Published in final edited form as:

Clin EEG Neurosci. 2017 November ; 48(6): 367–375. doi:10.1177/1550059417709177.

Determining Electrode Placement for Transcranial Direct Current Stimulation: A Comparison of EEG- Versus TMS-Guided Methods

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Abstract

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Author Contributions

TLR contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. JSM contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KDR contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MC contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy. GDM contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. EP contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. TF contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KB contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy. BG contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Transcranial direct current stimulation (tDCS) is increasingly researched as an adjuvant to motor rehabilitation for children with hemiparesis. The optimal method for the primary motor cortex (M1) somatotopic localization for tDCS electrode placement has not been established. The objective, therefore, was to determine the location of the M1 derived using the 10/20 electroencephalography (EEG) system and transcranial magnetic stimulation (TMS) in children with hemiparesis (CWH) and a comparison group of typically developing children (TDC). We hypothesized a difference in location for CWH but not for TDC. The 2 locations were evaluated in 47 children (21 CWH, 26 TDC). Distances between the locations were measured pending presence of a motor evoked potential. Distances between the EEG and TMS locations that exceeded the 2.5 cm $\times$ 2.5 cm rubber electrode area are reported in percentages [95% confidence interval] in CWH—nonlesioned hemisphere was 68.8% [41.3-89.0], lesioned: 85.7% [57.2-98.2]; TDC—dominant hemisphere 73.9% [51.6-89.8], nondominant: 82.6% [61.2-95.0]. Distances that exceeded the 3 $\times$ 5 cm electrode sponge area in CWH—nonlesioned was 25.0% [7.3-52.4], lesioned was 28.6% [8.4-58.1]; TDC—dominant was 52.2% [30.6-73.2], nondominant was 43.5 [23.2-65.5]. Distances that exceeded the 5 $\times$ 7 cm electrode sponge area in CWH—nonlesioned was 18.8% [4.0-45.6] and lesioned was 21.4% [4.7-50.8]; TDC—dominant was 21.7% [7.5-43.7] and nondominant was 26.1% [10.2-48.4]. Individual variability in brain somatotopic organization may influence surface scalp localization of underlying M1 in children regardless of neurologic impairment. Findings suggest further investigation of optimal tDCS electrode placement. EEG and TMS methods reveal variability in localizing M1 in children regardless of stroke diagnosis. This study was registered on clinicaltrials.gov NCT02015338.

Keywords

noninvasive brain stimulation; transcranial magnetic stimulation; transcranial direct current stimulation; neuroplasticity; pediatrics; stroke

Introduction

Neurologic injury resulting in weakness on one side of the body, or hemiparesis, affects both adults with stroke (1:350) and children with perinatal stroke (1:3500 live births).¹ One intervention for hemiparesis under investigation is noninvasive brain stimulation (NIBS) to influence cortical excitability and improve motor function. Transcranial direct current stimulation (tDCS) is a form of NIBS that can modulate corticospinal excitability using a weak electrical current between 2 configured electrodes to bias the neuronal membrane potential.² Electrode montages targeting corticospinal excitability at the hand region of the primary motor cortex (M1) may include anodal and cathodal stimulation to the respective lesioned and non-lesioned M1 (bihemispheric montage)³ or stimulation to the lesioned and nonlesioned M1 with a reference electrode on the contralateral supraorbital (SO) region (M1-SO montage).⁴ Although purported polarity-specific effects can be observed wherein anodal electrode montages result in excitation and cathodal electrode montages result in inhibition, reports of polarity-reversal of intended effects have been reported.⁵⁻⁷

Reorganization of the targeted M1 may occur after neurologic injury. For example, the corticospinal tract may (1) retain preserved corticospinal tract integrity (e.g. lesioned

hemisphere contributes to movement of the contralateral “more-affected,” or weaker, hand), (2) reorganize with ipsilateral corticospinal connections (e.g. the nonlesioned hemisphere controls movement of the more-affected hand), or (3) reorganize with mixed corticospinal pathways (e.g. both hemispheres contribute to movement of the more-affected hand).^{8,9}

Although tDCS interventions in adults with stroke hold potential translational application to children with hemiparesis, much is unknown regarding lesions in children and responsivity to tDCS. The timing of the lesion during early brain development can influence the morphology and architectonic changes of the developing brain and accurate somatotopic localization for electrode placement.¹⁰ Multiple tDCS neuromodulation studies in perinatal stroke have targeted the nonlesioned M1 to influence motor development in the more-affected limb with responsivity to tDCS measured by changes in motor function.^{11,12} An individual’s responsivity or lack thereof to intervention may be attributed to stimulation-dependent parameters (dosage, electrode placement, stimulation duration) and network-activity dependent factors (such as lesion timing, lesion location, and reorganization).

