

Original Research

An Open-Label Study of Cranial Electrotherapy Stimulation on Behavioral Regulation in a Mixed Neurodevelopmental Clinical Cohort

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Abstract

Objective: Individuals with neurodevelopmental disorders often report disturbances in the autonomic nervous system (ANS)-related behavioral regulation, such as sensory sensitivity, anxiety, and emotion dysregulation. Cranial electrotherapy stimulation (CES) is a method of non-invasive neuromodulation presumed to modify behavioral regulation abilities via ANS modulation. Here we examined the feasibility and preliminary effects of a 4-week CES intervention on behavioral regulation in a mixed neurodevelopmental cohort of children, adolescents, and young adults. **Methods:** In this single-arm open-label study, 263 individuals aged 4–24 who were receiving clinical care were recruited. Participants received at-home CES treatment using an Alpha-Stim® AID CES device for 20 minutes per day, 5–7 days per week, for four weeks. Before and after the intervention, a parent-report assessment of sensory sensitivities, emotion dysregulation, and anxiety was administered. Adherence, side effects, and tolerance of the CES device were also evaluated at follow-up. **Results:** Results showed a 75% completion rate, an average tolerance score of 68.2 (out of 100), and an average perceived satisfaction score of 58.8 (out of 100). Additionally, a comparison between pre- and post-CES treatment effects showed a significant reduction in sensory sensitivity, anxiety, and emotion dysregulation in participants following CES treatment. **Conclusions:** Results provide justification for future randomized control trials using CES in children and adolescents with behavioral dysregulation. **Significance:** CES may be a useful therapeutic tool for alleviating behavioral dysregulation symptoms in children and adolescents with neurodevelopmental differences.

Keywords: cranial electrotherapy stimulation; neurodevelopment; sensory sensitivity; anxiety; emotion regulation

1. Introduction

Youth with neurodevelopmental disorders often present with behavioral symptoms thought to be related to disturbances of the autonomic nervous system (ANS), including emotion dysregulation, anxiety, and sensory sensitivity [1,2]. As a result, there is growing research interest in therapeutic interventions that target ANS function to reduce anxiety and enhance emotional regulation. Cranial electrotherapy stimulation (CES) is a non-invasive form of transcranial current stimulation that is believed to modify brain activity, at least in part, through vagal and other cranial nerve pathways [3,4]. While CES has been studied in adults for conditions such as anxiety, insomnia, pain, and headaches, there is a paucity of research on its effectiveness in children [5,6].

Autism, Attention Deficit/Hyperactivity Disorder (ADHD), and other neurodevelopmental conditions often display symptoms of sensory over-responsivity and emotion dysregulation [1,2]. Treatment has traditionally been approached through methods such as sensory integration-based occupational therapy, behavioral therapies, and clinical drug trials [7–11]. However, drawbacks such as ad-

verse medication effects and high costs and time burdens for families have led to a need for research into complementary and novel treatment options [12–14]. Specifically, not all individuals respond in the same way to existing treatments, thus personalized plans must be developed to target specific symptoms and underlying causes for optimal outcomes [15,16].

Cohesive examinations of the biological etiology of behavioral regulation problems in neurodevelopmental populations point to a common physiological mechanism—the dysregulation of the ANS. The ANS has two branches: the sympathetic nervous system (SNS), also called the “fight, flight, and freeze” system, and the parasympathetic nervous system (PNS), or the “rest and digest” system [17,18]. The PNS modulates the homeostatic functions of the body and feelings of safety [19]. Low PNS activity is considered one of the main biological mechanisms responsible for ineffective self-regulation, particularly for individuals with neurodevelopmental concerns [20]. The vagus nerve, which contains afferent and efferent pathways, serves as the primary neural substrate of the PNS. Children with disrupted vagal activity have difficulty regulating re-



sponses to environmental stimuli, resulting in sensory sensitivities, anxiety, and emotion dysregulation [21].

Recently, there has been growing interest in modulating ANS activity using non-invasive brain neuromodulation techniques to remediate transdiagnostic symptoms associated with neurodevelopmental disorders. One such technique, CES, involves delivering low-level electric stimulation to cutaneous branches of cranial nerves via a pair of electrodes, which may be attached to the earlobes or the scalp, depending on the device being used. CES has been shown to produce physiologic effects on both the central and peripheral nervous systems, leading to changes in mood, cognition, and pain perception [22]. Several researchers have suggested that CES exerts its regulatory effect on the ANS by stimulating the vagus nerve [22,23], which in turn is thought to modulate neural activity and neurotransmitter systems in the brainstem, limbic system, and prefrontal cortex. Such modulation of brain and vagal activity is thought to underlie the observed stress regulation effect of CES on the brain and body. Indeed, neurophysiological evidence has shown that CES increases cortical alpha wave activity, promoting optimal states of arousal and alertness [24].

