Effects of Electrode Configurations in Transcranial Direct Current Stimulation after Stroke

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***Abstract*—Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation that can modulate neuroplasticity (the capacity for brain reorganization). Neuroplastic change correlates with upper extremity (UE) recovery after brain lesions. Different electrode configurations of tDCS paired with UE motor training can have different effects in distinct populations. We are conducting the first randomized, double-blind, placebo-controlled trial to investigate which tDCS configuration may best enhance outcomes of UE motor training for stroke survivors with chronic, *severe* hemiparesis (i.e., little or no wrist or hand movement). We have assigned subjects to 1 of 4 groups: 1) "Anodal": anodal tDCS to excite ipsilesional motor cortex; 2) "Cathodal": cathodal tDCS to inhibit contralesional motor cortex; 3) "Dual": a simultaneous combination of anodal and cathodal tDCS; or 4) "Sham" tDCS. Intervention (10 sessions) consists of tDCS followed by 3 hours of intensive, task-oriented UE training in each session. Our primary outcome measure is Fugl-Meyer Assessment. Our secondary outcome measures are Action Research Arm Test and Stroke Impact Scale. We have conducted evaluations at baseline and post-intervention. Preliminary results from 26 of (projected) 44 subjects indicate substantially greater improvement for the "Cathodal" group than other groups. These findings differ from evidence about tDCS in rehabilitation of mild-to-moderate hemiparesis. Completion of our study will include full analysis of neuroplastic change associated with intervention.**

Keywords— neuroplasticity; neuromodulation; occupational therapy; hemiparesis; motor function

I. INTRODUCTION

Stroke continues to be a major public health concern in the United States[1, 2]. Because there has been only limited success with interventions to minimize tissue damage in the acute phase of stroke[3, 4], it remains imperative to establish effective therapeutic interventions for long-term stages of recovery[5, 6]. These interventions can capitalize on neuroplasticity, or the capacity of the adult brain to reorganize. Neuroplastic reorganization can occur to a degree formerly thought possible only during early post-natal periods[6-9]. Knowledge of how the mature brain reorganizes in response to novel demands has dramatically proliferated in recent years[5, 9]. It is now understood that neuroplastic reorganization can occur in adults via modification of synaptic strength, axonal sprouting, and altered synaptic activation[6, 10].

Cortical excitability influences neuroplasticity[10-13]. Researchers have recently used a non-invasive form of brain stimulation called transcranial direct current stimulation (tDCS) to modulate motor cortical excitability[10, 14-16]. Modulation occurs in a polarity-dependent manner}[14, 16-18]: anodal stimulation increases cortical excitability, whereas cathodal stimulation diminishes it. Different tDCS configurations paired with upper extremity (UE) motor training can have different effects in distinct patient populations. For example, studies in subjects with mild-to-moderate hemiparesis after stroke have shown that either anodal or cathodal tDCS leads to significantly more improved motor function than sham tDCS[19-22]. Specifically, Boggio et al. reported significantly improved motor performance after 4 anodal or cathodal tDCS sessions administered once per week. There was an additive effect of daily tDCS as well as continued improvement over the course of 5 consecutive days[20]. A later study by Mahmoudi et al. compared dual tDCS (ie, anodal and cathodal stimulation delivered concurrently to bihemispheric motor areas), anodal tDCS, and cathodal tDCS in subjects with mild-to-moderate post-stroke hemiparesis. Significant improvement in UE motor function followed single sessions of each of these configurations[23]. Lindenberg et al. reported significant improvement for stroke survivors with chronic, mild-to-moderate hemiparesis in a sham-controlled study of UE motor function following 5 sessions of dual tDCS paired with motor training[24]. In a different study of healthy subjects without stroke, dual tDCS led to more improved motor learning than either anodal tDCS or cathodal tDCS[15]. However, very few studies in stroke rehabilitation have focused on neuromodulation for severe hemiparesis. Brandnam et al. evaluated the effects of a single session of cathodal tDCS to the contralesional hemisphere compared to sham tDCS in 12 stroke survivors with varying severity of motor deficit[25]. Investigators found that cathodal tDCS can improve motor evoked potentials (MEPs) in subjects with mild hemiparesis, but it decreases MEPs in subjects with moderate-to-severe hemiparesis. Conforto et al. applied repetitive transcranial magnetic stimulation (rTMS) in 30 subjects with mild-to-severe motor deficit after stroke[26]. Subjects were in the subacute phase of recovery and were randomized to receive