Consensus on the method for tDCS electrode placement based on somatotopic localization has not been determined in adults or children. Several noninvasive methods exist to localize M1 including neuroimaging, transcranial magnetic stimulation (TMS) and electroencephalogram (EEG). T1 magnetic resonance imaging (MRI) data can guide M1 localization of anatomical landmarks such as the hand knob.¹³ Task-fMRI provides an indirect measure of neural activity and reflects blood supply to relevant brain regions.^{14,15} TMS is a noninvasive measure of activation of the neuron itself with eliciting a motor evoked potential (MEP) while recording electromyographic (EMG) activity from a muscle of interest to provide information about the excitability of the motor cortex.¹⁶ EEG records electrical activity providing a measure of spatiotemporal pattern of cortical activity.¹⁷ Each of these noninvasive techniques reflects different attributes of neuronal activity therefore the location of M1 may be influenced by the technique utilized.

Electrode placement for tDCS intervention can influence the electric field distribution and current flow for a target brain region.¹⁸ Two common approaches that guide tDCS electrode placement targeting current flow directed toward M1 include head-specific measurements using the International 10/20 EEG coordinate system and the neurophysiologic method of TMS localization of the motor hotspot.¹⁹ Both 10/20 EEG coordinate and TMS methods for determining electrode location are currently utilized within tDCS studies involving motor recovery from stroke.^{3,20}

The 10/20 EEG coordinate system is based on the anatomical relationship of skull dimensions to underlying brain anatomy, thereby approximating the M1 with the EEG coordinate of C3 (left hemisphere) and C4 (right hemisphere) surface electrode coordinates generally recording EEG activity over the precentral gyrus.²¹ Use of EEG coordinates does not take into consideration the individual topographic variability that exists in humans with and without neurological deficits.²² Comparison of the techniques between the 10/20 EEG coordinate system and EMG activity from upper extremity muscles was evaluated in a pilot study on corticomuscular coherence, or degree of connectivity between structures, in

individuals with stroke.^{23,24} Differences in the coherence were noted with significant coherence to C3 or C4 for the less-affected, or stronger, limb only.²³

Populations in which the morphology and neurophysiology is altered due to neurological conditions like stroke, an enhanced understanding of the correspondence of electrode placement to underlying brain structures can guide placement. Reliable spatial resolution of electrode placement to target brain regions is integral to allow for consensus on optimal electrode placement for directed current flow to the M1 region for hand representation. The purpose of this study is to compare 2 methods (10/20 EEG C3/C4 coordinate and TMS motor hotspot) for somatotopic localization of M1 for hand representation in children aged 8 to 17 years in 2 groups: (1) children with hemiparesis and (2) children who are typically developing without a history of a neurological condition. We hypothesize a difference in 10/20 EEG and TMS-locations in children with hemiparesis and no difference in locations in children with typical development.

Methods

Participants

Participants aged 8 to 18 years were enrolled in this study. Participants were recruited through targeted flyers and physician letters to identify a population of children and young adults with and without hemiparesis. Written consent and assent was obtained from all legal guardians and participants, respectively. Inclusion criteria were group specific.