Several studies have established the safety of CES with relatively few reported adverse effects [5,25–32]. Research investigating the efficacy of CES has primarily focused on adult populations with anxiety and depression. Double-blind placebo-controlled studies have demonstrated promising effects of CES therapy in alleviating both anxiety and depression symptoms in adults [28,29,33]. However, therapeutic results have been mixed, with other studies showing limited efficacy relative to sham control conditions [32,34]. Moreover, very few studies have investigated the effectiveness of CES therapy in pediatric clinical populations. To the best of our knowledge, only one published study has examined its clinical effects in pediatric populations. Specifically, a randomized double-blind study in children and adolescents with Tourette syndrome showed decreased tic burden after CES use; however, there was no significant difference between the sham-CES and active-CES groups [30]. To our knowledge, this is the only CES research conducted on young individuals.

Given that CES is conjectured to modulate the mediating physiological system implicated in behavioral dysfunction, additional research examining the use of CES in young populations with sensory, anxiety, and emotional concerns is critical. It is also important to understand whether the use of CES is feasible within the context of routine clinical care for children and adolescents with neurobehavioral symptoms. To address this knowledge gap, we examined the feasibility and preliminary efficacy of a 4-week CES intervention on behavioral regulation in a mixed neurodevelopmental sample of children, adolescents, and young adults currently receiving care at clinical centers operated by Cortica Healthcare. Participants in this study received neuromod-

Table 1. Demographic characteristics.

Characteristic	
Age	10.26 (4.00)
Sex (male)	184 (70%)
Diagnosis (not mutually exclusive)	
Autism spectrum disorder	111 (42%)
Attention-deficit/hyperactivity disorder	136 (52%)
Anxiety	137 (52%)
Developmental coordination disorder	42 (16%)
Sensory processing disorder	98 (37%)

Note. Mean (SD); N (%). Diagnoses of autism spectrum disorder and attention-deficit/hyperactivity disorder were determined by the patient's physician, based on DSM-5 criteria. DSM-5, The Diagnostic and Statistical Manual of Mental Disorders.

ulation therapy using the Alpha-Stim® AID CES (Electromedical Products International, Inc., Mineral Wells, TX, USA), a mobile phone-sized device that delivers a low-level electrical current through electrodes placed on the earlobes. The clinical protocol involved using the device for approximately 20 minutes a day, 5 days a week, generally at bedtime. Our primary aim was to evaluate adherence, adverse effects, and tolerance to CES device use. Second, we aimed to evaluate change in 3 neurobehavioral symptoms thought to be associated with PNS activity: sensory sensitivities, emotion dysregulation, and anxiety.

2. Methods

2.1 Participants & Setting

This open-label study enrolled 263 participants across 7 clinical locations from August 2019–October 2021. Demographic information is provided in Table 1. Individuals were eligible for this study if they were between the ages of 4–25 and at least one neurodevelopmental concern was reported using the ESSENCE-Q-REV screening tool [35]. Contraindications to CES use included uncontrolled seizures, known cardiac arrhythmias, and implanted electrical devices. All participants were enrolled during a clinical visit. Of the 263 participants who completed pre-study data, 227 provided post-study data. The study was approved by the WIRB-Copernicus Group, Institutional Review Board (protocol # 20192706). Written informed consent from parents or caregivers, and assent from minor participants were collected prior to enrollment.

2.2 Outcome Measure

The RECESS. The Repeated CES Symptom Survey (RECESS) is a parent-reported survey used to evaluate changes in PNS-related conditions before and after CES. The survey was developed by the study authors (EJM and KAS). The RECESS includes 7 domains: anxiety, emotion dysregulation, sensory sensitivity, sleep, tics, gastrointestinal, and headaches. The first question within each domain

