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Is Transcranial Electrical Stimulation (TCES) a Safe Intervention for Children with Cerebral Palsy?

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We tested the safety of transcranial electrical stimulation (TCES) applied to seven children (age range 2.5 to 7.5 years) with a confirmed diagnosis of cerebral palsy (CP). Adverse responses were assessed by negative changes in the gross motor function measure test (GMFM), the popliteal angle, and the occurrence of any undesired systemic responses such as seizure, nausea, vomiting, or sleep disruption. The tests first were given before the commencement of a physical therapy exercise (PTE) program combined with a home program of TCES. The tests were repeated after 8 weeks of PTE + TCES and once again after an additional 8 weeks of PT + TCES. One of the 8-week periods involved placebo stimulation in a double-blind design. Stimulator amplitude was 0.5 mA of peak current, phase charge was 0.0166 μC, and the averaged RMS current was 249 microamperes. This level was below threshold of sensory nerve excitation, and the child did not perceive the stimulation. Electrodes were placed over the right and left temporal areas of the skull. The stimulation was applied by the parents for 10 minutes, twice a day, 7 days each week. The total goal GMFM scores were greater after both active and placebo stimulation. The popliteal angle improved irrespective of the stimulation intervention. No adverse systemic responses were reported. These results support the hypothesis that TCES as used in this study is a safe procedure. **Key Words:** Transcranial electrical stimulation—Safety—Cerebral palsy.

Sensorimotor dysfunction associated with cerebral palsy (CP) circumscribes the ability of the affected child to perform age-appropriate gross and fine motor tasks and greatly impedes performance of normal daily activities. There are many treatment programs to help reduce disability and neurologic dysfunction for victims of CP but few produce satisfactory results. New suggestions for treatment are needed but careful assessment for safety and effectiveness must be done before they can be recommended. The suggestion that TCES may produce benefits has been reported.

A number of studies have examined the efficacy of neuromuscular electrical stimulation (NMES) in the management of children with CP. A few of these investigations reported significant improvements in muscle strength and functional performance, including ambulation and manual skills (1–8).

Recently a new approach to the management of children with CP using TCES has been tried. The stimulating electrodes were placed transcranially and a peak current of less than 2mA was applied directly over the frontotemporal regions of the skull for periods of up to 45 minutes (9,10). Malden and Charash (9) transcranially stimulated a sample of 20 children with CP. Each child was given 6 weeks of stimulation followed by 6 weeks of placebo stimulation, or placebo first followed by active stimulation. The children's progress was assessed using the Malden Gross Motor Rating Scales. The authors re-

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ported significant improvement during the active stimulation versus the placebo of nonelectrical exercise periods. Similarly, Okoye and Malden (10) studied 16 subjects with CP and compared the effects of occupational therapy (OT), OT once a week plus home program of exercise, and OT once a week plus home program plus TCES. Four subtests selected from standardized sensory integration and hand function tests were used as measures of change. They reported a significant gain in motor function of the dominant extremities following TCES. Neither Malden and Charash (9) nor Okoye and Malden (10) reported any adverse reactions or drop out.

One possible way by which TCES may influence the central nervous system (CNS) is a direct consequence of the electric current passing through the brain parenchyma. Rush and Driscoll (11) have estimated that 45 percent of transcranially applied current passes through brain tissue. Dymond and colleagues (12) stimulated patients transcranially with a monophasic pulsed current, at a frequency of 100 pulses per sec and peak current up to 1.5 mA. Recording directly from sites in the hippocampal formation, these investigators measured membrane potential differences in the range of 0.5 to 27 millivolts. The latter data suggest that only approximately 5 percent of the voltages applied transcranially produce alterations in neurobiologic activity within the brain. It is probable that transcranially conducted electrical current stimulates neural activity wherever the electrical charge and its density are sufficient to vary the excitatory state of susceptible neurons. Several studies have reported an effect of TCES on production and/or release of neurotransmitters, neuromodulators, and/or neurohormones (13–15). These substances have been shown to have both short-term and long-term effects on neuronal circuits through primary and secondary messenger systems (16,17).