Participants with hemiparesis were included if they (1) were aged between 8 and 18 years, (2) had a diagnosis of periventricular leukomalacia (PVL) or perinatal stroke was confirmed by imaging, and (3) had no reported seizures within the past 2 years. Children with bilateral PVL were included if the child had a clinical presentation of unilateral weakness. The control group participants were included if they (1) were aged between 8 and 18 years, (2) had a caregiver verification statement of well-being (i.e. no neurological diagnoses), and (3) had no limitations in hand function. Exclusion criteria for *both* groups included the following: (1) contraindications for TMS (e.g. metal in the head, pregnancy), (2) contraindicated medical conditions (eg. presence of metabolic disorders, neoplasm, active epilepsy, disorders of cellular migration and proliferation, psychiatric disorders, hemiparesis secondary to acquired traumatic brain injury, and attention deficit/hyperactivity disorder), (3) communication deficits limiting the ability to respond verbally to safety questions during TMS testing, and (4) botulinum toxin or phenol intramuscular block within 6 months prior to study participation. Data from enrolled individuals who had the absence of a measurable MEP from either hemisphere were excluded. Refer to the supplemental materials for the Consolidated Standards of Reporting Clinical Trials (CONSORT) diagram. This study was approved by the University of Minnesota's Institutional Review Board.

Experimental Procedure

Baseline safety (blood pressure, TMS Tolerance Survey—Modified from Garvey et al,²⁵ and pregnancy test for females) and behavioral measures (grip strength, Jebsen Taylor Test of Hand Function) were completed. Additionally, hand dominance, was determined by the

Edinburgh Handedness Inventory for control group participants. Handedness cannot be appropriately inferred in children with congenital lesions and resultant hemiparesis. All participants were encouraged to continue any prescribed medications but to refrain from consumption of caffeine the day of the study.

Participants were positioned in a semireclined chair with earplugs. Investigators completed the scalp motor cortex measurements on all participants using the 10/20 EEG international system guidelines for C3 and C4.¹¹ A registered electroneurodiagnostic technologist from a pediatric hospital, with level 3 National Association of Epilepsy Center ranking, completed 10/20 EEG measurements on the majority of participants (45/47, 96% of participants). A measurement error of less than 1.0 cm is the clinical standard for proficiency in EEG measurement.²⁶ Because of scheduling conflicts, the principal investigator measured 2 participants (2/47, 4.3% of participants) following previous formal training by the electroneurodiagnostic technologist of which only 1 was included in analysis.

Investigators used a frameless stereotactic neuronavigation (SNN) system to co-register the position of the participant's head to an MRI template data using anatomical landmarks (Brainsight Rogue Research, Quebec, Canada) in 43 of 47 participants (91.5% of participants). Four participants (8.5% of participants) with hemiparesis completed the study using individual anatomical MRI data secondary to concurrent participation in a separate clinical trial. The same procedure of co-registering the position of the participant's head for stereotactic neuronavigation was followed regardless of templated or individual MRI data. In all participants, an SNN instrument pointer was used to record the scalp locations of EEG and TMS-derived locations.

TMS single pulse testing was used to locate the motor cortex hotspot using EMG recordings from the first dorsal interosseous (FDI) contralateral to TMS single pulse stimulation using a Magstim 200 stimulator (Magstim Company Ltd, Dyfed, UK). During single pulse testing, a 70-mm figure-of-eight coil was held tangentially at a 45° angle to the scalp overlying the motor cortex during stimulation to induce a posterior to anterior current flow. A resting motor threshold assessment at the motor hotspot was conducted using a criterion of MEP peak-to-peak amplitude of 50 μ V in 3 of 5 trials. Single-pulse TMS testing was conducted at a frequency of 0.1 to 0.2 Hz.^{27,28} Baseline resting EMG was defined as no EMG activity for 100 ms prior to TMS stimulation. The amplitude of the MEP in the FDI muscle contralateral to stimulation was monitored using surface EMG with stainless steel disc electrodes (Natus Medical Inc, Pleasanton, CA). Distances between the EEG-and TMS-derived locations were recorded both manually using a tape measure between locations marked with a nontoxic marking pen and calculated offline using the exported SNN coordinates.