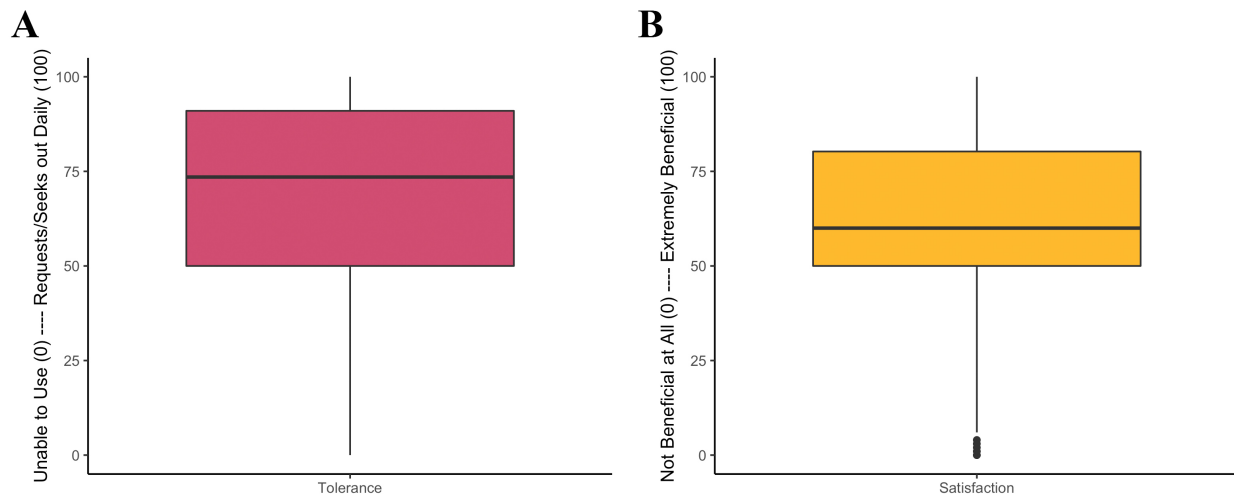


Fig. 1. Graphical representation of parent reported participant tolerance and satisfaction with the CES device. (A) Boxplot of reported CES tolerance. (B) Boxplot of reported CES satisfaction. CES, Cranial Electrotherapy Stimulation.

asks the parent to report whether a problem behavior was present in the past week (i.e., in the past week, has your child experienced generalized anxiety, separation anxiety, repetitive physical behavior, or repetitive verbal behavior?). Each domain also has continuous Likert scale questions to characterize the severity, duration, and or/frequency of behaviors (i.e., how disruptive was the anxiety incident?). Some of the domains are adapted from previously validated measures. The sensory sensitivity domain was adapted from [36], and the tics domain was adapted from [37]. Given the scope of the current paper, here we focus on the anxiety, emotion dysregulation, and sensory sensitivity domains.

For each domain, a dichotomous “absent or present” variable was calculated depending on whether the parent reported that a problem behavior occurred in the child in the past week. A continuous variable that averages each 5-point Likert scale question ranking the severity, duration and/or frequency was also calculated for each domain.

In addition, the RECESS post-CES survey asks parents to report on CES adverse effects, tolerance, and satisfaction. Specifically, parents were asked to rate overall tolerance and perceived benefit of CES on a scale of 1–100.

2.3 Study Design

The current study is a single-arm, prospective, open-label study. CES was used as a part of routine clinical care. If the parents and their children were interested in CES and children met study eligibility, families were invited to participate in a research study in which they would complete the RECESS before and after CES therapy and have their data used for research purposes. Parents and their children were recruited for this study during a clinical visit, either during their initial evaluation or at a follow-up visit.

A baseline visit was held in person or remotely via Zoom telehealth (during COVID-19). The study proce-

dures were discussed with the families during the baseline visit, and consent/assent was collected. Next, the parents completed the RECESS questionnaire described above. During the baseline visit, the site study coordinator discussed treatment protocol and trained the caregivers in home-based CES therapy administration. Next, families were given detailed instructions to use CES at home for 4 weeks. Two weeks after the baseline visit, families were scheduled for a remote check-in with a physician or nurse practitioner to assess for tolerability and adverse effects. Patients were scheduled for a follow-up visit immediately after the treatment phase concluded. After the 4-week trial, parents again completed the RECESS questionnaire, reflecting on their children’s behavior and adverse effects over the preceding week.

2.4 Intervention

Alpha-Stim Device. Alpha-Stim® AID CES (Electromedical Products International, Inc., Mineral Wells, TX, USA) is a small battery-powered CES device that delivers a microcurrent between 50–300 μ A through anode and cathode clips placed on both ears. The default microcurrent level for a given patient was adapted based on their CES tolerance during the caregiver training session at the baseline visit. During the baseline session, patients experienced a typical 20-minute session of CES. The initial current level was set to 100 μ A. If 100 μ A was not well tolerated, the current level for initiation of therapy was decreased to 50 μ A. If the patient tolerated a 20-minute CES session at either 50 or 100 μ A, they were eligible to continue with the trial of at-home, caregiver-administered CES. Caregivers received a thorough education session on proper administration technique at the baseline visit and were sent home with an instruction manual on CES administration. The manual specified that caregivers should administer CES 5–7 days per week for the entirety of the 4-week trial. Each CES session

