

BMJ Open Single-arm, open-label, dose escalation phase I study to evaluate the safety and feasibility of transcranial direct current stimulation with electroencephalography biomarkers in paediatric disorders of consciousness: a study protocol

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ABSTRACT

Introduction Children with disorders of consciousness (DOC) represent the highest end of the acquired brain injury (ABI) severity spectrum for survivors and experience a multitude of functional impairments. Current clinical management in DOC uses behavioural evaluation measures and interventions that fail to (1) describe the physiological consequences of ABI and (2) elicit functional gains. In paediatric DOC, there is a critical need to develop evidence-based interventions to promote recovery of basic responses to improve rehabilitation and aid decision-making for medical teams and caregivers. The purpose of this investigation is to examine the safety, tolerability and feasibility of transcranial direct current stimulation (tDCS) in children with DOC.

Methods and analysis This study is an open-label dose escalation trial evaluating the safety, tolerability and feasibility of tDCS in 10 children (5–17 years) receiving inpatient rehabilitation for DOC. This study will follow a modified rule-based design, allowing for inpatient escalation, where a cohort of patients will be assigned to an initial tDCS current of 0.5 or 1 mA based on participant's head circumference and according to the safety data available in other paediatric populations. The subsequent assignment of increased current (1 or 2 mA) according to the prespecified rules will be based on the clinical observation of adverse events in the patients. The study will include up to three, 20 min sessions of anodal tDCS (sham, 0.5 or 1 mA, 1 or 2 mA) applied over the dorsolateral prefrontal cortex. The primary outcomes are adverse events, pain associated with tDCS and intolerable disruption of inpatient care. Secondary outcomes are changes in electroencephalography (EEG) phase-locking and event-related potential components and the Coma Recovery Scale-Revised total score from prestimulation to poststimulation.

Ethics and dissemination The Johns Hopkins IRB (#IRB00174966) approved this study. Trial results will be disseminated through journals and conferences.

Strengths and limitations of this study

- This novel proof-of-concept clinical trial will provide a pivotal step toward designing and conducting larger clinical trials evaluating neural correlates of treatment in children with disorders of consciousness.
- This study will provide an initial structure to optimise dosage of neuromodulatory interventions in neurologically compromised paediatric populations.
- This study will provide safety data to permit and inform future neuromodulation trials in paediatric disorders of consciousness and in other medically vulnerable populations.
- This trial will set the stage for selecting interventions that may be most beneficial at a single subject level.
- This trial will not be able to establish preliminary efficacy as the order of the transcranial direct current stimulation sessions is not randomised.

Registration number NCT03618849.

INTRODUCTION

Children with disorders of consciousness (DOC) after acquired brain injury (ABI) are frequently encountered in paediatric rehabilitation settings. DOC are conditions of severely altered arousal and responsiveness and include the minimally conscious state (MCS) and the vegetative state/unresponsiveness wakefulness syndrome (VS/UWS (VS)).¹ The MCS is characterised by minimal but persistent evidence of self or environmental awareness.¹ The VS is defined by the presence of arousal without any clear evidence of self and environmental awareness.¹

Diagnostic, prognostic and treatment challenges exist in caring for all patients with DOC² and are enhanced in paediatric DOC due to (1) unclear applicability of diagnostic and treatment paradigms established for adults to the developing brain and (2) the ongoing developmental changes in the brain.³ However, accurate diagnosis and prognosis for children in DOC are of key importance for guiding caregivers and clinical teams, including for evaluating the effectiveness of treatment.² Timely rehabilitative management may be particularly important for optimising recovery in paediatric DOC,² as a critical therapeutic timeframe may exist.⁴ Brain-based markers may help identify therapeutic opportunities.

Precise diagnosis of MCS and VS is essential for determining the therapeutic approach and expected course of recovery.² Clinicians often encounter difficulty interpreting subtle and inconsistent behaviours that encompass MCS and VS.² Furthermore, sequelae of brain injury, for example, spasticity, may impact performance on behavioural assessments such as the Coma Recovery Scale-Revised (CRS-R).^{2,5} In adults, behavioural assessments of DOC have been shown to lack sensitivity in differentiating between MCS and VS when compared with neurophysiological evaluation techniques.⁵ Neurophysiological tools have not been examined in paediatric DOC.