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either inhibitory rTMS (1 Hz) or sham rTMS to the contralesional hemisphere over 10 days immediately before standard physical therapy. The authors demonstrated that inhibitory rTMS (1 Hz) can improve motor function in subacute stroke, regardless of degree of functional impairment.

Other interventions that capitalize on neuroplasticity include a form of therapy known as intensive, task-oriented motor training. Like tDCS, this form of therapy has recently been shown to effect significant neuroplastic change and motor improvement in subjects with mild-to-moderate hemiparesis after stroke[27-31]. For instance, studies applying intense motor traning after stroke have demonstrated expansion of motor maps as measured by transcranial magnetic stimulation (TMS) [32-35]. Several small-scale studies applying intensive, task-oriented motor training in acute [36, 37], subacute [31, 32, 38, 39], or chronic subjects[33, 40-42] have reported superior results compared with standard rehabilitative methods. Furthermore, a large multi-center trial enrolling 222 subacute stroke subjects showed that intensive motor training emphasizing paretic arm use during constraint of the non-paretic arm leads to statistically significant improvements compared with participants receiving usual and customary care [29, 43]. As a singular intervention, however, intensive training alone may not benefit patients with severe post-stroke hemiparesis[42] [44]. On the other hand, our preliminary studies indicate that subjects with severe hemiparesis may benefit from combining novel neuromodulatory interventions (such as tDCS) with intensive, task-oriented UE motor training. This combination may be optimal because training that occurs during a period of enhanced capacity for neuroplastic change (eg, post-tDCS) is more likely to have benefit than training when there is no enhancement of neuroplasticity (eg, without tDCS). To further optimize tDCS paired with motor training, we are investigating how various methods of tDCS (i.e., anodal, cathodal, or dual) affect outcomes of intensive UE motor training for stroke survivors with chronic, severe hemiparesis.

II. METHODS

The ongoing, randomized, double-blind, placebo-controlled study takes place in an outpatient rehabilitation research setting. Following Institutional Review Board approval, we have consented and enrolled 26 of 44 projected total subjects. Following baseline evaluation, we used an experimental design generator and randomizer program for simple random allocation of subjects into 4 groups (Table 1). Inclusion criteria: We recruited subjects with chronic (i.e., >1 year post-stroke), severe UE motor deficit after a single stroke. We defined severe motor deficit as the inability to extend the affected metacarpophalangeal joints at least 10°; and the wrist, 20°. Such deficit would normally exclude the subject from constraint-based intensive motor training [46]). We set age range as at least 18 years of age with no upper age limit. We obtained past data, including radiographic studies and medical history, in order to confirm diagnosis, site, volume, and type of lesion. We conducted routine neurological evaluation during the screening of potential subjects. Each individual received a verbal and written explanation of the purposes, procedures, and potential hazards of the study; and written consent was obtained. Exclusion criteria: a) within 3 months of recruitment, addition or change in the dosage of drugs known to exert detrimental effects on motor recovery, including alpha-adrenergic antagonists or agonists, phenothiazines, phenytoin, benzodiazepines, muscarinic receptor antagonists, dopaminergic antagonists, or other neuroleptics; b) untreated depression; c) history of multiple strokes; d) history of head injury with loss of consciousness; e) history of severe psychiatric illness or alcohol or drug abuse; f) positive pregnancy test or being of childbearing age and not using appropriate contraception; g) presence of ferromagnetic material in the cranium except in the mouth, including metal fragments from occupational exposure, and surgical clips in or near the brain; or h) cardiac or neural pacemakers or implanted medication pumps.