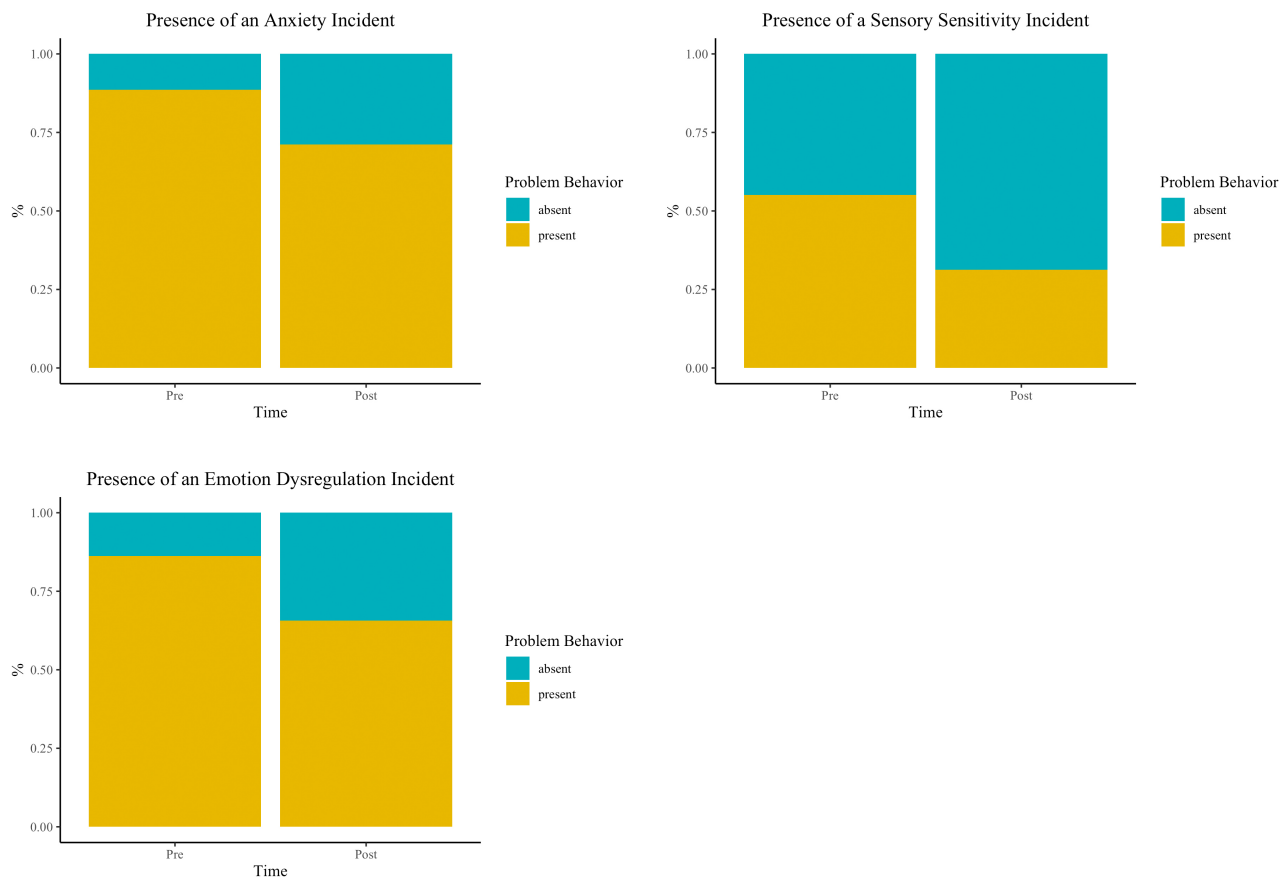


Fig. 2. Bar graph visualizing the frequency of reported problem behaviors before and after the intervention.

was preprogrammed to last 20 minutes, and patients were not instructed to deviate from this duration. The manual also provided a step-by-step protocol for CES administration: (1) apply ear pads with conduction solution on clips; (2) place ear clips on the ear; (3) activate the device with its default calibrated settings; (4) use the device until the timer shuts off current. This protocol was designed based on prior CES dosing schedules that have shown feasibility and efficacy [26,38]. If, after 2 weeks, families reported good tolerability and no adverse effects, caregivers were instructed to increase the microcurrent level by 50 μ A for the remaining 2 weeks.

2.5 Analytic Plan

The first goal of the study was to examine the feasibility of CES therapy in a mixed neurodevelopmental cohort of children, adolescents, and young adults. To do so, we examined descriptive statistics of study completion (ratio of pre-study questionnaires completed/post-study questionnaires completed), caregiver reports of participants' tolerance of CES, and caregiver reports of perceived satisfaction with CES therapy. Adherence was evaluated by calculating the percentage of reported CES use days over the prescribed days of CES use.