TCES may cause deleterious effects on the CNS. McCreery and associates (18,19) applied electrical stimulation directly over intact brain tissue and demonstrated that excessive amounts of both phase charge and phase charge density caused overt local damage to nerve cells. It is important to note that only when an electric current is applied directly over the brain tissue can calculations of phase charge and charge per phase density can be obtained reliably. During or following clinical application of transcutaneously conducted current, it is virtually impossible to determine with any confidence the amount or the density of the phase charges that actually directly reach brain tissues. Knowing the quantities of phase charge delivered by the stimulator is of limited value because the specific conductivity of the various tissues between the electrodes is nonuniform and unknown. So although ionic charges are conducted between the electrodes, the actual amount of charges that directly affect neuronal tissues and, more important, where these charges are condensed or dispersed is likely to remain unknown when TCES is applied clinically. The potential harmful effects of this procedure should be considered carefully so they may be weighed against the reported benefits of TCES. (9,10,15,20,21)

The purpose of this exploratory study was to examine the safety of transcranial stimulation when applied twice daily over 8 consecutive weeks to children with medically confirmed CP. Adverse reactions were assessed through monitoring of symptoms of nausea, vomiting, and sleep disruption; deterioration of motor function; changes in the popliteal angle; and the occurrence of seizures.

Methods

This double-blind cross-over design study was conducted at Pediatric Physical Therapy Services, a private practice located in Springfield, Virginia, U.S.A. The patients were selected from the pool of children who were undergoing a comprehensive physical therapy training (PTT) program. During the first 8 weeks of the study, each child received twice-daily TCES or placebo transcranial electrical stimulation (PTCES) followed by another 8 weeks during which the real and placebo stimulations were reversed. Neither the child, family, therapist, nor assessor were aware of which of the 8 weeks involved real or placebo intervention, thus ensuring a double-blind design. Throughout the 16 weeks of real or placebo stimulation, the children continued with their individualized PTT program.

Subjects

Seven children who had a medically confirmed diagnosis of CP were included in this study. Each child served as his or her own control. The children's personal data are summarized in Table 1. Four were classified as having moderate diplegia. Two of these children ambulated with a walker, one with crutches, and one without any assistive device. The other three children had quadriplegia, and all were severely involved and nonambulatory. One of the three also had athetoid movements. The ages of the children ranged from 2.5 to 7.5 years. All were prescreened for receptive, language, and cognitive ability. Before inclusion, each child's caregiver agreed to comply with the specified daily stimulation procedure. Those who qualified signed a parent/guardian consent form approved by the University of Maryland Institutional Review Board. (IRB No.842092-059202). The

Table 1. *Subjects clinical profile*

Subject (years)	Age	Diagnosis Status	Severity Status	Ambulation	Initial Goal GMFM
1	4.0	Spastic Di*	Moderate	Independent	70.3
2	7.5	Spastic Di	Moderate	Crutches	43.0
3	4.5	Spastic Di	Moderate	Walker	36.7
4	4.0	Spastic Di	Moderate	Walker	52.8
5	5.0	Spastic Quad#	Severe	None	42.0
6	4.5	Spastic Quad	Severe	None	8.0
7	2.5	Spastic Quad plus Athetoid	Severe	None	36.0

* Di = Diplegia, # Quad = Quadriplegia

protocol for this study was approved by the University of Maryland Institutional Review Board.

Assessment

Before initiation of the stimulation protocol, each child was assessed by the same independent assessor who was qualified to administer the GMFM test. The GMFM has been shown to be a valid indicator of motor function performance (22–24). The test consists of five performance domains: (1) lying and rolling, (2) sitting, (3) crawling and kneeling, (4) standing, (5) walking , running, and jumping. The children were tested a second time before the cross-over phase of stimulation and a third time at the end of the second stimulation period.

To indirectly assess the amount of spasticity and soft tissue shortening combined, the popliteal angles at both knees were measured. Measurements were made while the child lay supine with the hips at 90 degrees. An inclinometer was placed over the tibial crest; the knee was passively extended as much as possible, and the angle was recorded (Figure 1). Possible seizures, symptoms of nausea, vomiting, sleep disruption episodes, and any other unusual behaviors were monitored by the parents and tabulated in a chart each day.