A. Evaluation

Before the first intervention session, as well as after final intervention, we evaluated UE motor function using the UE portion of the Fugl-Meyer Assessment (FMA; primary outcome measure)[45] as well as secondary outcome measures: the Action Research Arm Test (ARAT) [46]and the Stroke Impact Scale (SIS)[47]. Additionally, we used TMS to establish the optimal site for the placement of electrodes. We localized the primary motor cortex on a template MRI using Brainsight™ neuronavigation system (Rogue Research Inc, Montreal, Canada). We designated the "hot-spot" as the cortical area that, when stimulated, elicited the largest response in the contralateral extensor digitorum communis muscles (EDC) at rest. We selected the EDC because it is the primary effector of a variety of functional motor tasks. In the absence of MEPs, we applied the surface 10-20 EEG system to identify the UE motor area (C3 and C4).

B. Intervention

Subjects were assigned to 1 of 4 groups:

Table 1: tDCS Configurations According to Group Assignment.

Group Name	**Anode placement (excitatory stimulation)**	**Cathode placement (inhibitory stimulation)**
"Anodal" (n=7)	ipsilesional M1	contralesional supraorbital
"Cathodal" (n=6)	ipsilesional supraorbital	contralesional M1
"Dual" (n=7)	ipsilesional M1	contralesional M1
"Sham" (n=6)	ipsilesional M1	contralesional supraorbital

Table 2: Subject Demographics

Demographics	Anodal	Cathodal	Dual	Sham
Age	58.0 ±4.4	63.8±2.5	51.6±7.1	61.8±4.8
Years after stroke	3.8±0.8	5.3±2.2	5.0±1.2	4.9±0.9
Gender (female/male)	3/4	4/2	2/5	1/5
Handedness (right/left)	5/2	3/3	7/0	4/2
Affected brain (right/left)	2/5	2/4	2/5	5/1
Lesion (cortical/subcortical)	6/1	5/1	6/1	4/2
Type (ischemic/hemorrhagic)	5/2	5/1	6/1	6/0

tDCS was the only independent variable. Subjects in the "Anodal," "Cathodal," and "Dual" groups received 20 minutes of tDCS on each of 10 consecutive weekdays at a current of 1.4mA using saline-soaked sponge electrodes. These values result in a current density of 0.04mA/cm^2 and a charge density of 480 Coulombs/M^2. This intensity falls within the range of safe stimulation parameters [48]. For sham tDCS, we used an identical setup to anodal tDCS (ipsilesional M1 and contralesional supraorbital) except that we ramped up intensity over 30 seconds, held at 1.4mA for 30 seconds, then down to 0mA over 30 seconds and kept at 0mA for the remainder of the 20 minutes. This sham protocol preserved the blinded fashion of the study by producing the same sensation as active stimulation[21]. For "Anodal" and "Cathodal" groups, we placed a stimulating electrode over the hot-spot and a reference electrode over the supraorbital region (see also Table 1). This method of using the supraorbital region as a reference location provided the greatest distance from skin surface to cortex of any acceptable location on the scalp (for safety reasons, both electrodes must be placed anterior to the brainstem)[49, 50]. For the "Dual" group, we placed the stimulating electrodes over bilateral hot-spots. For the "Sham" group, we placed one electrode over the hot-spot and the other electrode over the contralateral supraorbital region. We used a battery-operated direct current stimulator for delivery of stimulation (Magstim Ltd, Wales, UK). We visually monitored each subject during tDCS. Subjects, evaluators, and therapists delivering motor training were blind to group assignment. Following each tDCS session, each subject participated in 3 hours of intensive, task-oriented UE motor training (a modified constraint-based protocol).