Regarding treatment, evidence supporting clinical interventions in DOC is limited, and hence a lack of standard of care exists.² Currently, there are no evidence-based treatments for paediatric DOC.² The development of novel therapeutic methods such as non-invasive brain stimulation may improve function in children with DOC by directly facilitating activation of injured neurons.³

Transcranial direct current stimulation: emerging potential and safety

Transcranial direct current stimulation (tDCS) has been (1) widely accepted as safe in adult populations⁶ and (2) examined as a neuromodulatory intervention in a range of adult and paediatric populations.⁶⁻⁹ Specifically, in children, tDCS has been studied in neuromotor, neuropsychiatric and developmental disorders. tDCS influences the threshold of resting membrane potential by altering the neuronal firing rate.¹⁰ Electrode placement, current intensity and orientation of neurons,¹¹ among other factors, contribute to inhibition or facilitation of cortex excitability with the goal of eliciting neuroplastic effects that may result in improved behavioural outcomes such as increased responsiveness.^{8,12,13} Current is directed from the positively charged electrode (anode) to the negatively charged electrode (cathode); upregulation versus downregulation of neuronal activity is determined by various aspects of use such as the placement of electrodes, stimulation intensity and duration of stimulation.¹¹ tDCS has gained popularity in neurorehabilitation research because it is economical, easy to use and compact compared with other modes of non-invasive brain stimulation.¹⁰

Data from adults with DOC suggest that anodal tDCS may yield safe, short-term improvements in responsiveness/consciousness, as measured by the CRS-R, years postinjury in patients with MCS but not VS.^{8,13} While anodal tDCS shows promise in children with other forms of brain injury such as cerebral palsy (CP),¹⁴ to date, tDCS has not been examined in paediatric DOC.

One use of tDCS is for priming the brain to enhance response to concurrent neurorehabilitative treatment,¹⁵ as has been done in adult stroke rehabilitation¹⁶ and in paediatric motor disorders.¹⁷ tDCS will likely be used in combination with other rehabilitation interventions in future acute/subacute ABI research trials. Exposure to music is a readily available intervention supported by emerging data in adult DOC, suggesting effects of improved responsiveness¹⁸ and EEG markers of arousal/attention.¹⁹

Response and predictive biomarkers may aid understanding of the therapeutic effects of tDCS in DOC.²⁰ Response biomarkers can assist in understanding functional brain changes and the spatial and temporal dynamics of those changes. Collectively, this information can improve our understanding of the underlying mechanism of tDCS and its effects on targeted areas of the brain. Predictive biomarkers can help delineate good versus poor candidates using current stimulation protocols. EEG is a preferred modality due to its cost-effectiveness and portability;²¹ EEG biomarkers have not yet been explored in paediatric DOC.

Data from adults indicate that EEG functional connectivity measures such as coherence can be used as an objective approach for diagnosis, prognosis and evaluation of response to intervention for DOC.²² Resting state phase-locking value is an EEG functional connectivity measure that quantitatively describes the synchrony of brain activity produced within or across different brain areas and is understood to reflect communication between those areas.²³ Unlike coherence, phase-locking value differentiates between the effects of amplitude and phase for a given frequency, allowing for better detection of neural synchrony.²⁴

Additionally, there is growing literature examining event-related potentials (ERPs) from the passive auditory oddball paradigm as a diagnostic and prognostic biomarker in DOC.²⁵ The ERP components N1 and mismatch negativity (MMN) represent basic integrity of sensory cortices and pathways, while the presence of the later P3 strongly correlates with coma awakening.²⁵ ERPs provide an objective measure of neural activity without active patient participation and appear to be a good candidate for assessing response to tDCS interventions in DOC.²⁶