Because of a change in study location, 2 EMG systems were utilized yet the procedures, gain, and sampling rate were identical. EMG signals were amplified with a gain of 300 μ V and digitized with a sampling rate of 6.4kHz using either a bipolar EMG amplifier (Y03-2, Motion Lab Systems, Inc, Baton Rouge, LA) (gain, 300; bandpass filter, 20-2000 Hz), then digitized by NI 9234 analog-to-digital convertor (National Instruments, Austin, TX), or the Cadwell Sierra Wedge EMG amplifier (Cadwell Laboratories, Kennewick, WA). All EMG

data were monitored in real time and stored in a laptop computer for offline analysis. A standardized questionnaire of symptoms following TMS testing was asked of each participant. Additionally, participants were asked to report any changes in status (eg, fatigue, discomfort, headache) and each participant's general alertness was monitored throughout the TMS session. Safety measures (standardized questionnaire, blood pressure, heart rate) were repeated following TMS testing and a participant and family study satisfaction survey was administered.

Statistical Analysis

Means, standard deviations, medians, and ranges for continuous variables and counts, and percentages for categorical variables were computed for each group. The 3-dimensional (3D) distance between the EEG location and motor hotspot location was compared between lesioned and non-lesioned hemisphere for the hemiparesis group and inferred dominant and nondominant hemispheres based on the Edinburgh Handedness Inventory for the control group. Descriptive statistics were computed for the distance between the 3D EEG location and motor hotspot location from SNN using the Euclidean distance between 2 points in a 3D space, $d = \sqrt{(X_2 - X_1)^2 + (Y_2 - Y_1)^2 + (Z_2 - Z_1)^2}$. Here, the x -axis was oriented laterally on the head, the y -axis was from posterior to anterior on the head, and the z -axis was from inferior to superior on the head. The reference point was the individual EEG location on each hemisphere.

The distances between the EEG location and the TMS-derived motor hotspot for each person were categorized into 3 separate binary variables based on whether the distance exceeded the dimensions of a 2.5×2.5 cm conductive rubber electrode, a 3×5 cm electrode sponge, and a 5×7 cm electrode sponge. A 2.5×2.5 cm conductive rubber electrode would be covered in a 3×5 cm sponge. A 95% confidence interval (CI) was computed for each binary variable based on an exact binomial distribution. Comparisons of the proportion exceeding the 3 different dimensions were compared using McNemar's Test between hemispheres by group and comparisons across groups were compared using Fisher's exact test. Because of the orientation of the 3D axes, the anterior or posterior distance was used for determining whether the distance between the EEG location and the TMS-derived motor hotspot exceeded the width of the rubber electrode (2.5 cm) and/or electrode sponge (3 cm, or 5 cm). The hypotenuse of a triangle using the difference between the x -coordinates and the z -coordinates between the EEG location and the TMS-derived motor hotspot was used to determine whether the difference exceeded the length of the rubber electrode (2.5 cm) and/or electrode sponge (5 cm, or 7 cm) by approximating the curvature of the head. Note that this distance is conservative because the nonlinear distance between the EEG location and the TMS-derived motor hotspot will always be equal to or greater than the linear distance. Raw coordinate data were exported from SNN to create a 3D plot of distances from the EEG location to the TMS-derived motor hotspot. The origin was used as the center point for the plots and the differences between the EEG location and the TMS-derived motor hotspot were computed to draw 3D segments to show the relative distance and orientation between the C3 or C4 location and the TMS-derived motor hotspot point for each individual. To facilitate plotting by affected side or dominant hand, the difference on the x -axis between the EEG location the TMS- derived motor hotspot was computed as the algebraic inverse for

points that were shifted to the opposite side of the head. All analyses were computed using R statistical software.²⁹

Results

Forty-seven participants enrolled in the study including 21 participants with congenital hemiparesis and 26 participants with typical development who served as a control group. Sixteen participants in the hemiparesis group and 23 participants in the control group had data appropriate for analysis. Participants in both groups were excluded from analysis for multiple reasons. Of the participants with hemiparesis, 5 participant's data were excluded from analysis. Two participants were excluded due to technical error using SNN, 2 participants were excluded due to poor T1 MRI data acquisition from a concurrent clinical trial, and 1 participant did not have an MEP on either hemisphere. Four additional participants with hemiparesis lacked an ipsilesional MEP. Of the participants in the control group, 3 participant's data were excluded from analysis. Two participants were excluded due to technical errors using SNN and 1 control group participant was excluded following consent and assent secondary to arriving with a cast on one upper limb from an injury unrelated to research. Baseline characteristics reporting gender, age, side of hemiparesis, or hand dominance are reported in Table 1.