The second goal was to examine the preliminary efficacy of CES therapy on behavioral dysregulation symp-

toms. To examine the effects of a 4-week CES treatment on emotion, anxiety, and sensory dysregulation, we created multilevel repeated measure models with random intercepts [39]. Several multilevel models were created with each domain score modeled as the dependent variable. On level 1, or the time-variant level, we included time as the independent variable. On level two, or the time-invariant level, we included age and relevant covariates (clinic site, voltage of CES, duration of session, and frequency of weekly change in medications).

Results can be interpreted about the change in behavior from pre- to post-CES treatment, after accounting for time-level random variation.

When the dichotomous (present/absent) behavioral dysregulation score was modeled as the dependent variable, we employed a multilevel logistic regression to estimate the relative change in odds that an event will occur while accounting for the nested structure of the data. The outcome of a logistic regression model is an odds ratio, or the odds that a behavioral dysregulation event will occur based on the function of time. An odds ratio close to 1 indicates that there is no significant change in the odds of an incident occurring over time. An odds ratio greater than 1 suggests an increased likelihood of an incident happening from pre to post time point, while an odds ratio less than 1 indicates a decreased likelihood. Given the documented in-

teractions between pharmaceuticals and other non-invasive brain stimulation therapies [40,41], we also included a time $\times$ change-in-medications (dummy coded) interaction. Except for age, all covariates and interactions that were included in initial models were not significant. We, therefore, removed these variables from the final models to reduce model complexity.

3. Results

3.1 Tolerance, Adverse Effects, Adherence

The completion rate of the study protocol was calculated to be 86% (227 participants out of 263 enrolled). Of the 36 individuals without post-study questionnaire data, 23 subjects dropped out during the trial (3 discontinued medical treatment at the clinic, 7 did not tolerate the CES, 13 discontinued for unspecified reasons), and 13 completed the trial but were lost to post-study questionnaire follow-up. On a scale of 0–100, parents rated their child's tolerance of the CES device at 68.20 on average ($SD = 27.26$) and rated perceived satisfaction with the CES device at 58.82 on average ($SD = 26$) (see Fig. 1). Adherence was calculated to be 91% in the first week, which dropped to 76% by the final week of therapy.

A total of 13 out of 227 (6%) participants who completed the trial reported at least one adverse effect. Adverse effects included single reports of vertigo, sleep disturbances, respiratory issues, nausea, diarrhea, urinary accidents, and anxiety. Five parents reported temporary rashes.

Adherence data are presented in Table 2. In the initial week of the trial, 91% of parents adhered to the recommended CES usage of 5–7 days per week. However, by the final week of the trial, adherence slightly decreased to 76%. Regarding the microcurrent level settings, during the first week, the majority of parents (64%) reported setting the device at 100 μA . Around 30% of parents opted for a lower level of 50 μA , while the remaining participants reported using levels above 100 μA . In the final week, 40% of parents continued to utilize the device at 100 μA , while 48% reported using levels above 100 μA . The remaining parents reported usage at 50 μA . Furthermore, adherence to the prescribed usage time was consistently high throughout the study. In the initial week, 100% of parents reported using the CES device for the recommended 20 minutes. During the final week, all parents, except for one, adhered to the prescribed 20-minute usage. A single parent reported using the device for an extended duration of 40 minutes.

3.2 Primary Research Question

At the pre-test, 54% of parents reported that in the past week, their child had experienced sensory overresponsivity (e.g., sensitivity to sounds, smells, sights, and/or tastes). At the post-test, 33% of parents reported a sensory sensitivity incident within the past week (see Fig. 2). At the pre-test, 89% of parents reported instances of anxiety for their child (e.g., general anxiety, separation

Table 2. CES adherence diagnostics.

	First Week	Last Week
Days of CES therapy		
Less than 5 days	20 (9%)	54 (24%)
5–7 days	207 (91%)	173 (76%)
CES amplitude		
50 μA	68 (30%)	30 (13%)
100 μA	144 (64%)	89 (40%)
150 μA	10 (4%)	87 (39%)
200 μA	3 (1%)	17 (8%)
250 μA	N/A	1 (0.5%)
N/A	2	2
Duration of CES therapy		
20 minutes	212 (100%)	198 (99.5%)
40 minutes	N/A	1 (0.5%)
N/A	15	28

Note. Mean (SD); N (%). CES, Cranial Electrotherapy Stimulation.

anxiety, or repetitive physical or verbal behavior) within the last week compared to 71% at the post-test. Finally, 86% of parents reported emotion dysregulation (e.g., meltdown, outburst, or shutdown) in the past week at pre-test, which was reduced to 64% at post-test.