While tDCS has been shown to be safe in other paediatric populations,¹⁷ these safety outcomes may not be relevant to children with acute DOC due to atypical cortical activity.²⁷ Of particular concern is the theoretical risk of seizure.²⁷ To date, one study in adult DOC and one Letter to the Editor regarding a child have reported

the occurrence of seizure in the hours or days following tDCS.^{28 29} In both cases, the contribution of tDCS to seizure cannot be clearly assessed due to confounding factors such as pre-existing epilepsy and recent medication changes.²⁸ Safety and tolerability of tDCS in paediatric DOC may vary with dosage and electrode placement; due to neurophysiological differences in children, the parameters used in adult DOC may not be appropriate.^{7 30} Lastly, the time-consuming care needs of the acute DOC population receiving inpatient rehabilitation (eg, therapy sessions, nap/sleep needs) may limit the feasibility of study designs used in outpatient settings with adults with chronic DOC. In particular, the feasibility of a research protocol incorporating neurophysiological assessments before and after multiple study treatment sessions must be evaluated in the inpatient paediatric rehabilitation setting.

Significance of the present study

This safety, tolerability and feasibility study, in the setting of dose escalation, represents a crucial first step in evaluating tDCS as an intervention in paediatric DOC. Secondly, we will evaluate the sensitivity of EEG biomarkers to response to treatment and potential for recovery. This proof-of-principle study will assist in planning subsequent efficacy trials.

METHODS

Objectives

These hypotheses will be tested:

1. Children with DOC will not display differences in adverse events (AEs) or pain severity when comparing baseline assessment and sham tDCS to 0.5, 1 and 2 mA of tDCS.
2. The study procedures will not cause intolerable disruption to the care of the participant or other inpatients.
3. Children with DOC will show prestimulation to post-stimulation differences in EEG phase-locking and ERP responses with 0.5, 1 and 2 mA but not sham tDCS.
4. Anodal tDCS (0.5, 1 and 2 mA) will yield increased signs of responsiveness on the CRS-R poststimulation compared with baseline, post-sham tDCS and pre-tDCS.

Study design

This is a sequential, phase I, single-site, single-group, open-label, dose escalation study investigating the safety, tolerability and feasibility of incrementally higher tDCS currents in paediatric patients with DOC. This study will follow a modified rule-based design, allowing for inpatient escalation, where a cohort of patients will be assigned to a tDCS current level based on a participant's head circumference³¹ (0.5 mA in children with smaller head circumference (ie, 43–52 cm)³² vs 1 mA in children with large head circumference (ie, >52 cm)) and according to the safety data available in other paediatric populations (eg, CP and stroke).^{33 34} The subsequent assignment of

increased current (1 or 2 mA based on head circumference), both of which are considered safe doses in children 5 years and older with neuromotor disorders,^{7 35} in accordance with the prespecified rules will be based on observation of AEs. The study will include up to three sessions of tDCS (sham, 0.5 or 1 mA, 1 or 2 mA).

Participants

We will study a convenience sample of up to 10 children meeting inclusion and exclusion criteria (table 1) during admission to our inpatient rehabilitation unit at any time postinjury. All screening and tDCS procedures will take place while children are undergoing inpatient rehabilitation.

Recruitment

We propose to enrol up to 25 child participants with the goal of accruing 10 who complete the protocol. The principal investigator (PI) and coinvestigators will verbally provide information about the study to the parent/guardian of their patients. If interested, parents will meet with another study team member to review additional information. A study team physician will obtain written informed consent from the parent/guardian.

A parent or guardian is welcome to be present during the tDCS session. However, given that a child may respond differently in the presence of a parent, we will attempt to keep the presence versus absence of parent/guardian consistent between sessions.

General procedures

Postconsent screening will occur to determine final eligibility. An extended EEG will be performed to exclude the presence of interictal epileptiform discharges and electrographic or previously unrecognised electroclinical seizures. Pubertal/postpubertal females will undergo a urine pregnancy test.

Baseline data on AEs, pain severity and responsiveness (as described in primary outcomes) will be collected over 1 week (see figure 1). Eligible participants will proceed to the sham tDCS session (study visit 1) then 0.5 or 1 mA (study visit 2) and 1 or 2 mA (study visit 3) sessions if eligible as outlined in figure 1. The proposed length of each study visit is approximately 3 hours.