In all participants, regardless of group or hemisphere, the TMS-derived hotspot location was not equivalent to the EEG location. Within-hemisphere distances between the EEG and TMS-derived motor hotspot are shown in Table 2. The general direction of the TMS-derived location with respect to the 10/20 EEG location was medial-posterior or medial-anterior in both groups. However, not all TMS-derived locations followed this general direction regardless of hemisphere or group.

The 3D plot displays a superior-inferior view of the 10/20 EEG and TMS-derived motor hotspot locations with distances between the 2 locations denoted by adjoining lines. Data are displayed with dominant and nondominant data in the control group participants (Figure 1a and b) and lesioned and nonlesioned data in participants with hemiparesis (Figure 1c and d).

The primary outcome of determining the proportion of children whose distances are within or outside of the electrode area requires consideration of the 2.5×2.5 cm rubber electrode and the 3×5 cm or 5×7 cm electrode sponge. For the rubber electrode, in using the methodology of placing the center of the rubber electrode on a designated location, the majority of participants, regardless of the presence of a stroke lesion, demonstrated differences in distances greater than 1.25 cm for location of the M1 hand region when comparing between the 10/20 EEG C3/C4 coordinates to TMS-derived hotspot (children with hemiparesis—nonlesioned: 68.8% [95% CI 41.3-89.0], lesioned: 85.7% [95% CI 57.2-98.2], typically developing controls—dominant: 73.9% [95% CI 51.6-89.8], nondominant: 82.6% [95% CI 61.2-95.0]). For the 3×5 cm electrode sponge, a smaller proportion of children exceeded the area of the sponge (children with hemiparesis—nonlesioned: 25.0% [95% CI 7.3-52.4], lesioned: 28.6% [95% CI 8.4-58.1]; typically developing controls—dominant: 52.2% [95% CI 30.6-73.2], nondominant: 43.5 [95% CI 23.2-65.5]). For the 5×7 cm electrode sponge, an even smaller proportion of children

exceeded the sponge area due to the increased size of the electrode (children with hemiparesis—nonlesioned: 21.4 [95% CI 4.7-50.8], lesioned: 18.8% [95% CI 4.0-45.6]; typically developing controls—dominant: 21.7 [95% CI 7.5-43.7], nondominant: 26.1 [95% CI 10.2-48.4]). No significant association within hemisphere was found comparing the proportion exceeding the 2.5×2.5 cm electrode ($P = .617$, typically developing children; $P = .371$, children with hemiparesis), 3×5 cm sponge ($P = .617$, typically developing children; $P = .683$, children with hemiparesis) or 5×7 cm sponge ($P > .999$, both groups). No significant association across groups was found comparing the proportion exceeding the 2.5×2.5 cm electrode ($P > .999$, non-dominant or lesioned hemisphere; $P = .734$, dominant or non-lesioned hemisphere), 3×5 cm sponge ($P = .491$, nondominant or lesioned hemisphere; $P = .111$, dominant or nonlesioned hemisphere) or 5×7 cm sponge ($P > .999$, both respective hemispheres). Of the 2 participants measured by the principal investigator, 1 child was excluded as the child was unable to tolerate full motor hotspot TMS testing. Removing the other child measured by the principal investigator did not change the results.

Because of the size of the groups, there is a lack of statistical power to test the association between distance and hand function and the following comparisons are considered exploratory. No significant association was observed between distance and timed scores on the Jebsen Taylor Test of Hand Function in the subgroups children with hemiparesis nonlesioned hemisphere ($P = .800$) and lesioned hemisphere ($P = .760$) and typically developing controls dominant hemisphere ($P = .820$) and non-dominant dominant hemisphere ($P = .500$). No significant association was observed between the distance and grip strength in the subgroups children with hemiparesis lesioned hemisphere ($P = .613$), and typically developing controls dominant ($P = .810$) and nondominant ($P = .920$). A significant association was observed comparing the distance and grip strength for the children with hemiparesis on the lesioned hemisphere ($P = .028$); however, this was primarily due to an observation that was outside range of observed values for the other participants.