Logistic mixed model regressions demonstrated a significant negative effect of time (see Table 3) on sensory sensitivity, anxiety, and emotional dysregulation incidences; each main effect showed a decrease in incidence at the post-test. The odds ratio coefficient suggests that the probability of a behavioral dysregulation incident significantly decreased after the intervention.

To investigate the change in the severity of symptoms following CES use, we examined the change in outcome variables on a continuous scale. Multilevel models of change in sensory sensitivity (frequency at which various levels of sensory sensitivity occur), anxiety (level of anxiety disruptiveness), and emotion dysregulation (average of frequency, duration, and intensity) from pre- to post-CES treatment were analyzed (see Fig. 3). When the outcome variables were modeled on a continuous scale, results indicated a significant negative relation between time on all outcome variables (see Table 4), suggesting a reduction in behavioral dysregulation frequency, duration, and intensity after CES treatment.

3.3 Robustness Analysis

As a robustness check for possible attrition-related bias [42], we replicated the reported models, including only individuals who provided pre- and post-CES treatment data. There were no substantive differences in the model results. All dichotomous and continuous models showed a significant reduction in sensory, anxiety, and emotion dysregulation symptoms from pre- to post-test. These results are presented in **Supplementary Materials**.

Table 3. Logistic regression results.

	Sensory	Anxiety	Emotion
Intercept	0.74	18.44	27.77
Time	0.18 (0.10–0.34) ***	0.0002 (0.0002–0.0003) ***	0.0002 (0.0000–0.001) ***
Age	1.03 (0.93–1.13)	0.95 (0.71–1.28)	0.83 (0.61–1.13)

Note: Odds Ratio (95% CI); *** $p < 0.001$.

Table 4. Linear regression results.

	Sensory	Anxiety	Emotion
Intercept	0.15	3.04	3.42
Time	−0.17 (−0.23 – −0.11) ***	−0.18 (−0.25 – −0.12) *	−0.33 (−0.40 – −0.27) ***
Age	0.00 (−0.11 – 0.11)	−0.02 (−0.09 – 0.12)	−0.12 (−0.22 – −0.02) **

Note: Standardized β (95% CI); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