Exit criteria

Participants will completely exit the study if (1) parent/guardian requests removal; (2) female participant becomes pregnant; or (3) participant emerges to the conscious state as measured by the CRS-R. In the case of an AE, clinically significant increase in pain with tDCS or intolerable disruption of care (as defined in primary outcomes), participants will be withdrawn from study visits but remain in the study for assessment of state of consciousness at discharge from inpatient rehabilitation.

Non-enrolled group

We will review the medical records of patients that were eligible but did not enrol to allow for descriptive

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> ▶ 5–17 years old ▶ *Diagnosis of MCS or VS based on clinical evaluation by the inpatient neuropsychology team⁴⁷ ▶ Hearing test completed as part of clinical care ▶ Parent/guardian must be proficient in English ▶ Parent/guardian report that the child demonstrated proficiency in English prior to acquired brain injury
Exclusion criteria	<ul style="list-style-type: none"> ▶ Presence of extensive focal lesions in the left dorsolateral prefrontal cortex as determined by review of imaging/imaging reports obtained as part of clinical care ▶ Known seizures in the prior month ▶ Non-conclusive seizures and/or interictal epileptiform discharges observed on any study EEG ▶ History of craniotomy ▶ Presence of metallic cerebral, cochlear or electronic implant or ventricular shunt or pacemaker ▶ Presence of skin lesion, severe rash or open wounds ▶ Children with head circumference less than 43 cm ▶ Bilateral severe or profound hearing loss ▶ Presence of hairstyle interfering with tDCS application and/or high-quality EEG signal ▶ Females with confirmed pregnancy ▶ Youth on daytime mechanical ventilation ▶ Youth in foster care

*Children meeting criteria on the CRS-R for any of the items indicating MCS but not items indicating conscious state will be considered to be in MCS. Children not meeting criteria for MCS will be considered in VS.

CRS-R, Coma Recovery Scale-Revised; EEG, electroencephalography; MCS, minimally conscious state; VS, vegetative state; tDCS, transcranial direct current stimulation.

comparison. We will collect information on state of consciousness at admission and discharge, age and aetiology of brain injury, in order to compare with enrolled participants.

Concomitant therapies

Participants' clinical care, including pharmacological and therapeutic interventions, will not be influenced by study participation except that antiepileptic medications will not be electively weaned between study enrolment

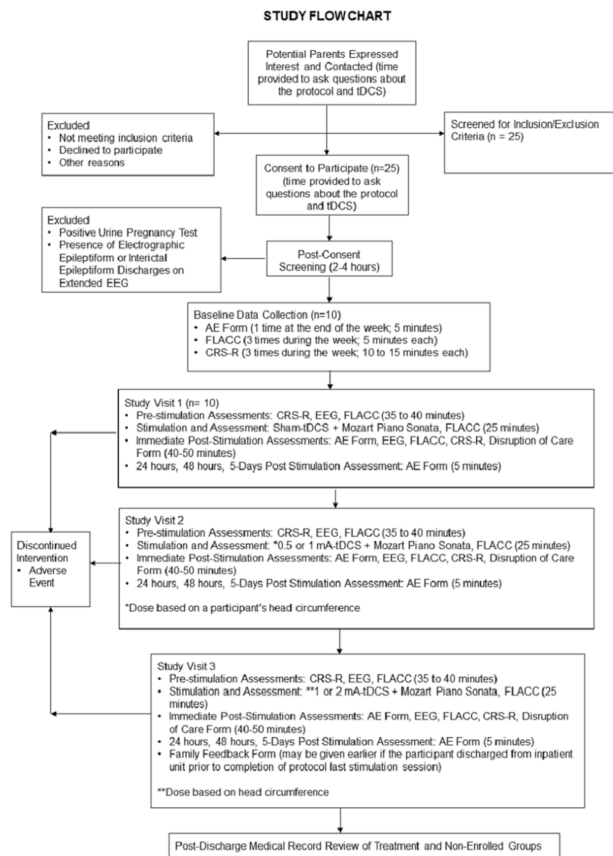


Figure 1 Study flow chart. AE, adverse event; CRS-R, Coma Recovery Scale-Revised; EEG, electroencephalography; FLACC, Face, Legs, Activity, Cry and Consolability; tDCS, transcranial direct current stimulation.