Discussion

This study leveraged SNN to compare the location of the M1 hand region using TMS and 10/20 EEG methods. Children from both groups had observed distances between the M1 hand region when evaluated with 2 methods that exceeded the dimensions of tDCS equipment including the 2.5×2.5 cm rubber electrode, the 3×5 cm electrode sponge, and the 5×7 cm electrode sponge. As the dimensions of the hypothetical tDCS equipment increased, fewer children displayed a TMS-derived motor hotspot outside of the target (ie, the larger the tDCS equipment, the smaller proportion of children outside of the target).

The variability in distance observed in both groups of children was unpredictable as children with hemiparesis demonstrated greater ranges in the distance between the 10/20 EEG coordinates and the TMS hotspot (eg, the largest range was observed in children with hemiparesis in the nonlesioned hemisphere [0.29-13.92]), yet higher proportions of control participants exceeded the 3 established cutoff points (26.1% of typically developing controls [nondominant hemisphere] exceeded all 3 cutoff points compared with 21.4% children with hemiparesis [lesioned hemisphere]). The distances observed in both groups of children exceeded the ranges previously reported in an adult study that evaluated the MEP center of

gravity with respect to the EEG location. Although the TMS methodology differs in the adult study, we observed that differences in EEG and TMS-derived locations exist regardless of age.³⁰

In children with hemiparesis, the lesion could affect the location of the TMS-derived motor hotspot in both hemispheres due to reorganization. Specific to bilateral PVL, it could be argued that both M1 locations may be altered due to a bilateral lesion. In typically developing controls, developmental maturation may have influenced the TMS-derived motor hotspot; however, we did not observe this in our study. Because of limited sample size, we are not powered to conclusively demonstrate the lack of a clinically significant association between age and distance from the EEG location to the M1.

Depending on the methodology of placing the center of the rubber electrode or the sponge electrode on the determined location, a distance discrepancy between the EEG C3/C4 coordinates to the TMS-derived hotspot exceeding either of those cutoff points may impact the influence of M1 targeted current stimulation. For the hotspots located medial-posterior to the EEG C3/C4 locations, stimulation from tDCS using a montage referenced with C3/C4 coordinates may potentially provide sub-maximal stimulation of the M1 hand region. The use of tDCS at locations not centrally placed over the hand region of M1 may contribute to interparticipant variability and decreased the efficacy as a therapeutic intervention. As we were unable to fully test the association between distance and function in children, future studies exploring this association are indicated.

Despite the potential clinical applicability of tDCS for individuals with stroke, an accepted methodology for tDCS electrode placement does not exist. The 10/20 EEG coordinates, although originally designed to record population networks of neuronal electrical activity underlying the scalp, have been applied to guide NIBS input to selected brain regions.³¹ EEG, as used in clinical and research applications, records depolarization of grouped populations of neurons, with a single 10/20 EEG coordinate recording from a population of 100 000 neurons over a volume per cubic millimeters of brain tissue.¹⁷ The use of the 10/20 EEG coordinates to guide targeted current flow to specific brain regions, such as the hand representation of M1 region, may be limited by the assumption that superficial EEG scalp coordinates provide an accurate anatomical localization of underlying cortical structures.

The applicability of EEG coordinates to accurately identify specific brain regions may be particularly affected by such neurologic conditions such as pediatric stroke, wherein lesion size and cortical reorganization may change over time. For example, an intraventricular hemorrhage can evolve into cystic encephalomalacia over several months following birth, which could negatively impact the predictability of somatotopic localization.³² The propensity of cerebrospinal fluid filled regions to “shunt” electrical current can create unanticipated electric field hotspots within the brain, potentially compromising the established safety and tolerability of tDCS using the 10/20 EEG electrode placement.^{19,33} Single participant modeling in a typically developing child revealed the peak electrical fields from conventional stimulation intensities (2 mA) were nearly twice as high in the child as compared with adults for a given stimulus intensity.³⁴

As this study was not constructed with individual MRI data, we were limited to comparing the participants in the navigational software space instead of the native scanner or MNI (Montreal Neurological Institute) standard space.³⁵ The neuro-navigation software space serves as a reference to provide relative distance information. In a recent software update (Brainsight 2.3.1), there is this ability to register a participant to a MNI-152 standard template which would allow for the collection of coordinate data relative to a templated head for future studies.