We performed group analysis of intervention-related changes with fixed effects comparison of baseline versus post-intervention measurements, taking into account the scores of all outcome measures (baseline versus post). We used 2-way factorial ANOVA with factor stimulation (anodal, cathodal, dual and sham) and changes (baseline versus post) to estimate the effect on all outcome measures. This model is similar to testing differences in change in the outcome (post-intervention compared to baseline) but is a more efficient method for estimating and testing intervention effects[51]. Fisher post hoc tests were performed. Data are expressed as mean±SE and considered significant if $p<0.05$.

III. RESULTS

No significant motor function difference existed between groups at baseline (see Table 3; FMA p=0.091, ARAT p=0.192, SIS p=0.114). As anticipated, evaluation after

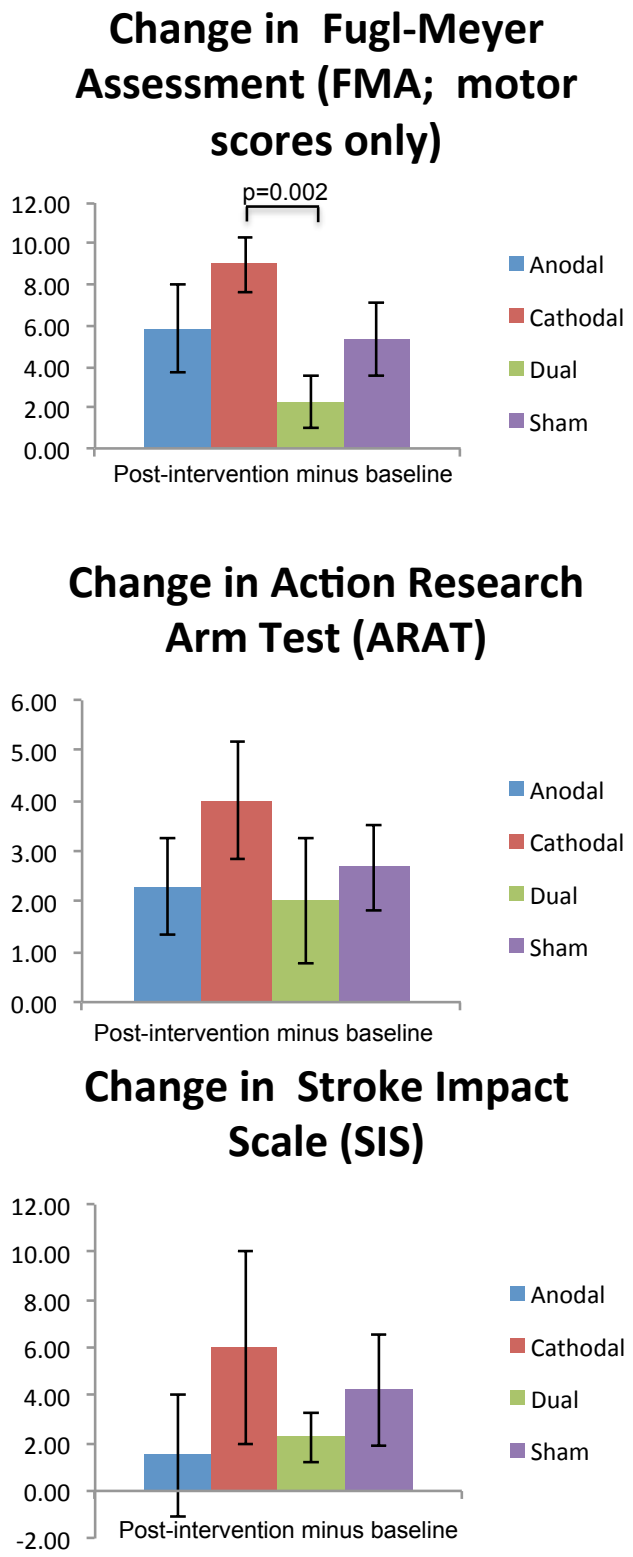

Figure 1. Differential effects on severe upper extremity (UE) motor deficit after various configurations of transcranial direct current stimulation (tDCS) paired with motor training. On all measures, increase in score indicates improvement. On all measures, the "Cathodal" group showed more notable improvement compared with every other group. Variability bars refer to standard error.