and 1 week following the last tDCS session. Testing visits will be scheduled as not to interfere with therapy or medical appointments. No rehabilitation therapies will occur during the tDCS session. Nursing will be permitted to administer medications, enteral feedings and provide other cares during testing sessions. We will keep a log of any nursing cares that occur during the session.

Primary outcomes

The first primary outcome, reflecting safety, is occurrence of AEs. AEs of interest include (1) skin problems: severe erythema, rash and/or burn that requires oral medications and with effects persisting 5 days poststimulation and (2) seizures. AEs will be assessed by attending physician report via an AE form (online supplementary appendices S.1A and S.1B) created for this study.

The second primary outcome, assessing tolerability, is pain associated with tDCS. Pain will be assessed utilising the Face, Legs, Activity, Cry and Consolability (FLACC) Scale, a reliable and valid observation tool for assessing pain/discomfort in children with limited communication and cognitive impairment (figure 1).³⁶ If pain behaviours increase with the introduction of tDCS then, based on experience of conscious individuals with tDCS,⁶ we will infer that the pain is most likely at the site of the electrodes.

The research team will perform the FLACC and will not be blinded to stimulation conditions. The FLACC is comprised of five subscales each with scores ranging from 0 to 2 and total scores ranging from 0 to 10 (0=relaxed/comfortable, 1–3=mild discomfort, 4–6=moderate pain, 7–10=severe discomfort/pain). Qualitative changes in appearance/behaviour of the child related to comfort will be recorded along with FLACC scores. A clinically significant difference for FLACC scores has not been well-established.³⁷ Based on study team consensus, for this study, an increase of greater than 4 points during/after tDCS sessions compared with the baseline week and/or immediate prestimulation ratings combined with qualitative description of development of severe pain will be considered clinically meaningful as an indicator of pain related to tDCS.

The third primary outcome, reflecting feasibility, is occurrence of intolerable interruption of inpatient care due to child's study participation as determined by the child's assigned nurse and following review by study and clinical teams. A Disruption of Care form was designed for this study (online supplementary appendix S.2) that reflects the nurse's assessment of missed or delayed cares. The child's nurse will complete the form once following each testing session. The child's therapy team will be contacted after each study visit to determine whether any therapy sessions were missed or shortened due to study participation.

Secondary outcomes

EEG biomarkers

We will record resting state EEG (10 min) and ERP (20 min) data using a Nihon Kohden LS-120 system using the 10–20 international system for electrode placement.³⁸ Resting state and ERP data will be sampled at a rate of 512 Hz, with a 138 Hz antialiasing filter. Scalp resistance will be maintained at less than 10 k Ω .

Spontaneous EEG will be recorded from 26 electrodes (10–20 configuration plus F1, F2, F5, F6, P1, P2). EEG data preprocessing and artefact correction will be performed using EEGLAB running in a MATLAB environment (V.2017b, MathWorks Inc, Natick, Massachusetts, USA). For resting state EEG data, preprocessing will be comprised of high-pass and low-pass filtering (0.2 and 40 Hz cut-off, respectively, 24 dB/Oct slope), principal component analysis-based elimination of eye blinks, eye movements and manual rejection of muscular and movement artefacts. We will then convert signals to current source density³⁹ to minimise spatial blurring due to volume conduction. The EEG data will be divided into epochs of 10 s with 50% overlap; at least 30 artefact-free epochs will be obtained from each patient. The dependent measure of phase-locking will be computed from every combination of five frontal and two parietal channels on each side (left side: Fp1, F1, F3, F5, F7 and P1, P3; right side: Fp2, F2, F4, F6, F8 and P2, P4). Consistent with the existing literature,²² differences in the theta and alpha band synchronisation in the fronto-parietal region

from prestimulation to poststimulation of each tDCS session will be quantified.