The Euclidean distance in 3 dimensions (ie, straight line) is a limitation of this study related to the use of a common MRI brain template as opposed to individual T1 data allowing for the length of the arc, wherein an arc would require consideration of the convexity of the skull and thickness of the skin, skull, and cerebrospinal fluid volume. In 4 participants with hemiparesis, individual 3.0-T MRI data was available due to concurrent clinical trial participation. Future studies with individual MRI data should include cortical surface-based analyses to provide identification of the hand area of M1 while accounting for variability in structural anatomy and functional connectivity.

Individual T1 data allow for individual stereotactic neuronavigation providing a relative position of the TMS coil with respect the cortex. However, 2 of the 4 participants with individual MRI data did not tolerate the MRI procedure well due to anxiety and involuntary movement. Poor tolerance for the MRI procedure resulted in movement artifact in the T1 images and exclusion from analysis in this study. SNN is unable to compensate for poor T1 data acquisition therefore a tape measurement between the 2 locations on the scalp could be more reliable for children who do not tolerate MRI scanning procedures well.

A contributing factor of the location difference could be the error rate of the 10/20 EEG measurements. In a small sample of four adults and the 10/20 system, 1 rater demonstrated an average within-session variability of 1.4 mm and between-session error of 2.5 mm due to head measurements done on different days.³⁶ Although there is a potential for EEG measurement error in our study, this is not likely explanation for the distances observed between the 2 locations given the high proportion of children in both groups exhibiting a difference in location.

Another potential factor of the location differences could be the precision of the EEG coordinates to approximate the intended hand area of M1. The location of C3 and C4 can record underlying neuronal electrical activity of both the pre- or post-central gyrus.³⁷ The 10/20 EEG C3/C4 locations may in fact represent M1 but not the hand representation sought for this study.

Conclusion

Intervention studies using tDCS targeting motor recovery commonly place the electrodes in locations based on the C3 and C4 locations of the 10/20 EEG system. In this study, comparing the locations of the 2 measurement techniques in children with hemiparesis and typically developing children, we observed variability in both groups as to the surface localization for underlying hand region of M1. In all participants, regardless of the presence

of a stroke lesion, the 10/20 EEG and the TMS-derived motor hotspot location differed to some degree. The TMS-hotspot for the majority of children was outside the perimeter of the 2.5×2.5 cm rubber electrode. In a smaller proportion of children, the perimeter also exceeded the electrode sponge.

Based on our findings, clinical populations have added challenges for electrode placement. Without the guidance of TMS, it is difficult to assess how the location of M1 will be influenced by inter-individual variability in anatomy.³⁸ Myelination, functional connectivity,³⁹ and development may influence the location of M1. Without the guidance of TMS, the structures have unknown integrity. Studies on methodology and longterm follow-up will be essential in clarifying the individual effects and influence of tDCS target location on the developing brain.

As this study did not assess efficacy of tDCS intervention at the different locations, future studies with larger samples could evaluate the influence of stimulation and current distribution, both on reproducibility of neurophysiologic effects of cortical excitability and the behavioral impact on motor recovery. Further investigations of the optimal tDCS electrode placement is indicated given the proportion of children we found with TMS-derived M1 locations outside both the defined boundaries of a typical tDCS electrode and sponge.

Acknowledgments

We thank the following graduate students: Shannon Groth, SPT; Nessa Johnson, PhD(candidate); Katelyn Kubat, SPT; Kaitlyn Lorschach, DPT; Josa Martin, SPT; Stephanie Mathiowetz, DPT; Carly McQuillan, DPT; Joshua Meuwissen, DPT; Timothy Miller, SPT; Stephanie Morse, SPT; Karen Myhrman, SPT; Nik Sell, SPT; and Andrea Tobias, SPT. Finally, and most important, we are grateful to the children and families who participated in this study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health (K01–1K01HD078484-01A1); KL2 (UL1 RR033184 and 1KL2RR033182); the National Center for Advancing Translational Science (NCATS) Award (UL1TR000114); the Center for Magnetic Resonance Research (University of Minnesota) Grant (P41 EB015894); Minnesota's Discovery, Research, and Innovation Economy (MnDRIVE) Fellowship; and the Center for Neurobehavioral Development (University of Minnesota).