Treatment Procedure

The treatment program consisted of a combination of PTT and TCES. Each child received a comprehensive PTT program tailored to his or her level of motor development. A typical PTT program included facilitation of movements necessary for transitions between various postures, balance/equilibrium, and functional training of mobility, locomotion, and activities of daily living. Each PTT session lasted 50 to 60 minutes and was provided from one to three times per week, depending on the family's ability to participate. The parents/guardians also were instructed in a home exercise regimen and therapeutic handling of the child.

TCES was provided by a cranial stimulator model SBL 201-M (Medi Consultants, Paterson , NJ). This particular unit delivers monophasic pulses, with a carrier frequency of 15 KHz, phase duration of 33.3 microseconds, and interpulse interval of 33.3 microseconds. The pulsed current was time modulated first into 500 Hz, then again into 15 bursts each lasting 50 milliseconds and separated by interburst intervals of 16.6 milliseconds (Figure 2). All of the aforementioned stimulation parameters remained constant during the study. The stimulus amplitude was set at 0.5 milliamperes of peak current. The preceding parameters represented 0.0166 μCoul of phase charge and 249 μAmp of averaged root mean square (RMS) current (Coul/sec). This level of stimulation was chosen because it is below the threshold of sensory nerve excitation, so the child did not

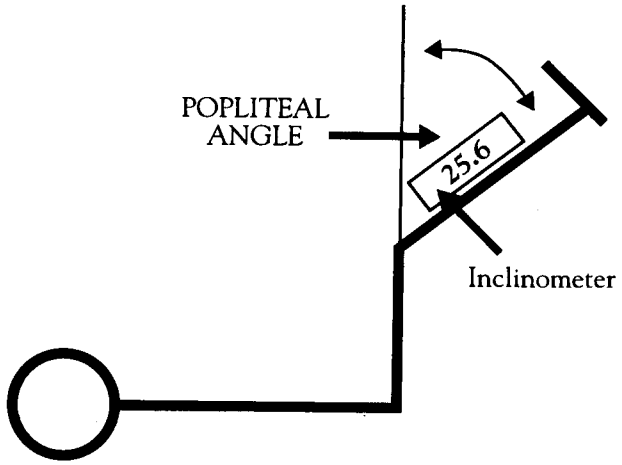

Figure 1. Measurement of knee joint (popliteal) angle.

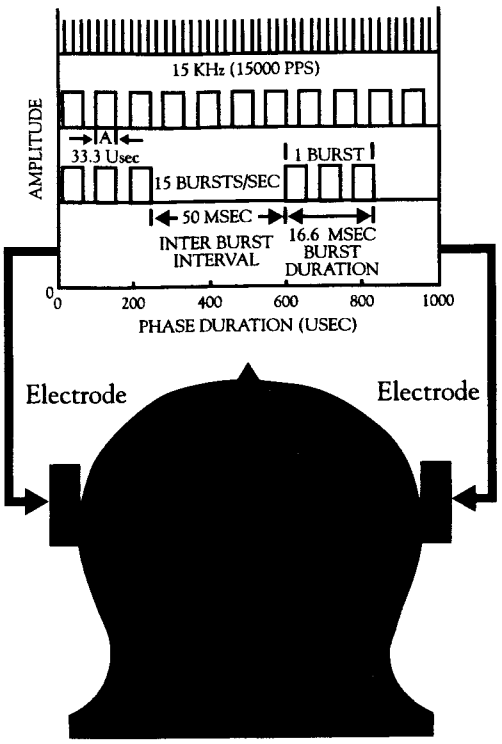

Figure 2. Parameters of the TCES unit. A = duration of a single phase. The internal frequency of 15 KHz is modulated twice so the pulsed current is delivered as 15 bursts per sec. Each burst lasts 16.6 msec.

perceive the stimulation. The electrodes were made of a stainless steel base (diameter 3.8 cm), covered with a water-wet sponge held in a rubber cup. One electrode was placed over the right temporal area of the skull in front of the ear, and the other electrode was placed on the opposite side of the skull in the same location (Figure 2).

During the child's first session in the clinic, the parents were instructed how to apply and operate the stimulator. Thereafter, the child received stimulation at home, twice a day, for 10 minutes in each session, 7 days a week. After a total of 8 weeks, the stimulator was replaced and the second period of 8 weeks stimulation was begun. A log was provided so that the parents could write the dates and time when the stimulation was given, and document any observed adverse response.