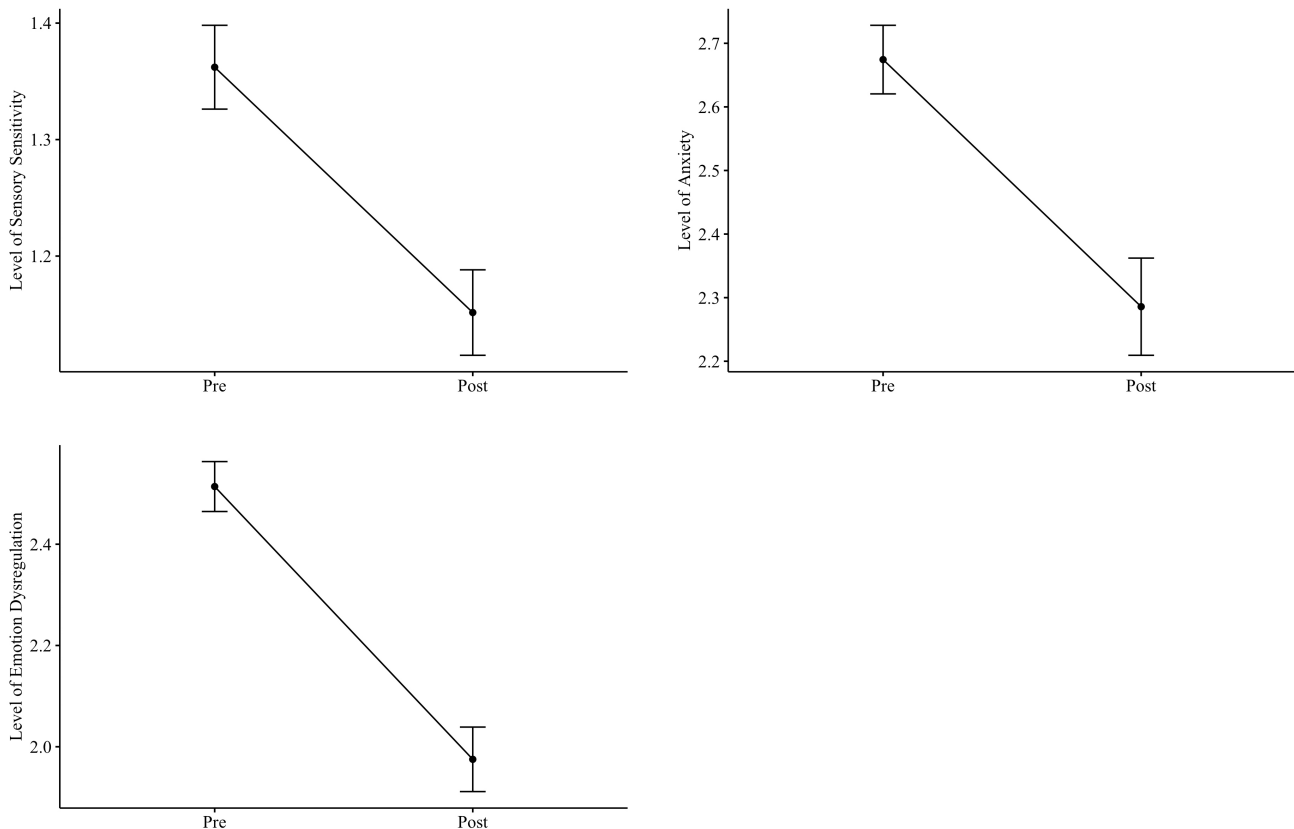


Fig. 3. Line graph represents the change in average behavioral dysregulation scores from pre to post intervention.

4. Discussion

In the current study, we investigated the feasibility and preliminary efficacy of a novel neuromodulation therapy in a clinical cohort of children, adolescents, and young adults. We measured symptoms associated with PNS dysregulation commonly experienced by individuals with neurodevelopmental differences: sensory sensitivities, anxiety, and emotion dysregulation [43]. The current work is the first study, to the best of our knowledge, to demonstrate the feasibility and preliminary efficacy of CES therapy on behavioral regulation in a mixed neurodevelopmental cohort within a routine clinical setting.

To assess the feasibility of a scalable CES intervention embedded within an existing clinical practice, we measured adherence to the study and evaluated parent-reported side effects, tolerance, and satisfaction with CES treatment. Approximately 25% of participants were lost to post-test follow-up due to a combination of intolerance of treatment, study dropout, and failure to complete the follow-up survey. Importantly only 9% of participants dropped out of the study during the 4-week trial, compared with 16% of participants who completed the trial but did not complete the post-study questionnaire. This moderate attrition rate, particularly in post-study questionnaire dropout, is likely

explained by the fact that the study was conducted within the context of routine clinical care. For example, some patients stopped receiving care at the centers for reasons not related to the intervention (e.g., loss of insurance) and therefore did not follow up. Similarly, families may have been less incentivized to complete follow-up surveys, given that this was an open-label study embedded in a clinical context.

Similarly, while patients were instructed to use the CES device according to a specific protocol (20 minutes a day, 5–7 days a week, at a microcurrent level between 50–150 μ A), the self-reported use statistics show some deviation from these instructions. In the first week of the trial, 9% of participants reported using CES for less than 5 days, and there were some reports of microcurrent levels greater than 150 μ A. In the last week of the trial, 24% of the participants reported using CES for fewer than 5 days, and participants still reported using the CES device with microcurrent levels outside the specified range. This finding suggests some protocol deviation from the specified instruction and highlights the importance of a remote monitoring system to better regulate home-based CES treatment in future clinical trials.

We also evaluated any reported adverse effects of CES treatment. Adverse events were reported in less than 8% of participants and included rash, headache, sleep problems, vertigo, nausea, diarrhea, anxiety, and urinary accidents. The rate of adverse effects reported in the current study was lower than what is seen in most drug trials [12,44]. Further, parents reported an average tolerance of 68 (out of 100) for CES, use where 100 was described as “requests and seeks out daily” and 1 designated “unable to use”. A score of 68 can be interpreted as moderately positive tolerability. Similarly, parents reported an average satisfaction score of 59 out of 100. When prompted, “how beneficial do you think CES was for your child?”, a score of 0 reflected “not beneficial at all”, and 100 reflected “extremely beneficial”. Thus, the group-level satisfaction score can be interpreted as average-to-moderate satisfaction. While there are substantial individual differences in participants’ adherence, tolerance, and satisfaction, these findings demonstrate that CES treatment is feasible in this population.

These results offer preliminary evidence for the effectiveness of CES in treating behavioral regulation in children, adolescents, and young adults with neurodevelopmental differences, as an adjunct to other elements of routine clinical care. Specifically, we demonstrated a significant reduction in reported sensory sensitivity, anxiety, and emotion regulation incidents.