For the ERP recording, we will use a passive auditory oddball paradigm. We will deliver auditory stimuli binaurally through inserted earphones at an intensity of 65 dB HL using E-prime. Three types of stimuli will be presented pseudo-randomly. Participants will be presented with one block of 2000 stimuli, including 1620 standards (probability 81%), 300 deviants (probability 15%) and 80 novels (probability 4%). The standard and deviant tones will be tone bursts of 1000 Hz lasting 75 ms (standards) and 30 ms (deviants). The novel stimulus will be the subject's own name (SON) digitally recorded by the parent/caregiver. Stimulus onset asynchrony will be set at 610 ms, except for the tone appearing following the SON, which will appear 1220 ms after the onset of the novel stimulus. The ERP paradigm will last about 20 min.

BESA software will be used to conduct all offline EEG analyses. For the ERP components, data will be filtered from 3 to 30 Hz, and averaged ERPs for the standard, deviant and novel tones will be composed from the running EEG data. Data will be segmented time-locked to the stimulus onset with a duration of 200 ms prestimulus onset to 800 ms poststimulus onset, and baseline correction relative to a baseline of 200 to 0 ms will be performed. Standards following a deviant or novel stimulus will not be included in averaging. Peak amplitude and latency detection—N1 to standards, MMN in the deviant minus standard difference and P3 to novels—will be performed using software written in MATLAB.

Change in responsiveness

The CRS-R consists of 23 hierarchically arranged items that comprise of six subscales (auditory, visual, motor, verbal, communication, arousal) to assess consciousness.⁴⁰ A clinician trained in the administration of the CRS-R will conduct the assessment immediately prior to and following tDCS (see figure 1). The clinician performing the CRS-R will not be blinded to stimulation conditions. The CRS-R is considered appropriate to use in children aged 5 to 17 years.¹

Parent/guardian satisfaction

Caregiver satisfaction with study participation will be measured via a Feedback Form adapted from Gillick *et al*⁴¹ (online supplementary appendix S.3). The parent/guardian will complete the form once, at the end of the last stimulation session.

Intervention

Participants will receive up to three sessions of tDCS according to their head circumference (sham, 0.5 or 1 mA, 1 or 2 mA; described in detail below). The Mozart Piano Sonata (K.448)⁴² will be played via speaker for the duration of the tDCS application. For real and sham tDCS, the neuroConn DC-Stimulator Plus device will be used (neuroCare Group, Munchen, Germany). Two sponge electrodes moistened in 0.9% saline solution will

be used to deliver tDCS. We will choose the electrode size based on the participant's head circumference.^{31–43} In participants with medium to large head circumferences (ie, >52 cm),³² we will use large electrodes (eg, 5×5 cm), while in children with smaller head circumference (ie, 43–52 cm; most children under the age of 10 years) we will use small electrodes (eg, 3×3 cm). The distance between anode and cathode electrodes will be maintained at a minimum of 8 cm.⁴³ We will use a syringe filled with an optimal amount of saline solution to wet the sponges. For example, we will use approximately 6 mL of saline solution to wet 5×5 cm sponges (AJ Woods, personal correspondence, 2018). The electrodes will be placed following the 10–20 international system³⁸ with the anode placed over the left dorsolateral prefrontal cortex centred at F3, and the cathode placed over the right supraorbital area (SO) centred at Fp2.

The sham stimulation session will last 20 min. tDCS current will be ramped up to 1 mA over the first 30 s, then held constant for 15 s at 1 mA, then ramped down to zero over 15 s. For the remaining 20 min, the electrodes and stimulator will be left in place without current delivered.