Data Analysis

The scores of the individual GMFM domains that were set as treatment goals for the individual child were tabulated, and the goal total of all the domains combined were calculated (22–24). Data were tabulated for each of the three test periods. The first test provided baseline performance before the initiation of TCES. The second test followed the first 8 weeks of stimulation (active or placebo). The final test was performed at the end of the second 8-week period of stimulation. GMFM data derived after the active stimulation period were compared with those of the placebo stimulation period by calculating the percent change (PC) relative to the baseline values using the formula:

$$PC = \frac{\text{test 2 (or 3)} - \text{baseline}}{\text{Baseline}} \times 100$$

Descriptive statistics for all seven children during the placebo and real stimulation were obtained using the PC values.

Results

All children tolerated the active stimulation procedure well. There were no reports of seizures, episodes of nausea or vomiting, or sleep disruption by any of the participating children or their parents. The percent change in GMFM goals scores (22,24), during the placebo and active stimulation periods is illustrated in Figure 3. Six of the seven children improved during the active and placebo stimulation periods. Only one child had slight functional deterioration, which occurred during the placebo term. The mean and standard deviations of improvement of the groups were 28.2 ± 12.3 percent during active stimulation and 19.7 ± 13.1 during the placebo period, showing no effect on motor performance. The coefficients of variation were 0.43 and 0.66 for the active and placebo periods, respectively, indicating more consistent improvement during active TCES.

The popliteal angle of the right and left knees increased after both active and placebo TCES, as seen in Figure 4. The mean deficiency in popliteal angle of both knees was 57.9 degrees at study onset. This was reduced to 28.6 degrees after active stimulation and 32.9 after placebo stimulation. Relative to baseline measurements, these represented 50.6 percent and 43.2 percent improvement after the respective interventions of active and placebo stimulation. None of the children had a decrease in popliteal angle.

Discussion

This is the first report to carefully determine the safety of TCES applied to children with confirmed CP. This study is the first step in the goal of determining the specific clinical benefits of such stimulation. The fact

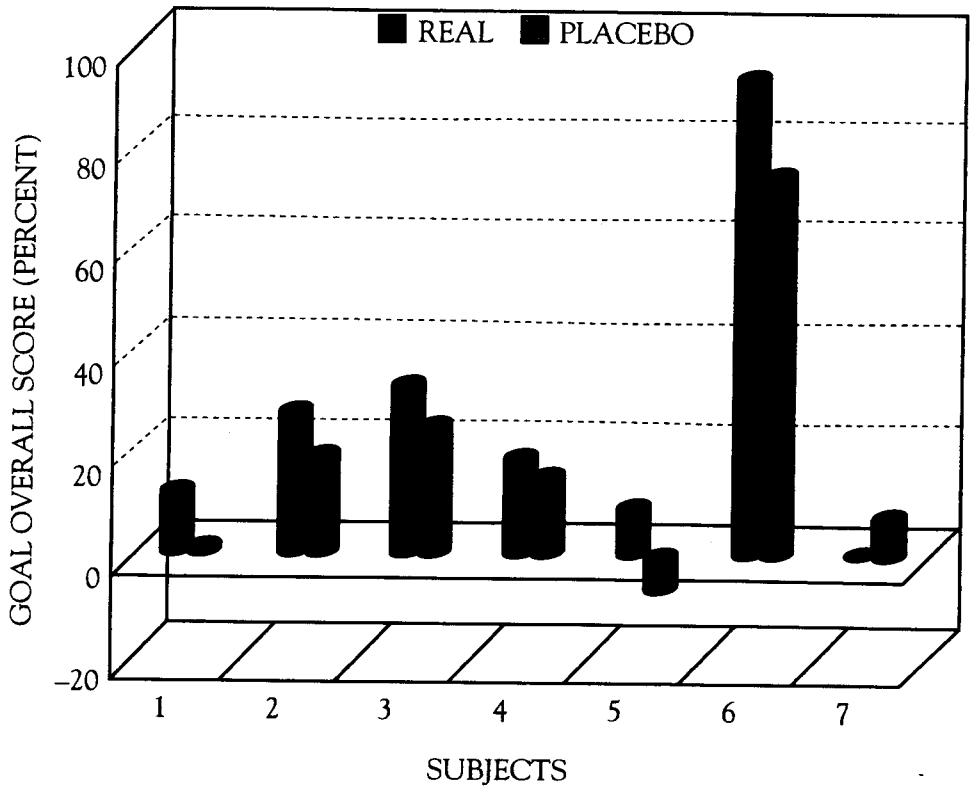

Figure 3. The GMFM percent change in goal score after the real and placebo stimulation periods. Only subject 5 showed slight deterioration but only after the placebo period.