In the sensory sensitivity domain, there was a 21% decrease in parent-reported incidences of over-responsivity to sounds, smells, sights, and/or taste problems after CES treatment. Similarly, when analyzed on a continuous scale, the frequency of sensory sensitivities was also significantly reduced. Aside from sensory integration-based occupational therapy, there are few treatment options available

for treating individuals struggling with sensory processing disorders [45]. To the best of our knowledge, this is the first study that used neuromodulation techniques to alleviate sensory sensitivities. It has been hypothesized that children with sensory sensitivities have elevated levels of arousal [46]. Therefore, a therapeutic intervention that lowers resting stress physiology may be advantageous in regulating the perceived effects of sensory over-responsivity. These findings suggest the possible utility of CES treatment alongside existing developmental and behavioral therapies.

In the anxiety domain, parents reported 18% fewer incidences of separation anxiety (i.e., difficulty being in a room apart from family or going to school), general anxiety (i.e., feelings of worry or nervousness), repetitive physical behaviors (i.e., jumping, spinning, pacing, flapping), and repetitive verbal behaviors (i.e., repeated questioning or commenting). Further, the level of disruptiveness of anxiety-related behaviors was also significantly reduced. The positive effects of CES on anxiety symptoms are aligned with adult literature using CES on anxiety [29,33,47]. This finding extends the literature by suggesting the preliminary benefits of CES treatments for anxiety in youth populations.

Finally, parents reported 22% fewer incidences of heightened emotional reactivity (i.e., resistance to novelty or transition, particularly from preferred to non-preferred activities), outbursts (i.e., kicking, hitting, biting, or screaming), meltdowns (i.e., crying, expression of worry or concern, escape/run away), and shutdowns (i.e., laying on the floor, hiding, becoming still and unresponsive). Further, the severity, duration, and frequency of the emotion dysregulation behaviors were significantly reduced. This finding is aligned with research using other forms of neuromodulation therapies that have shown promising effects on children’s inhibitory control [48,49].

For families of children with neurodevelopmental disabilities, daily life is often impeded by frequent sensory over-responsivity, anxiety-induced behaviors, or other meltdowns or shutdowns related to emotional dysregulation [2,50]. Behavioral dysregulation symptoms occur when innocuous environmental stimuli are interpreted as threatening, and individuals lack the inhibitory control needed to respond adaptively [1]. The findings presented here suggest that CES may be a useful supplemental treatment method to improve the ability of children and adolescents to adapt to changes in their environment, appropriately perceive and respond to sensory stimuli, and regulate feelings of anxiety and anxiety behaviors.

This study was open-label and did not employ a randomized double-blinded sham-control experimental design, which naturally limits the conclusions that can be drawn about the effects of CES specifically. For example, it is possible that the effects we observed could be attributed to placebo or other subjective biases. Furthermore, it is difficult to draw conclusions about the prevalence of adverse

effects from this CES trial without a sham control group. This limitation is partially offset by the fact that we examined real-life applications of CES within the context of clinical care for a large sample of participants, suggesting that it is feasible to use this type of neuromodulation routinely as an adjunct to other treatments and therapies. However, a more rigorous randomized controlled trial would, of course, be necessary to support the evidence-based use of CES as an efficacious treatment modality.

This study would have been strengthened by the inclusion of remote monitoring to reduce participant attrition and increase compliance with the protocol. On the other hand, the results suggest that CES may be beneficial even assuming an “intent-to-treat” type of analysis which may more closely reflect the vicissitudes of clinical care. Another drawback of this study is the lack of self-report or direct observation to evaluate CES treatment efficacy and adverse effects. In other words, our estimates of tolerability and benefit based on caregiver report may not accurately reflect the experiences of children participating in the trial. Finally, this research study would have been strengthened by including a delayed follow-up survey to investigate whether the positive effects endure past the treatment time-frame.

Overall, the current study’s findings provide justification for future research on the use of CES therapy in children, adolescents, and young adults with neurobehavioral symptoms. Ideally, this would take the form of a sham-controlled, double-blinded, randomized clinical trial.

5. Conclusions

The current study demonstrated acceptable adherence, generally good tolerance, and moderate satisfaction with CES usage. Further, we showed the positive effects of CES usage on behavioral regulation in individuals with neurodevelopmental differences. This study warrants future research using CES in children and adolescents as an adjunct to existing therapeutic options.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

EJM, KAS, and NH designed the research study. MG and EJ performed the research. ABA analyzed the data and contributed to writing the original draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the WIRB-Copernicus Group Institutional Review Board (protocol #20192706). Written informed consent from parents or caregivers, and assent from minor participants was collected prior to enrollment.

Acknowledgment

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Conflict of Interest

ABA, MG, EJ, NH, and KAS are employed by Cortica and EJ, NH, and KAS have an equity stake in Cortica. All authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2205119>.

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