Group	Fugl-Meyer Assessment		Action Research Arm Test		Stroke Impact Scale	
	Baseline	Post-intervention	Baseline	Post-intervention	Baseline	Post-intervention
Anodal	26.14±4.68	32.00±4.91	11.29±3.00	13.57±3.16	59.25±5.62	60.75±5.15
Cathodal	22.83±0.95	31.83±1.42	6.17±0.40	10.17±1.33	60.99±5.78	66.99±5.49
Dual	26.14±2.60	28.43±3.03	7.86±1.62	9.86±1.96	65.50±3.98	67.75±3.97
Sham	23.67±3.46	29.00±3.57	10.67±4.10	13.33±4.49	57.25±7.37	61.50±6.94

Table 3: Mean scores of measures of motor function (mean±SE)

intervention revealed significant improvement in motor function irrespective of group (Table 2 post minus baseline; FMA $p<0.0001$, ARAT $p<0.0001$, SIS $p=0.0174$). Two-way factorial ANOVA (changes and stimulation) revealed a significant difference between the "Cathodal" group and the "Dual" group on FMA (see Figure 1, FMA $p=0.002$) as well as a similar but nonsignificant trend for the ARAT and SIS. No other significant differences existed between groups.

IV. DISCUSSION

Previous studies of both healthy subjects and subjects with mild-to-moderate post-stroke hemiparesis have indicated that dual tDCS leads to similar or more benefit than anodal or cathodal tDCS. In contrast, our findings indicate that dual tDCS may be much less effective than either anodal or cathodal tDCS for promoting motor recovery in stroke survivors with severe hemiparesis. Moreover, in these severe cases, cathodal tDCS appears to yield greatest improvement in motor function. Several explanations could account for our results. First, in cases of severe hemiparesis, comparatively larger lesions may change the path of current flow in a way that leads to a pattern of stimulation that is different than that for subjects with comparatively smaller lesions. Second, in stroke leading to severe hemiparesis, comparatively less ipsilesional neuronal substrate may be available for stimulation. Therefore, the "Anodal" and the "Dual" configurations, which incorporate ipsilesional stimulation, may not have the needed substrate for neuroplastic change and motor improvement.

Other studies applying inhibitory neuromodulation to the contralesional hemisphere have shown contradictory results. Conforto et al. applied inhibitory rTMS at 1 Hz, which yielded results indicating that the contralesional hemisphere plays a fundamental role for motor recovery after stroke[26]. While the authors applied a different type of neuromodulation (rTMS versus tDCS), the training protocol was very similar to ours in the present study (they administered rTMS immediately before motor training for 10 days). On the other hand, Brandnam et al. reported decreased cortical excitability after a *single* session of cathodal tDCS to the contralesional hemisphere [25]. Subjects performed isometric contractions *during* evaluation (TMS). This contrast of methodology could have accounted for the different findings in comparison to our study. Because mechanisms of action in non-invasive brain stimulation are complex, it is conceivable that cortical spontaneous oscillatory rhythms could be distinct when applying neuromodulation before or during a motor task or training [52]. Additionally, cumulative effects of multiple sessions of tDCS could also yield differential outcomes.

Our ongoing investigation will allow us to refine these and other plausible explanations. To this end, we will continue to enroll subjects and, upon reaching sufficient enrollment, will use factors such as lesion location (e.g., cortical vs subcortical), lesion side, time from stroke, and presence or absence of MEPs at baseline as covariates in our analysis.

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