that no adverse systemic reactions such as seizures, nausea, vomiting, or sleep disruption episodes were reported, and no evidence of any added neuromuscular impairments were found is promising. A most important factor that must be considered in the safety in using TCES is the amount of phase charge and the average RMS current(Coul/sec). High levels of these parameters have been associated with neural and other tissue damage (18,19). Other important factors include treatment time (both per session and number of sessions), electrode size, and placement location. In this investigation very low phase charge (0.0166 μCoul) and average RMS current magnitude (249 μAmp) were used. Previous reports have not reported these relevant stimulus parameters. The studies of both Malden and Charash (9) and Okoye and Malden (10) used the same stimulator as in this study. In contrast, Childs and Crimson (20), and Smith and co-workers (21) used a stimulator that delivered a sinusoidal continuous alternating current. At their reported peak current intensity of 1.5 mAmp, the phase charge may be calculated as the product of 65 percent of the peak current, multiplied by the phase duration. Phase duration may be calculated as the reciprocal of twice the frequency, which they reported to be 100 Hz. We estimate that these authors delivered a stimulus phase charge up to 4.87 μCoul and an average RMS current of up to 487.5 μAmp. These values are appreciably higher than those used in this study. These investigators also did not report any deleterious signs or symptoms. This difference in stimulus strength raises the question of the level of stimulus parameters that may cause adverse reactions.

The duration of each treatment episode may be a factor in causing beneficial or undesired responses. In this investigation, a conservative period of 10 minutes twice daily was used, as was done by Malden and Charash (9) and Okoye and Malden (10). In a single case study, Childs (15) stimulated for 20 to 40 minutes three times per day without reporting adverse reactions. Smith and colleagues (21) stimulated survivors of traumatic brain injury with TCES for 45 minutes daily over 6 weeks, and reported significant improvement in mood profile. Only one seizure was reported in this study, and it occurred during the placebo stimulation period. Smith and colleagues (21) studied a group who received stimulation at an intensity above sensory threshold or level of perceived stimulation, but no side effects were noted. Stimulation at levels perceived by the patient are likely to cause stimulation of one or more of the mixed cranial nerves, which may lead to additional indirect input to higher CNS centers (25).

Determining the maximum stimulation time both within session and cumulatively over days, without inflicting significant adverse reaction, is an important task of future research. The accumulation of electric charges over time theoretically may reach excessive levels and

