if transcranial direct current stimulation induces opposite and maladaptive plasticity, and these

potential risks can be even enhanced in diseases in which the anatomic substrate is not well known. For this reason, it is important that studies perform a careful assessment with prolonged follow-ups.[7]

Stimulation protocols in infants have to account for particular age-related difficulties. For instance, specific characteristics of the pediatric skull, such as diminished perimeter and bone thickness, have to be considered. Because of smaller size and perhaps less shunting, children's brains can receive stronger electric currents if the same stimulation parameters used in adults are adopted.[15] It is also known that engaging in specific activities during transcranial direct current stimulation sessions can help to modulate the targeted area and consolidate plastic changes. However, recruiting a child's attention in a repetitive task is also more challenging than doing so in an adult.

Past and Further Research

Pediatric population in general lacks specific research and, for this reason, infantile patients tend to be the last to receive the benefits of a particular therapy, relying mostly on off-label prescriptions of therapies approved for adults.[16,17] The absence of phase I trials,[18] the ethical requirement for more rigid safeguards,[19] and the greater diversity between strict age groups create a high-complexity, low-income market,[20] which serves to only further hamper the development of specific high-quality evidence for this population.

The annual number of publications concerning the use of transcranial direct current stimulation in adults is 13 times larger than 10 years ago, with most of the trials showing clinical benefits and safety.[21] These advances, however, have not yet reached the pediatric population. There is need to start translating established research findings from adults to children,[19] taking into account their brain's differences.

Transcranial direct current stimulation is a poorly studied technique in children. A study regarding its use in infancy-onset schizophrenia demonstrated the tolerability of the technique on a population 13 to 17 years old.[11] A sham-controlled, crossover trial in 5 children 6 to 11 years old showed tolerability of cathodal stimulation with 1 mA for 20 minutes with different electrode montages, although no standard questionnaire was applied.[22]

Other noninvasive brain stimulation techniques that have been more studied in children, such as repetitive transcranial magnetic stimulation and theta-burst stimulation, have shown promising results and safety. In another, noncontrolled trial, Ho Jang Kwon applied 10 sessions of 1-Hz repetitive transcranial magnetic stimulation at 100% of the motor threshold (1200 stimuli/session) to the supplementary motor area of 10 children aged 9 to 14 years, with a diagnosis of Tourette syndrome. The intervention was well tolerated, with only 1 patient complaining of scalp pain after 1 session. A posterior reduction on the Yale Tic Rating Scale was observed on the follow-up weeks.[23] Kirton et al[24] randomized 10 children with arterial ischemic stroke between sham stimulation or 1-Hz repetitive transcranial magnetic stimulation over the contralesional motor cortex for 20 minutes, and those receiving active stimulation showed improvement in hand function and minimal side effects. This technique was therefore considered safe, feasible, and a promising option for this population.[24]

Repetitive transcranial magnetic stimulation has already been investigated in pediatric patients with autism spectrum disorders, because of the perception that neuromodulation can improve regional imbalances throughout brain circuits in such cases. Sokhadze et al[25] administered 0.5-Hz repetitive transcranial magnetic stimulation 2 times per week for 3 weeks in 13 individuals with autism spectrum disorder, including children (mean age 15.6 $\pm$ 5.8 years), without adverse effects or any complication reported.[25] In a trial for the effects of inhibitory repetitive transcranial magnetic stimulation on movement-related potentials in patients with autism spectrum disorder, Enticott et al applied repetitive transcranial magnetic stimulation at 1 Hz to 11 subjects (mean age = 17.55 $\pm$ 4.06 years) in a 3-arm crossover trial with interventions separated by 1 week. Stimulation was applied to the primary motor area, supplementary motor area, and sham stimulation of the left-frontal cortex. A subsequent improvement of the early component of movement was observed, although no changes in movement time were found.[26] Finally, a study investigating the effects of repetitive transcranial magnetic stimulation for epilepsia partialis continua patients, including 3 child subjects of ages 7, 8, and 11, continues to support the safety and efficacy of this method as no side effects have been observed.[27]

Single- and paired-pulse transcranial magnetic stimulation have a low profile risk, as demonstrated by Gilbert et al.[28] No cases of epileptic seizures—the most feared but rarely observed effect of brain stimulation—were reported in any of the 850 children that underwent both these transcranial magnetic stimulation techniques across 28 trials. Most trials report no adverse events with these techniques, with 2 trials reporting mild transient headache in some patients. Of the 850 children across these trials, only 2 failed to tolerate the technique and complete the study.[28]

In spite of the ever-present possibility of noninvasive brain stimulation inducing seizures in younger patients, D'Agati et al[29] found that there were no reports of seizures in clinical trials with adolescents exposed to either transcranial magnetic stimulation or repetitive transcranial magnetic stimulation, regardless of predisposing risk factors. One trial reported 2 syncopal episodes in adolescents exposed to single-pulse transcranial magnetic stimulation, but these were attributed to circumstantial factors such as hunger and stress. According to the authors, the adverse events profile is similar to that of adults, with mild headache and scalp pain being the most common ones.[29]

There are currently 7 transcranial direct current stimulation trials, including subjects under 18 years old, but only 2 are specifically targeting the pediatric population. Our results serve to further strengthen transcranial direct current stimulation as a tolerable tool in the pediatric population, while also broadening its age range. Currently, studies should include only children who could actually benefit from the technique. We expect that

in the future, randomized and controlled trials can be conducted in order to establish higher evidence levels. We also expect coming studies to present a longer follow-up period and more powerful assessments for neuropsychological and neurophysiological changes, like standardized questionnaires targeted at diagnosing cognitive decrease and functional magnetic resonance imaging (fMRI), respectively.

Conclusion

The aim of this study was to demonstrate if transcranial direct current stimulation could be considered safe and tolerable for treatment of children with several different language disorders. It has several limitations, however, for the short-term follow-up including the inefficacy of telephone interviews and absence of techniques to further assess the modifications induced by transcranial direct current stimulation in the infantile brain. We also have not taken into account the differences in the skull size, bone density, and proportion of white and gray matter between different age groups within the pediatric population. Attesting and quantifying the efficacy of transcranial direct current stimulation in language diseases was beyond the scope of this study. We hope this encourages further research in this field in order to better evaluate the benefits of transcranial direct current stimulation in children.

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Author Contributions

ACA, GMM, JVBNA, and CEBPN collected the data. ACA and GMM organized and analyzed data and wrote the first draft. JVBNA, CEBPN, and RdCSL recruited the patients. RdCSL evaluated the patients. RdCSL and FF provided support and mentorship. All authors reviewed the manuscript. ACA and GMM are the equally contributing first authors.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by research ethics committee/institutional review board of Hospital Santo Antonio, Salvador, Brazil (IRB submission number: 22/07). All parents were asked to sign an informed consent document.

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