Eligibility to proceed to the 0.5 (participants with small head circumference) or 1 mA (participants with large head circumference) tDCS session will be based on the exit criteria. If indicated, the 0.5 or 1 mA testing session will occur approximately 7 (minimum 5) days postsham stimulation. The 0.5 or 1 mA stimulation will be provided for 20 min; the current will be ramped up for 30 s, held constant at the determined intensity for 20 min, and then ramped down for 10 s. If indicated based on the exit criteria, the 1 or 2 mA (current intensity based on head circumference) testing session will occur approximately 7 (minimum 5) days after 0.5 or 1 mA stimulation with the ramping procedure as above. The entire treatment period will last for approximately 26 days.

Risk mitigation, safety monitoring and stopping rules

The current for all stimulations will be gradually ramped up to minimise sensations of itching, tingling and discomfort. A physician and rescue medication will be immediately available during tDCS sessions in case of a seizure. Due to the possibility of delayed seizure, we will avoid stimulation sessions within 5 days of the child's planned discharge date. If a participant is unexpectedly discharged from the inpatient unit within 5 days of a stimulation session, we will (1) provide seizure education to the parent/guardian; (2) provide a rescue medication for home use; (3) contact the parent/guardian by phone 24 hours, 48 hours and 5 days postdischarge to assess participant status.

After any AE and after data collection from five participants, the PI will review collected data with a data safety monitoring board comprised of the senior coinvestigators and non-study team members with expertise in tDCS to decide whether potential benefits of study continuation outweigh risks to determine whether to stop or continue the study.

STATISTICAL ANALYSIS

Sample size/power calculations

Given the pilot nature of this protocol, we did not conduct a sample size analysis.

Data analysis

For all analyses, we will dichotomise participants in younger versus older group based on tDCS dosages. Participants receiving low tDCS doses (sham, 0.5 mA, 1 mA) will be categorised to the younger group, and those receiving higher doses (sham, 1 mA, 2 mA) will be classified to the older group. We will analyse data using repeated measures analysis of variance (ANOVA) (as described below) if we have at least three participants in a group and the response variable is normally distributed.⁴⁴ We will qualitatively analyse data for all primary outcomes if we fail to attain a minimum of three participants in any group category. For non-normally distributed response variables, we will explore non-parametric approaches involving rank-score tests.^{44–45} We will examine the number of children who experience skin problems or signs of itching, tingling, other discomfort at baseline, sham, 0.5, 1 mA and 2 mA tDCS conditions. For each group category (younger vs older), we will perform a separate repeated measures ANOVA with stimulation condition (baseline, sham, 0.5 or 1 mA, 1 or 2 mA) to examine differences in skin problems and discomfort across four conditions. If the main effect of condition is significant, we will run post hoc analyses to see where the difference lies between conditions. For each group, we will conduct a two-way repeated measures ANOVA with stimulation condition (sham, 0.5 or 1 mA, 1 or 2 mA) and time (pre-tDCS, post-tDCS) to examine differences in pain severity across three conditions and six time points. If a significant interaction is encountered, we will run post hoc comparisons to examine where differences exist. We will qualitatively analyse disruption of care data to gain insight into the planning of future studies in youth with DOC.

For each group, we will analyse phase-locking data by conducting two (left and right hemispheres) repeated measures ANOVA with stimulation (sham, 0.5 or 1 mA, 1 or 2 mA) by time (pre-tDCS, post-tDCS) for fronto-parietal and thalamic synchrony. Similarly, for each group category, ERP data will be analysed using three repeated measures ANOVA with stimulation (sham, 0.5 or 1 mA, 1 or 2 mA) by time (pre-tDCS, post-tDCS) for the N1, the MMN and the P3. The CRS-R data will be analysed using separate repeated measures ANOVA for each group with condition (baseline, sham, 1 mA, 2 mA) by time (baseline (highest and lowest to account for variability in scores between testing sessions); pre-tDCS, post-tDCS).

Data monitoring

The data will be deidentified and will be stored in locked cabinets. For data quality improvement, checks for double data entry and data values will be performed.

Patient and public involvement

Patient and public were not involved in study design and will not be involved in study recruitment and conduct. We have not established a plan to announce the study results to the participants.

Trial status

The trial will begin recruitment in August 2019.