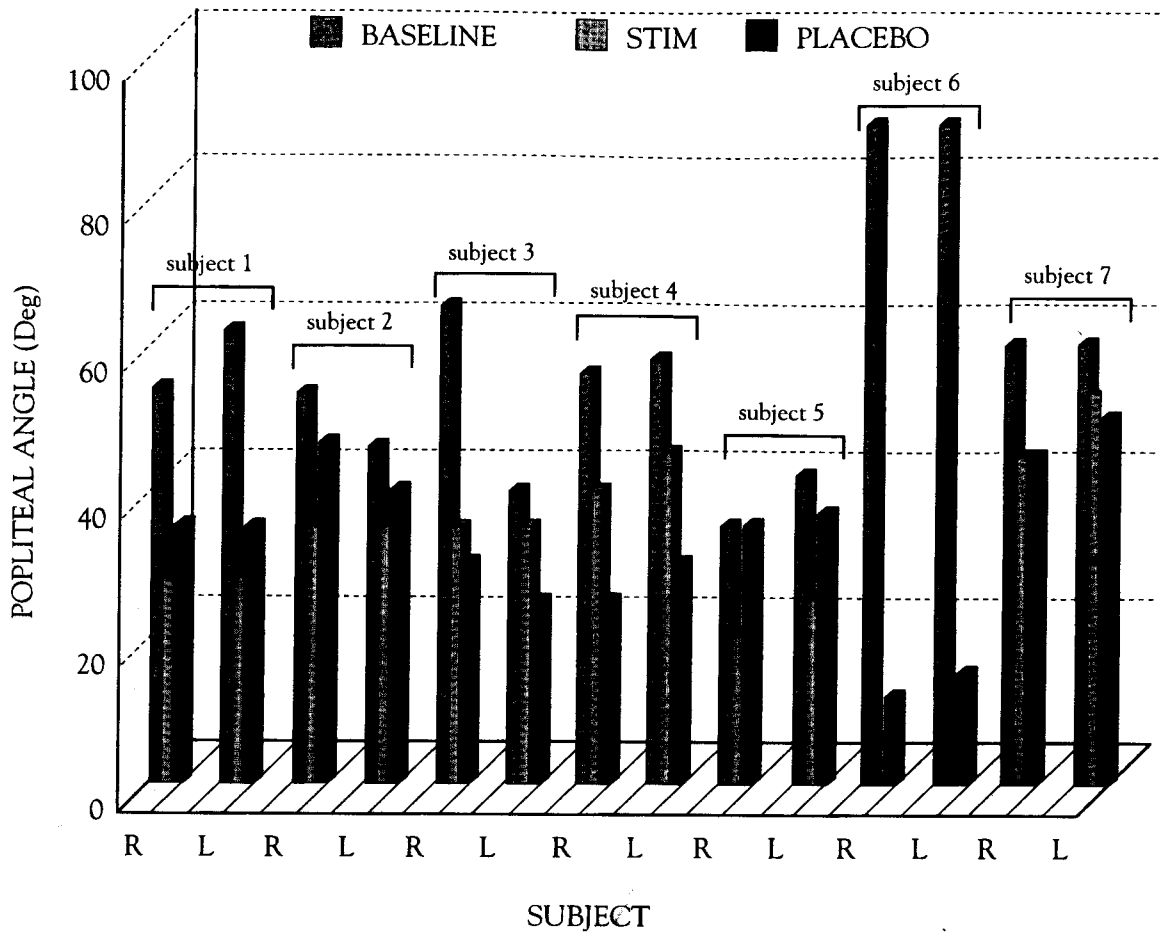

Figure 4. Knee joint range of motion limitation (popliteal angle). Note that the lower the bar the greater the joint range. Both left and right knees were measured. Subject 6 had a full recovery of knee extension after the real stimulation.

cause electrochemical alteration of cellular pH (for monophasic waveform), direct electrical damage, or both. Increasing treatment time within the boundaries of desired physiologic responses may help optimize clinical results by prolonging the electrophysical and/or electrochemical influence on the neural networks, thereby enhancing the desired adaptation of the CNS.

It also must be determined whether the safety of TCES is associated with the electrical stimulation being a pulsed current (PC) or alternating current (AC). Commercially available stimulators typically are designed to deliver either a simple unmedullated, nonpolarizing sine wave AC (12,21,25,26) or 15 KHz monophasic PC that offers polarity and is time modulated to 15 bursts per sec. Like Malden and Charash (9), Okoye and Malden (10), Childs (15), and Shealy and associates (14), we used a PC stimulator. Despite the overall differences in stimulator design, the relevant output characteristics of the phase charge and averaged RMS current as reported or deduced from the literature have been similar for both AC and PC stimulators, as is their safety record. In future reports it would be useful for investigators to report the stimulus phase charge and averaged RMS current as an alternative to disclosing only peak current, peak voltage, or the type of current being AC or PC. Because most of the scientific reports suggest that the physiologic responses, the controversial clinical efficacy, and the safety of stimulation is the same for the variety of stimulators, favoring one type of stimulator over the other is not warranted.

Electrode size and position are factors that may affect the safety of TCES. Because the electrode-skin interface constitutes the sole area of current delivery, optimal electrode location and size may determine the target centers in the brain that are affected by the stimulation. Our group and other investigators (9,10) have placed the electrodes over the temporal area bilaterally using 3.8 cm diameter round electrodes. Other reports have not specified the electrode size and have preferred placing them at the maxillo-occipital juncture just behind the ear lobe (14,20,21,25). The well-documented

phenomenon that electric current always follows the path of least impedance virtually precludes any possibility of accurately determining in clinical setting whether electrode size and position have any measurable effect on which parts of the brain will be stimulated or damaged by transcutaneously applied stimulation.

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