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Figure 1.

Three dimensional plots of the shifted distance between the EEG coordinate (black) and the transcranial magnetic stimulation (TMS)-derived motor hotspot (gray) with the coordinates represented by ear-to-ear (X coordinate), posterior-to-anterior (Y coordinate), and inferior-to-superior (Z coordinate). Distance represents unscaled distance and is reported in centimeters. (a) Dominant hemisphere of typically developing children. (b) Nondominant hemisphere of typically developing children, (c) Lesioned hemisphere of children with hemiparesis, (d) Nonlesioned hemisphere of children with hemiparesis. Ant, anterior; Inf, inferior; Pos, posterior; Sup, superior.

Table 1

Participant Characteristics by Group.

	Participants With Hemiparesis	Control Group Participants
N (% of total)	16 (41.0)	23 (59.0)
Sex, n (%)		
Male	9 (56.2)	8 (34.8)
Female	7 (43.8)	15 (65.2)
Age, y		
Mean (SD)	14.0 (2.6)	13.9 (3.4)
Median [range]	14.5 [9.6, 17.9]	13.6 [8.2, 18.6]
Side of hemiparesis, n (%)		
Right	10 (62.5)	NA
Left	6 (37.5)	NA
Hand dominance, ^a n (%)		
Right	NA	22 (95.7)
Left	NA	1 (4.3)

Abbreviations: SD, standard deviation; NA, not applicable; y, years.

^aHand dominance was determined by the Edinburgh Handedness Inventory.

Table 2

Within-Hemisphere Distances Between 10/20 EEG and TMS-Derived Motor Hotspot of the Primary Motor Cortex.

	Participants With Hemiparesis		Control Group Participants	
	Nonlesioned	Lesioned	Dominant	Nondominant
N (% of group)	16 (100)	14 (87.5)	23 (100)	23 (100)
Distance, Euclidean (3D), cm				
Mean (SD)	3.16 (3.48)	2.28 (1.12)	2.81 (1.45)	2.96 (1.73)
Median [range]	2.02 [0.29, 13.92]	2.40 [0.76, 4.66]	2.53 [0.70, 5.24]	2.29 [0.98, 6.43]
% Exceeding electrodes ^a (2.5 × 2.5cm), [95% CI]	68.8 [41.3, 89.0]	85.7 [57.2, 98.2]	73.9 [51.6, 89.8]	82.6 [61.2, 95.0]
Yes, n (%)	11 (68.8)	12 (85.7)	17 (73.9)	19 (82.6)
No, n (%)	5 (31.2)	2 (14.3)	6 (26.1)	4 (17.4)
% Exceeding sponge ^a (3 × 5 cm), [95% CI]	25.0 [7.3, 52.4]	28.6 [8.4, 58.1]	52.2 [30.6, 73.2]	43.5 [23.2, 65.5]
Yes, n (%)	4 (25.0)	4 (28.6)	12 (52.2)	10 (43.5)
No, n (%)	12 (75.0)	10 (71.4)	11 (47.8)	13 (56.5)
% Exceeding sponge ^a (5 × 7 cm), [95% CI]	18.8 [4.0, 45.6]	21.4 [4.7, 50.8]	21.7 [7.5, 43.7]	26.1 [10.2, 48.4]
Yes, n (%)	3 (18.8)	3 (21.4)	5 (21.7)	6 (26.1)
No, n (%)	13 (81.2)	11 (78.6)	18 (78.3)	17 (73.9)

Abbreviations: EEG, electroencephalogram; TMS, transcranial magnetic stimulation; N: Number of participants with a motor evoked potential on the hemisphere assessed, SD, standard deviation.

^aPercentage of group where the distance between the EEG and TMS-derived motor hotspot exceeds the electrodes (distances that exceed 1.25 cm using the center to the perimeter of a 2.5 × 2.5 cm rubber electrode) and exceeds the electrode sponge (distances that exceed 2.91 cm using the center to the perimeter of a 3 × 5 cm electrode sponge and 4.30 cm using the center to the perimeter of a 5 × 7 cm electrode sponge) as reported with 95% confidence intervals (95% CI).