DISCUSSION

The findings from this study may be useful for considering the safety/tolerability of tDCS in other groups of children who are (1) unable to communicate, (2) at high risk for seizures and/or (3) medically vulnerable. This study will provide an initial structure to optimise dosage in neurologically compromised paediatric populations. Research has taken a cautionary approach to tDCS dosage in such populations; a study in autism with minimally verbal children used lower dosages and increased duration to maximise tolerability.⁴⁶ This study will use standard tDCS dosages in accordance with head circumferences of children to evaluate the appropriateness of this approach in medically fragile children.

The results of this study will contribute data on the safety and tolerability of escalating dosages of anodal tDCS in acute DOC, which may be applicable to adults as well. The risk for seizure is high in acute DOC,¹ which may impact tDCS safety. Understanding response to tDCS early after injury, when patients may be at highest risk for medical complications (eg, paroxysmal sympathetic hyperactivity, skin breakdown), will be important for considering inclusion/exclusion criteria and possible AEs for future study designs.

The study will also provide preliminary data on logistics for study designs incorporating pre-post physiologic data during inpatient rehabilitation. While most adult trials of DOC have been conducted in outpatient settings,^{26 29} it is possible that tDCS will be most efficacious when combined with intensive rehabilitation early after injury.

The EEG biomarkers used in this study may identify responders to tDCS and may be beneficial in prognosticating recovery. While this study will only serve to pilot the use of such markers in children with DOC, it provides a pivotal step toward designing and conducting larger clinical trials evaluating neural correlates of treatment in children with DOC.

At the conclusion of this trial, some gaps will remain in the literature. We will only be able to establish safety and tolerability of anodal tDCS based on one session of each tDCS dosage administered at least 5 days apart. While a critical starting point, the findings may not be generalisable to study designs utilising daily anodal tDCS, which may cause significant skin irritations in some individuals.¹¹

Cumulative sessions have been shown to increase the efficacy of tDCS.¹¹ Nevertheless, it is possible that we encounter favourable effects of anodal tDCS on responsiveness from just two real sessions of tDCS; however, we

will not be able to establish preliminary efficacy as the order of the tDCS sessions is not randomised. Given that some children will be recruited early after ABI, during the active stage of recovery, natural recovery may confound the effects of tDCS in the current study.

We have used classical music as an example of a concomitant therapy for the purpose of assessing tolerance to tDCS when applied in the setting of another intervention. We anticipate that future efficacy trials would use other rehabilitative interventions (eg, physical or occupational therapy) rather than classical music alongside tDCS. However, we felt that disrupting a patient's regular therapy sessions would not be justified for this initial safety and feasibility study.

Here, we have provided a detailed description of a sequential, proof-of-concept clinical trial to demonstrate the safety and feasibility of tDCS interleaved with EEG in a dosage-escalation setting in children with DOC. We anticipate that the review of this protocol may be useful to other researchers planning future clinical trials in DOC. Additionally, a detailed protocol of the safety and feasibility clinical trial is presented primarily to provide a reference for the interpretation of the results of this study. The results of this trial will support the understanding of the safe and feasible usage of anodal tDCS under different dosage parameters in paediatric DOC during inpatient rehabilitation. Further, identifying the response and prognostic biomarkers will set the stage toward developing methods for selecting interventions and biomarkers that may be most beneficial at a single subject level. Overall, this study will assist in providing preliminary data to inform future study designs.

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Contributors GTS designed the trial, wrote the statistical analysis plan, drafted and revised the paper. JBE assisted with designing the trial, with statistical analysis and revised the paper. JEC assisted with designing the trial, with statistical analysis and revised the paper. BSS assisted with designing the trial, with statistical analysis and reviewed and revised the paper. GLC assisted with designing the trial and revised the paper. SJS assisted with designing the trial, with statistical analysis and reviewed and revised the paper.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The proposed study has been approved by the Institutional Review Board, which considered tDCS a non-significant risk device and the study as posing no more than minimal risk. This protocol is registered on Clinicaltrials.gov. The results of this study will be disseminated through peer-reviewed journals and scientific conferences.

Provenance and peer review Not commissioned; externally peer reviewed.

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